Primary-Process Separation-Distress (PANIC/GRIEF) and Reward (SEEKING) Processes in the Ancestral Genesis of Depressive Affect and Addictions: Why does Depression Feel so Bad? Why does Addiction Feel so Fine, for a While?

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Decades of research with preclinical (animal) models, Affective Neuroscience has clarified the functional neuroanatomy of seven *primary process* (i.e., genetically provided) emotional systems in mammalian brains. All are subcortically situated (See Panksepp, 1998 for summary), allowing animal models to guide the needed behavioral and neuroscientific analyses at levels of detail that cannot be achieved through human research, including modern brain imaging. They consist of the following neuronal processes (capitalized, to highlight their primary-process nature): SEEKING, RAGE, FEAR, sexual LUST, maternal CARE, separation-distress PANIC/GRIEF (henceforth, simply PANIC) and joyful PLAY. Several of these systems figure heavily in social bonding and addictions.

In this chapter, we will focus especially on the genesis of depression. We will focus on two antecedent mechanisms of depression. One, sustained overactivity of the separation-distress PANIC/GRIEF system (typically reflecting severed social bonds and at higher levels, intrapsychic alienation) which can, if sustained, lead to a downward cascade known as psychological depletion (a theoretical view originally formulated by John Bowlby) and the ascendancy of negative emotional systems. Two, the despair phase that follow the acute PANIC response, a shift which may be characterized by abnormally low activity of the SEEKING (so-called "brain reward" networks) leading to amotivational states that characterize depression. Both states can promote drug addictions in order to restore psychic homeostasis: Separation-distress promotes opioid addiction; the emptiness of diminished desire, can be temporarily alleviated by psychostimulants. Depressive affect is promoted by such brain mechanisms of social loss and desire. To understand why depression feels so bad, we must understand the neural mechanisms that mediate such social feelings. As John Bowlby well recognized, separation distress—the panicy 'protest' that promptly follows social loss, especially in young animals—feels bad in a special way. It is a variant of psychic pain, which if prolonged, promotes psychic emptiness. This knowledge can help clinicians craft new psychotherapeutic approaches, including the better utilization of positive affects that arise from SEEKING and PLAY systems, including new pharmacological and other brain-mind based treatments.

Introduction: The Affective Neuroscience Strategy to Understanding the Emotional Mind

The affective neuroscience approach (Panksepp (1998, 2005) to understanding the emotional mind of all mammals makes two key assumptions that allow us to address important and difficult fundamental questions in both basic psychological research and clinical practice in novel and productive ways. First, emotions evolved to *do* something specific in relation to

biologically significant and life-challenging situations. They are not mere epiphenomena. Second, *felt* aspects of primary-process emotions—specific kinds of affects that have been built into the brain and shared homologously by all mammals -- serve three key adaptive evolutionary 'purposes': i) They code for key survival issues, with positive affects indexing the paths of survival and negative affects the paths of destruction. ii) They motivate organisms to behave in ways that promote survival, providing psychobehavioral compass bearing for individual flourishing and reproductive success. iii) They promote memory construction through neural systems that "reinforce" learned behaviors by yet unfathomed "Laws of Affect" that should replace the behaviorist "Law of Effect" that simply talked about "rewards" and "punishments--increasing and decreasing behaviors—without considering the inner psychological lives of humans or animals. They led to a scientifically 'solid' – perhaps rigid—outer view of psychological life in animals and then, for a while, humans. Here we advance the inner view in all mammalian species, without neglecting the outer one.

Thus, positive affects—among the most myserious psychological effects to understand scientifically--automatically tell animals they are on paths that are likely to increase their fitness at various levels of brain-mind organization, and negative affects inform them that they are in life-threatening situations, and provide heuristics to escape from them and avoid them in the future. Because our interest is largely in the foundations of psychiatrically significant emotional imbalances in humans, here our goal is chiefly to relate affective neuroscientific facts and novel epistemological perspectives to understanding the foundations of human emotions, through a distinct type of 'basic emotion' theory—increasingly criticized by certain psychologists (Barrett, 2006; Ortony & Turner, 1990)--that has the potential to shed new light on many psychiatric disorders (Panksepp, 2005, 2006). Here our specific goal will be to envision how an

understanding of the brain SEEKING and PANIC/GRIEF (social separation-distress) systems can promote better understanding of depression and drug addictions and their treatments. A brief word about nomenclature, and more later: The capitalizations highlight that we are speaking of inherited neuro-mental tools for living, namely evolutionarily provided primary-processes of the brain and mind.

What allows us now to begin talking about specific emotional feelings in animal brains, are the discoveries (and explicit recognition) of distinct affectively rich emotional operating systems (Panksepp, 1982, 1998, 2005). The key finding is robust and has not been seriously challenged in the four decades it has been advanced: Wherever in the brain we arouse emotional-instinctual behavior patterns in all mammalian brains ever studied, other vertebrates too, we can demonstrate that those brain arousals can serve as "rewards" and "punishments" in the control of behavior. Thus, we believe that all of the various social-emotional systems of the brain may become potential players in distinct depressive phenotypes. In the most common variant of depression, if psychologically desirable outcomes of social protest (i.e., the psychic pain of separation-distress) does not materialize, then the additional shut-down of positive feelings promoted by diminished SEEKING urges changes the negative affect into a deeper and more prolonged phase of sustained negative affect. Unfortunately, animal research cannot illuminate the higher-order thought and rumination processes that characterize human depression, but it can clarify the affective infrastructure of social attachments and social loss, and thereby the underpinning of depression and certain drug addictions.

Affective Neuroscience has now outlined the functional neuroanatomy of seven *primary process* (i.e., genetically provided) emotional systems. All are subcortically situated (See Panksepp, 1982, 1998, 2005 for full discussion), allowing animal models to guide

neuropsychological analyses at levels of precision not afforded by any type of human research, including modern brain imaging. The emotional primes include at least the following seven fundamental neuropsychological processes (capitalized, to highlight their primary-process nature; because they are official names of universal brain systems, they do not need to be translated into other languages): i) SEEKING, ii) RAGE, iii) FEAR, iv) sexual LUST, v) maternal CARE, vi) separation-distress PANIC/GRIEF (henceforth, simply PANIC) and vii) joyful PLAY. Although every aspect of the affective life can be influenced by depression, it seems likely that depression is especially significantly influenced by i) sustained over-activity of the separation-distress PANIC system that can, if sustained, lead to a downward cascade known as psychological despair, and ii) the despair phase that follows the acute PANIC response is characterized by abnormally low activity of the SEEKING (so-called "brain reward" networks) leading to depression. In terms of a relatively straightforward animal (i.e., preclinical) models, depression reflects the pervasive behavioral and emotional shutdown (despair) following a protracted PANIC phase of separation distress. The initial agitation in response to social loss may partly reflect an agitated state partly mediated by the SEEKING system, while the 'despair phase' following protracted separation distress, is characterized by diminished SEEKING urges and depressive affect.

From this point of view, depression may be an evolutionarily selected mechanism (present in some form in virtually all mammals) to terminate protracted and unsustainable separation distress, as first formulated by John Bowlby (1960, 1980). Thus, among these emotional primes, four mediate affectively positive behavioral urges: namely SEEKING, LUST, CARE, and PLAY, with the last three heavily utilizing the SEEKING urge. And three mediate affectively negative emotions: RAGE, FEAR and PANIC/GRIEF (henceforth, just PANIC). The

unusual full-capitalization terminology employed to discuss these systems was selected to explicitly highlight that we are talking about *evolutionarily primal* or *basic* emotional processes that have been evolutionarily built into all mammalian brains. It can serve as a rigorous, and hence useful, way to discuss aspects of mind not widely recognized in modern psychiatry (Panksepp, 2006). This primal level of the emotional mind, with executive neural networks, concentrated in medial subcortial regions of the brain, was not recognized until recently, and may serve as a foundation for affective neuroscientific perspective on psychiatric disorders (Panksepp, 2004). Because of that, we have devoted some effort to develop personality tests that are specifically designed to evaluate the strengths and weaknesses of the primal emotions in humans (see Davis, Normansell & Panksepp, 2003; and Davis & Panksepp, 2011). This may be of special value for psychotherapists so they can have a common metric by which one can estimate the status of the primal emotions in the lives of their clients, and possibly have a common metric to compare different individuals.

These system can be considered to be "evolutionary-memories"—namely mental functions built into the brain—interact with world events to generate learning (what we will call "secondary processes" for they are situated in higher brain regions, especially in brain areas called the basal ganglia (in brain regions such as amygdala, bed nucleus of the stria terminalis, and ventral striatum. Such learning and memory functions of the brain appear to be largely unconscious, while the primary-process generate a foundational form of consciousness—raw phenomenal affective experiences, which can be studied in animals by the capacity of subcortical DBS of distinct emotional systems to yield "rewarding" and "punishing" effects, namely those aspect of learning that is commonly called "reinforcement" in the Anglo-American tradition.

Here we briefly summarize the role of these systems in psychiatrically significant distress, and to also discuss new psychiatric modalities in treatment resistant depressive disorders through the use of DBS (Coenen, et al., 2011; Schlaepfer, et al., 2008). We will argue that the "primary-process" emotion systems that, in affective neuroscience terminology, are labeled as SEEKING and PANIC, are of direct importance understanding and treating the underlying affective dynamics that can lead to depression. The discussion of one of the underlying systems, namely the PANIC system, is framed within the seminal contributions of John Bowlby , who provided the clearest statement of how the genesis of depression is related intimately to the loss of supportive social-bonds, such as the loss of parents in young children, and the death life-companions, now widely recognized as major antecedents to the psychological despair that can lead to depression upon which the present view is explicitly based (for a more detailed summary, see Watt & Panksepp, 2009, and also see Panksepp & Watt, 2011; and Zellner, et al., 2011 for neuro-psychoanalytic perspectives). Since these two systems are of cardinal importance in both early childhood as well as adult social bonds, we also note how various addictive processes emerge from the capacity of drugs to modify affective states to artificially simulate social bonding feelings that are of critical importance for mental health.

The Primal Affective Foundations of Depression

So what does affective neuroscience add to the discussion of the genesis of depression? Among other contributions, it begins to answer the question of why depression feels so bad. This is because it is the only basic neuroscience approach that specifically aims to take the affective infrastructure of the evolved mind as its central focus. Thereby it can offer testable hypotheses concerning the precise nature of the affective imbalances, and psychological dynamics, that contribute to clinical depression (Solms & Panksepp, 2010; Zellner et al., 2011).

In other words, the most important questions, still unanswered, that needs to guide our thinking about the genesis of depression is as follows: What are the specific negative affect-generating networks of the mammalian brain, whose excessive activities initiate and sustain the cascades of brain-mind changes that characterize depression? We suggest that a cardinal system is the PANIC system of the brain, which has been well modeled preclinically by the study of separation-induced crying in the young of various species (for early reviews on work with dogs, guinea pigs and baby chickens, see Panksepp, 1981; Panksepp, et al., 1980, 1988). We argue that the despair generated by this system eventually weakens the status of the dopamine-energized, reward SEEKING system, which engenders chronic anhedonic (despair) and amotivational (depressive) states of mind, which may be reversed by psychotherapy in mild cases, and new concepts in pharmacotherapy as well as direct DBS of the reward SEEKING system, when nothing else has helped (see Coenen, et al., 2011; Schlaepfer, et al, 2008). From an affective perspective, abundant new perspectives about the underlying neuroscientific and neuropsychological processes is emerging, with fundamental implications for understanding the sources of depressive "pain" in the brain and addictive urges, as well as new therapeutics that such knowledge can lead to (for medicinal developments, see Burgdorf, et al., 2010, 2011; Moskal, et al., 2011).

A more detailed exposition of the neurochemical foundations of the current view, accompanied by seven expert commentaries, is available in Watt & Panksepp (2009). The present essay provides only a synopsis of those arguments, while focusing more on new therapeutic implications. It is noteworthy that much of the basic science in this area has been conducted on pre-clinical (i.e., animal) models, but we will not summarize past models in the area, but to simply note that most used a variety of coarse and general physical stressors (chronic

unpredictable punishments) or social stressors (e.g., repeated social-defeats in adult aggressive encounters) which do not really access, as directly as is currently possible, the underlying emotional-affective systems of the brain. (For extensive summaries of such preclinical models of depression, see the Special issue of *Neuroscience and Biobehavioral Reviews* vol. 30 (2006)).

Although putative depressive phenotypes characterized by 'learned behavioral helplessness' emerge readily in response to such severe life challenges, they leave the neutrally based affective lives out of the overall analysis. This reduces their translational (animal-to-human) utility.

Flaws with Current Preclinical and Medicinal Approaches to Depression

Although the general stress-induced preclinical models of depression have many shortcomings, one is especially problematic: Few have sought to specifically and directly evoke and measure depression by modifying and monitoring the activities of the most relevant affective networks of the brain. Because most models use rather general behavioral outcome measures, they typically have little clear functional relationship to human affective, psychodynamic or interpersonal issues, that are of foremost importance for clinical practitioners. They do not address the underlying psychological issues most relevant to feelings of social loss and social defeat in the genesis of both depression and drug addictions (see Solms & Panksepp, 2010, and Zellner, et al., 2011 for psychodynamic discussion of those perspectives).

As depression research during the last four decades of the 20th century focused most heavily on the consequences of stress (DeKloet, et al. 2005; McEwen, 2007) and brain norepinephrine and serotonin dynamics (from Schildkraut, 1965 to Harro & Oreland, 2001, so to speak), one key question was largely neglected: Why specifically does depression feels so bad? Generalized behavioral analyzes were excessively impressed by the capacity of very generalize

brain neurochemical systems, such as serotonin, to dampen all emotional behaviors. But few were seeking understanding of the more specific affective changes of organisms. Thus, it is no great surprise that SSRIs can treat so many psychiatric problems, while also having only modest effects when evaluated across large cohorts of individuals (highlighted well by the disappointing recent STAR*D findings (Rush et al, 2003, Rush, 2007).

Thus, it is becoming much harder to believe that such general brain serotonergic and/or noradrenergic changes, which regulate everything animals do, would *specifically* explain the morbid moods of depression, although they certainly regulated affective arousal (Delgado, et al., 1990). Indeed, we can be confident that serotonin and norepinephrine serve to regulate quite general brain arousal functions that influence all emotions and virtually all related cognitive processes. Of course, more recent preclinical work has usefully focused heavily on various neurotrophic factors (Koziek et al., 2008), stress-induced hippocampal shrinkage and CNS inflammation (Miller, et al., 2009) and various genetic underpinnings of such autonomic, psychophysiological problems (Levinson, 2006), those approaches have not yet generated new medicines. Perhaps this is because such strategies provide little insight into the affective feelings that characterize depression. Here our goal is to address how more specific affective neuroscience approaches may yield more specific understanding of the causal underpinnings of depressive affect (e.g., as addressed by Burgdorf, et al., 2011; Kroes, et al., 2007; Watt & Panksepp, 2009).

Here we develop the idea that an emotional-systems analysis will not only help promote the needed interdisciplinary dialogues, but also lead to more specific types of therapeutic interventions than are currently available in biological psychiatry, where general amine manipulations still prevail, as well as in psychotherapeutics, where cognitive-behavioral

regulatory strategies are emphasized, often at the expense of more immediately affect-oriented therapies (but see Fosha, et al., 2009 for such interventions, and especially Shedler, 2010 which summarizes impressive evidence in support of the efficacy of emotionally based psychodynamic approaches).

In contrast to general behavioral approaches, the affective neuroscience views promotes the use of preclinical models that seek to instigate depressive cascades by directly stimulating the relevant negative affective systems of the brain, while monitoring chronic changes in affect with validated measures of declining capacities to sustain positive social affect (Wright & Panksepp, 2011). The development of new medicinals is facilitated by the emerging understanding of changes in the relevant genetics and brain neurochemical systems (e.g., Burgdorf, et al., 2011; Moskal, et al., 2011; Normansell & Panksepp, 2011), framed in an understanding that often drug addictions emerge from individuals trying to achieve emotional homeostasis through the intake of addictive drugs (Panksepp, 1981; Panksepp, et al., 1980). As we will elaborate here, on the psychotherapeutic front, affective neuroscience concepts and approaches may promote the better and more specific utilization of positive emotions in psychotherapy, such as facilitated SEEKING, CARE and PLAY dynamics, whether psychologically or biologically, or through the use of direct deep brain stimulation (DBS) of the relevant affective circuits (Bewernick, et al., Coenen, et al., 2011; Mayberg, 2009; Schlaepfer, et al., 2008).

An Affective Neuroscientific Perspective on Why Depression Feel so Bad

Recently, we fully summarized the Bowlby theory-based analysis of depression (Watt & Panksepp, 2009), we will not repeat those detailed arguments here. Rather, here we emphasize that affective neuroscience has provided distinct brain networks that can help explain the psychological pain and general dysphoria of depression, especially as envisioned through the

overactivity of brain separation-distress PANIC and the underactivity of the SEEKING system. The PANIC system has been proposed to be a primary emotional systems for social-loss induced psychological pain (Panksepp, 2003a,b, 2005a,b, 2010), and hence a conceptually clear foundation process for the biggest epidemiological stressor which most commonly leads to depression – social loss (Bowlby, 1980; Heim & Nemeroff, 1999).

A solid neuroscience of such brain processes has been garnered through the mapping of the neuroanatomies and neurochemistries of separation distress, and they tell us something specific about social attachments and loss, as summarized in Figure 1 (Panksepp, 1998, 2003). It is remarkable that these same systems mediate various addictive urges that can emerge from fundamental social bonding systems of the brain (Panksepp, 1981).

The PANIC circuitry starts in midbrain central gray regions, currently commonly called the periaqueductal gray (PAG), and it ascends through medial diencephalic structures, especially the dorsomedial thalamus, and terminates in more ventral or subcallosal anterior cingulate forebrain regions. Inhibition of this system with DBS may have already figured positively in the direct neural systems modulation of treatment resistant depressions (Mayberg et al., 2005).

The key neurochemistries that promote separation calls (protest) are declining opioid and oxytocin chemistries and elevated CRF, combined with increased glutamatergic drive in PANIC circuits of the brain—with the neuropeptides being presumably more important than the excitatory amino acid in controlling he specific social-affective responses of the brain. Still, inhibition of both neuropeptide and excitatory amino acid (e.g., glutamatergic) promoters of PANIC (e.g., Normansell & Panksepp, 2011; Panksepp, et al., 1988) should help alleviate the bad feelings of depression, and recent work along these lines has been consistently promising (Holsboer, 2000; Zarate, et al., 2006).

The key brain chemistries that can specifically reduce separation-distress are opioids that activate mu-receptors, oxytocin and prolactin (Panksepp, 1981; 1998). Each could be considered as a potential vector for beneficially countering the affective changes that promote depression. Of course, one would hesitate to use addictive opioids, which very effectively, but only temporarily, alleviate depression as routine treatments, because of their addictive liability (even though they were widely used as a last resort prior to the modern era of pharmacotherapy of psychiatric disorder starting in the mid 1950s (Tenore, 2008). However, as we will elaborate later, safe opioids such as ultra low-dose buprenorphine (which only stimulate opioid receptors at low doses, and become antagonists at high doses) are very effective anti-depressants for individuals where no other medications have provided sustained relief of depression (Bodkin et al, 1994), and with the advent of possible low-dose buprenorphine delivery via skin-patches, any development of a behaviorally-mediated addictive cycle is further minimized.

Centrally administered oxytocin is also remarkably effective in alleviating separation distress and social bonding in animal models (Panksepp, 1992; Nelson & Panksepp, 1998; Uvnäs-Moberg, 1998). Whether non-peptide oxytocinergic drugs that cross the blood brain barrier, yet to be developed, can be harnessed to help re-establish affective homeostasis in an excessively aroused PANIC system in human beings (but psychological effects observed in intranasal studies are promising (e.g., Heinrichs & Domes, 2008; Insel, 2010; Nelson & Panksepp, 1998). In this context, we would note that one of the rarely considered effects of this neuropeptide is its capacity to sustain the activity of endogenous opioid processes, thereby sustaining positive social feelings, by inhibiting the development of tolerance to opioids (Kovacs, et al., 2007) which is a pathway for better social affect regulation as well as diminished drug addiction (Panksepp, 1981, 1998, 2005).

Separation Distress/PANIC is One Gateway to Depression.

The PANIC system probably evolved from general pain mechanisms (Panksepp 1981, 1998, 2003) presumably well over a hundred million years ago or more (birds possess a homologous system). This critical opioid modulated system promotes social connection, helps forge social attachments and dependencies between infants and mothers, probably fortifies sexual relationships, and may ultimately be the foundation of group solidarity among group living species. As a reasonable index of its role in attachment, we would argue that when one misses someone with whom one is bonded, this system is aroused to some extent, underscoring its centrality in human social affairs. If someone is never missed, this suggests that one does not have an attachment to that individual. Indeed, when socially separated, the affective consequences of severed attachment bonds make individuals suffer in a distinct and powerfully aversive fashion. This type of psychological pain, which most humans will generally avoid at almost all costs, is apparently a gateway to major forms of depression

The acute separation-distress response, although providing affective impact for depressive disorders, may not constitute a sustained depressive psychopathology on its own. For that, a set of neuroaffective changes are set in motion that promote feelings of lassitude and despair, and the neuroscience of these processes is not yet so complete. One line of research is suggesting that immune modulators—e.g., cytokines such as Interleukin 1, IL-6 and TNF-α—that can instigate sickness-type affective states that (Hennessy et al, 2001) that may simulate the sustained despair of depression. An equally promising possibility, which we will focus on here, is that sustained separation-distress, cascades into despair because of the ensuing diminution of SEEKING urges.

When protest fails to ensure social reunion, a gradual behavioral and psychological shutdown/depression emerges. At this critical transition--from the protest to the despair phase of depression--a new form of sustained negative affect emerges which is a fully developed depressive phenotype. The further elevation of negative affect contributed by 'giving up' may yield a mixture of the sustained psychic pain of separation intermingled with the inability to recruit mental energies such as SEEKING-euphoria that characterizes a positive attitude to life. This end state is characterized by diminished engagements with the world and reduced pursuit of rewards, real or imagined.

This giving-up 'despair' phase may need to be counteracted not only by brain chemistries that reduce the psychic pain of loss but also ways to elevate dopamine-driven SEEKING urges that characterize depressive despair. In a sense opioid drugs can do both, yielding a dopamine-independent pleasures as well as promoting dopamine-SEEKING urges, especially at low doses. Thus, in the emergence of depressive affect, it is as important to emphasize the lassitude of diminished SEEKING as the lingering psychic pain and emptiness of separation distress. Indeed, ever since Anisman and Matheson's (2006) discovery that stressors that promote depressive profiles in animal models are accompanied by elevated thresholds in 'brain reward' SEEKING arousal, there have been periodic reports of similar findings by others (Nestler & Carlezon, 2006; Pereira Do Carmo, et al., 2009). What causes this reduction in SEEKING urges is a central question for depression research. A key candidate is the gradually increasing influence of dynorphins—powerful and pervasive brain opioids that mediate a very distinct form of negative affect that is recruited by social loss, and demonstrably reduces the responsivity of the brain reward-SEEKING system (McLaughlin, et al., 2006) both at synaptic terminals (Mu, et

al., 2011), as well as closely related global neuropeptide modulators of positive arousal and affect such as orexin (Nocjar, et al., 2012).

In sum, although negative affective changes in the opioid- and oxytocin-driven attachment and affectional systems may be the pivotal precipitants of both addictive urges and depressive cascades, it is the affective dysphoria of diminished SEEKING urge that puts "the nail in the coffin" so to speak. This scenario remains consistent with biogenic amine theories of depression, because those general features of brain-mind organization participate in the overall arousal level of every emotion animals exhibit. Because of the multi-dimensionality of depression, there are bound to be many variants on these basic themes among the many subtypes of depression. For example, the sustained affective separation-induced psychic-pain response, may characterize some depressions more than others, while dynorphin-facilitated shutdown of dopamine-driven appetitive SEEKING (i.e., when some depressed persons 'give up' in an almost illness-type of amotivational lassitude) may constitute another major variant of depression (Nocjar, et al., 2012).

Beside the neurochemistries already highlighted, there will be many brain growth factors and other neurochemical cascades that are bound to promote or retard this downward spiral (e.g., Feder, et al., 2009). Just like psychotherapeutic disciplines , the goal of psychopharmacology is to counteract and reverse this downward cascade. In our estimation, new therapeutic approaches that take advantage of the positive hedonics of social CARE systems (the primal foundation of empathy) and PLAY systems (the primal source of social joy) may be especially important for better therapeutic outcomes. However, rather than develop psychotherapeutic concepts for treatment of acute depressive episodes by promoting social re-connection and re-attachment of depressed individuals, our remaining goal here will be to i)

introduce new emerging concepts in chemotherapeutics of depression, ii) a synopsis of how the neural trajectories of the above PANIC and SEEKING systems, of such great relevance for depression, are being analyzed in human beings, and iii) how modern brain stimulation approaches in humans are providing dramatic proof of concept support for the efficacy of direct manipulations of these systems as well as affirming the importance of basic affective systems in human mental health.

New Psycho-Chemotherapeutic approaches

In addition to the discovery of new uses for old chemistries such as D-cycloserine, an indirect glutamate facilitator, for the consolidation of psychotherapeutic outcomes in various disorders (e.g., Wilhelm, et al., 2008), we can now envision other beneficial mind-brain influences from our emerging understanding of the primary-process social affective systems of the brain (Panksepp, 2004, 2006, 2009). With respect to cardinal brain chemistries of social bonding and alleviation of separation distress, we can envision direct anti-depressant effects with existing positive affect facilitation neurochemistries. Here, because of limited space we will only discuss the anti-depressant effects of moderate doses of the safe opioid buprenorphine. We will also highlight how positive affect facilitating chemo-therapeutic agents may emerge from the genetic analysis of the affective understanding of SEEKING and PLAY systems.

With regard to buprenorphine, prior to the modern era of psychopharmacology, psychiatrists only had opioids for treating mental suffering (Tenore, 2008). Although very effective antidepressants in the short-term, their addictive potential discouraged long-term use, even though we suspect that a low prescription doses, one could also obtain potent sustained effects. Still, widespread addiction phobias have precluded full empirical evaluation of such ideas. The mixed mu-opioid receptor agonist/antagonist buprenorphine solves most of these

problems, and open-trials have highlighted the high and sustained efficacy of low doses in depressed clients who have had no relief from many accepted anti-depressants (Bodkin, et al., 1995). This "miracle drug" (long off patent) also has the uniquely desirable effect of blocking dynorphin receptors that are widespread in the brain, including suppressive effects on the euphoric potentials of the brain's reward SEEKING system. Since high doses of buprenophine actually block addictive mu-receptors, the drug has a fail-safe mechanism that limits addictive escalations and the ensuing abuse that characterizes pure opiate receptor stimulants, with their risk of respiratory arrest. One reason this medication has been badly neglected in research (no proper follow-up to Bodkin et al 1994 provocative study in refractory depression) is its seriously diminished profit margin (it is off-patent), as well as the resulting diminished financial investments available for conducting expensive clinical trials needed for medical approval.

However, in terms of new drug development, the analysis of the genetic changes in animals undergoing abundant social PLAY, which operates in part through the mesolimbic dopamine energized function of the medial forebrain bundle centered SEEKING system (Burgdorf, et al., 2007; Panksepp & Moskal, 2008), has yielded a variety of targets for new drug development (Moskal, et al., 2011; also see Krishnan & Nestler, 2008 for related work). The first to be evaluated was Insulin Like Growth Factor I, which proved to be an affectively positive molecule (Burgdorf, et al., 2010), but because of its capacity to promote tumor growth, further development of this medicinal concept was abandoned. The second top candidate was within glutamate receptor related family of regulatory systems, that were found to facilitate positive affect in our preclinical models, and a medicinal vector having xxx for proved to have and antidepressive, pro-hedonic profile; one agent, GLYX-13, was taken through both animal and

human toxicology (with no adverse effects observed), and is currently in Phase 2 clinical testing (Burgdorf, et al., 2011).

In this context, we would also note that the "power of PLAY" in psychotherapy remains largely completely untapped, at least in any systematic way. There are good reasons to believe that the long-term recruiting of such mental energies would be effective for the amelioration of various recalcitrant childhood problems, such as childhood impulsivity (Panksepp, 2007), through the capacity of such pro-social activities to promote both socialization and brain maturation. For instance, play can "fertilize" the brain by promoting growth factors such as Brain Derived Neurotrophic Factor (BDNF) gene-expression within the brain (Gordon, et al, 2003). BDNF is well known to promote anti-depressant effects in the brain through various genetic cascades, and thereby opposes the hippocampal dysgenesis that often accompanies depression (McEwen, 2007).

In this context, it is noteworthy that animal models of positive affect we developed (i.e., systematic tickling of rats, which can bring hedonic 50 kHz ultrasonic vocalizations under experimental control, which can be used as a positive affect "assay") have demonstrated anti-depressant type hippocampal neuronal proliferation to be promoted by systematic playfulness that elevates such happy-playful USVs in rats (Wöhr et al., 2009). Indeed, these 50 kHz USVs, most intensely exhibited during social play, have been mapped within the brain to activation of the mesolimbic dopamine system providing a direct readout of the responsivity of this positive affective response (e.g., euphoric eagerness) that can help counteract depressive affect (Burgdorf, et al., 2007). Those affectively positive vocalizations, along with the negative 22 kHz USVs, can be used to index specific affective shifts that can illuminate the underlying affective shifts that characterize depression (Kroes, et al., 2007)

Indeed, the robust effects of play on cortical gene-expression patterns (Burgdorf, et al., 2010; Krishnan & Nestler, 2008) has led to the identification of other growth factors that may prove to be affectively positive adjuncts to playful psychotherapy. One of the biggest gene-expression changes we have seen (Burgdorf, et al., 2010) in the neocortex is in the elevated expression of Insulin Like Growth Factor-1 (IGF-1). When this growth factor was tested for functional changes in relevant social behaviors, using direct intracerebral injections of an IGF-1 receptor antagonist, as well as siRNA inhibition of IGF-1 brain activity, yielded convergent evidence for the role of IGF-1 in promoting positive affect (Burgdorf, et al., 2010). There are reasons to suspect that further research on the positive social-affect systems of the mammalian brain will yield new ways to promote feeling of secure affective well-being that can help counteract depressive cascades.

The Anatomy of the Human Medial Forebrain Bundle and Related Systems: Implications for Depression.

If we propose the existance of the SEEKING system in the human then it should be possible to detect it as very robustly hard wired subcortical pathway with sophistiacted imaging techniques. Since a first report about the inadvertant activation of the human MFB during subthalamic nucleus deep brain stimulation (STN DBS) in a Parkinson‘s patient (Coenen et al. 2009) and its depiction with the diffusion tensor magnetic resonance (DTI) fiber tracking technique (FT) we have gained more insights into the detailed anatomy of the MFB (grossly representing the SEEKING system) and its counter player ATR (being the anatomical realization of the PANIC system) which we will not describe further. Both were recently indentified and exhaustively described (Coenen et al. 2012, in press). In detail, the MFB as depicted with DTI FT is a massive and truly bipartite structure. Individual mapping results show that the main trunk

splits into two main parts that then follow distinct directions. Caudal to the VTA the main trunk connects to the dentate nucleus of the cerebellum, including perhaps Arnold's bundle from where it follows the superior cerebellar peduncle and connects, possibly bidirectionally, to the upper pons, retrorubal area and the periaquaeductal grey (PAG). The location of the bifurcation of the two main truncks is the ventral tegmental area (VTA) in the midbrain. From here an infero-medial branch (imMFB) traces the wall of the third ventricle anteriorly until finally reaching the lateral hypothalamus (LH) lateral to the fornix. The imMFB represents the traditional description of the MFB in the rodent. A second, superolateral branch (slMFB), leaves the main trunk. This branch originates laterally, undercuts the thalamus and ascends into the inferior portion of the anterior limb of the internal capsule (ALIC).

Direct Stimulation of the MFB as a Therapeutic Modality for Treatment of Resistant Depression

Conceptually it was proposed above that a dysbalance between the two proposed dichotomic systems, the SEEKING system and the PANIC (or GRIEF) system, promote the feeling of separation distress that plays a major role in the clinical syndrom of depression (Coenen et al. 2010, Coenen et al. 2012). A dysbalance and uncoupling of the two systems implies a pathologically low activity of the SEEKING system. Since this system finds its quasi anatomical expression in the medial forebrain bunde (MFB) it appears reasonable to suggest, that stimulation of this system with the deep brain stimulation (MFB) technique would result in clinical alleviation of the depression syndrome. In a previous studiy we were able to show that distinct historical lesional operations had also implicitly utilized the MFB and ATR as remote target structures (Schoene-Bake et al. 2010) for the alleviation of depression syndromes.

Moreover, we were able to demonstrate in yet another study (Coene et al. 2010) that the MFB plays a key role for the effectiveness of two (if not all) of todays experimentally stimulated DBS targets for depression (Nucleus accumbens=Nacc and anterior limb of internal capsule= ALIC). The MFB was thus directly stimulated by our group in an experimental setting for the treatment of very treatment resistant depressive patients in a study under the prerequisits of local ethics committee permission in n=7 individuals. With help of the DTI-FT technique, the area of the most densely packed MFB fibers was aimed for, implanted stereotactically and effectively stimulated. The acute effects that were seen intra-operatively with unilateral high frequency stimulation are very reminiscent of what would be the human correlate to an accute activation of the SEEKING system: All 7 patients showed clear effects of increased appetitive motivation thus anticipation of reward but not reward itself. All patients showed explorative behaviour, turned their had to the interviewer, which they had not done in the previous unstimulated phase of the operation. They visually searched the room instantaneoulsy after initiation of test stimulation and reported motivational behaviour like an increased interest in travels or other activities they would not have performed for years. In our understanding, these are clear signs of what is best explained as "SEEKING behaviour". However, none of the patients reported any sign of or was observed with any form hypomania/mania or altered mood, other then had been reported in some individuals of the Parkinson's disease population (Coenen et al. 2009), indicating that in the depressed population acute stimulation induces anticipation of reward and not reward itself as has been described in Panksepp's description of the mode of action of the SEEKING system (euphoric drive, Panksepp 1998).

Conclusions

Our brain analysis has built upon the psychological insights of John Bowlby (1980), who originally conjectured that depression arises from sustained separation distress which is followed, if sustained for too long, by chronic depressive despair. Based on affective neuroscience strategies (Panksepp, 1998) we now have abundant data on the brain mechanisms of separation-distress, and hence the protest phase that leads to depression, and ever better neuroscience views of how diminished SEEKING urges tends to promote a depressive phenotype when this system fails to sustain protest (e.g., sustained separation calls), but with diminished activity, leads to despair. The separation-distress mediating PANIC system is regulated by various prosocial neuropeptides that also promote CARE and PLAY behaviors (e.g., endogenous opioids, oxytocin, and prolactin). The ability of these systems to consolidate social bonds (Panksepp, 1981, 1998) may also help explain why depression is almost twice as common in females than males--namely, female brains may be intrinsically more responsive to pro-social emotions than male brains (Swain, et al., 2007)

The pain of depression – arising commonly from social loss and social defeat--may be the price we mammals pay for the evolutionary advantages of social bonds that enormously enhance our survival and procreation, to say nothing of enriching our affective lives. Although animal research cannot inform us of the complex cognitive-affective amalgams (especially the ruminations and the "darkenings" of cognitions) that emerge in humans during depression, they can inform us of the evolutionarily conserved brain-mind affective mechanisms that lie at the very heart of depressive despair. From this point of view, the potential for depression is intimately linked to the pain of social loss and resulting diminution of engagement with the world that is an intrinsic vulnerability of highly pro-social brains.

The breadth and depth of our human cognitive consciousness has been widened enormously by the thought-filled intellectual potentials of our enlarged brains, and the resulting cultural supports that have been constructed historically. But we remain inheritors of ancient biological values that constitute the very ground of meaning and being within our minds. Although this affective ground of meaning is very hard to talk about clearly (which requires us to use a special functional-emotional nomenclature to discuss these systems clearly), it is from within our ancient animalian nature, full of primary-process affects that the subjectively experienced blessings and curses of our existence emerge. The primary-process emotion/affect generating systems are all situated in ancient medially situated subcortical brain regions that all mammals share because of their common ancestry, with large longitudinally coursing emotional systems, such as the MFB. These powers of the mind get connected to many life experiences through learning, but their affective intensity is an evolutionary birthright of all mammalian minds. This makes the study of comparative neurophenomenology critically important for unraveling the affective processes that make depression, and many other emotional problems of the mind, affectively horrible.

In sum, affective neuroscience strategies have allowed us to envision how John Bowlby's seminal conceptual work on the genesis of depression can now be linked to specific affective networks that can be studied, in causal detail, in preclinical animal models.

In conclusion, why does depression feel bad? It feels bad, from our view, for two reasons, both related to diminished feelings of internal security: First, because of its intrinsic relationship to separation distress, to encourage us to form *and maintain* addictive attachments, particularly to early care-giving figures, but also with our adult companions and children, as well as extended social groups. We should not forget that in primates social grooming releases brain opioids

(Keverne, et al., 1989, 1997) and human voices are, in part, a way for our species to groom each other. Secondly, depression persuades us to give up hope if our attempts to re-unite with such figures or groups do not succeed within a limited timeframe, and thereby we become psychologically detached from the world. This sustained loss of affective "energy" which depletes cognitive "meaning" may be intimately linked to diminished SEEKING urges, which has long been known to be the epi-center of all major forms of drug addiction. In short, at the neurochemical level, we are addicted to the ones we love.

In light of the existence of brain structures that generate such feelings, it seems reasonable to hypothesize that the linchpin of at least one major form of depression is none of the things that have preoccupied contemporary psychiatric researchers over the past three decades, but rather the evolutionarily-conserved brain state that mediates the transition from 'protest' to 'despair' in the wake of social loss. We see this to be intimately linked to reduced arousal of the dopamine energized SEEKING system. In other words, it seems reasonable to hypothesize that the core brain basis of depression revolves around the process by which separation distress is normally shut down (possibly by diminished dopamine arousal, declining mu and delta and increasing kappa-opioids- (dynorphin) activities--and various inflammatory cytokines, which prompt animals and humans to 'give up' when the affective mind, which supports our cognitive apparatus, is overfilled with distress. Affective neuroscience offers new strategies to counteract such degradations of mind, by analyzing the underlying details of the core affective processes that all mammals share.

Notes

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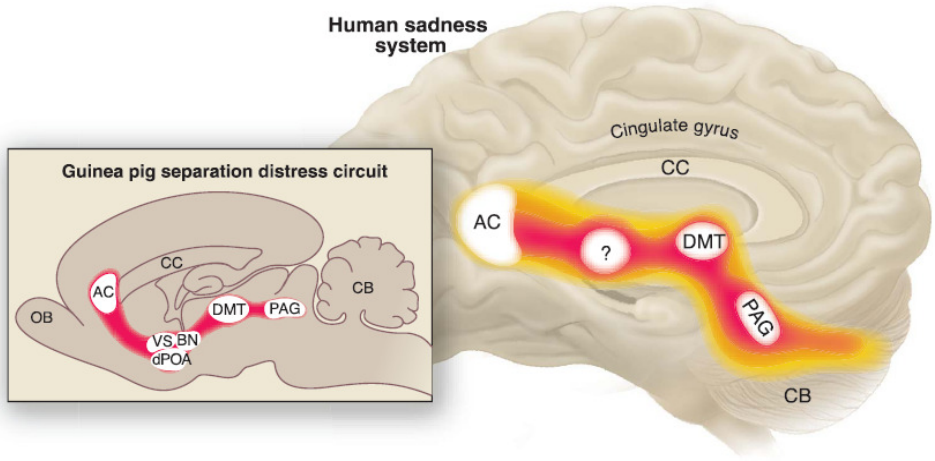

Figure. 1. Human and animal sadness of sadness and separation-distress systems. Animal data comes from localized brain stimulation mapping of separation distress circuits in guinea pigs (Herman & Panksepp, 1981) and human data from Damasio, et al., 2000.

Figure A: MFB sketch **Figure B:** Three dimensional propability maps of human MFB (green) and ATR (yellow) as visualized in an axial scan of the MNI 125 brain.

This latter part connects the ventral tegmental area (VTA) with the Nucleus accumbens, the anterior limb of the internal capsule, possibly cg25 and the prefrontal cortex. In a way, the MFB integrates some (if not all) reward centers of the human brain to an anatomical and functional unit.