Why Does Depression Hurt? Ancestral Primary-Process Separation-Distress (PANIC/GRIEF) and Diminished Brain Reward (SEEKING) Processes in the Genesis of Depressive Affect

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What can affective neuroscience add to the discussion of the genesis of depression? Among other contributions, it may begin to answer the question of why depression feels so bad. Since it is the only basic neuroscience approach that specifically aims to take the affective infrastructure of the evolved mind as its central focus, it offers testable hypotheses concerning the affective imbalances that contribute to clinical depression (Solms & Panksepp, 2011). A critical question about genesis of depression is: Which negative affect-generating networks of mammalian brains are most important for understanding depressive "pain" and what new therapeutics might such knowledge engender?

Affective neuroscience has outlined seven *primary process* (i.e., genetically provided) emotional systems. All are subcortically situated (Panksepp, 1998), where animal models allow causal (vs. correlational) analysis, not afforded by human research, including modern brain imaging. These primary functions consist of SEEKING, RAGE, FEAR, sexual LUST, maternal CARE, separation-distress PANIC/GRIEF (henceforth, simply PANIC) and joyful PLAY (neural systems are capitalized to highlight their primary-process nature). Although every aspect of the affective life can be influenced by depression, depression is intimately related to 1) sustained overactivity of the separation-distress PANIC system that can, if prolonged, lead to a downward cascade of psychological despair (a theoretical view originally formulated by John Bowlby); and 2) the despair phase that follows the acute PANIC response which is characterized by abnormally low activity of the SEEKING system. In terms of animal modeling, depression reflects the behavioral agitation of separation distress followed by emotional shutdown. The initial behaviorially agitated panic state may include SEEKING arousal, followed by dramatically diminished SEEKING during the depressive "despair phase." From this perspective, depression may have evolutionary advantages, such as conservation of resources following unalleviated separation distress. A more detailed exposition of this view, along with seven expert commentaries, is available in Watt and Panksepp (2009). Here, we briefly summarize the implications of this perspective for research and therapeutics.

Many stressors used to evoke depressive phenotypes—from physical to psycho-

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logical (e.g., social-defeat in adult aggressive encounters)—remain to be clearly linked to specific emotional network activities, although neuroanatomical correlates have been identified (e.g., Kanarik et al., 2011). Most animal models of depression not only employ very general stressors but also general behavioral outcome measures—various timid behaviors and diminished pleasure responses (e.g., hopeless swimming patterns and diminished sexual eagerness). Rarely are specific emotional circuits prescribed as targets of analysis. Because of general stressors and nonspecific outcome measures, such preclinical studies rarely provide insights into psychodynamic or interpersonal considerations of primary concern for clinical practitioners, especially the feelings of social loss and defeat that promote depressive affects. Modern neuroscience, especially as applied to animal models, has little room for discussions of mental phenomena—especially the affective experiences—that characterize psychopathologies.

In line with Watt & Panksepp (2009) and Solms & Panksepp (2011), we believe emotional-systems analyses will promote better interdisciplinary dialog, yielding better therapeutic interventions, where general biogenic amine and cognitive-behavioral regulatory strategies are commonly emphasized more than affect-oriented therapies (but see Fosha, Siegel, & Solomon, 2009, and Shedler, 2010, for counter-examples). On the psychopharmacological front, affective neuroscience views promote the development of new medicinals that target neuropeptide systems, such as endogenous opioids (both mu and kappa varieties) and corticotrophin releasing factor (CRF) dynamics, as well as amino acid transmitters, such as glutamate and glycine, that substantively control many affective states, including emotional learning. On the psychotherapeutic front, affective neuroscience approaches promote better and more specific utilization of positive emotions, such as facilitated SEEKING, CARE, and PLAY dynamics, which currently remain underdeveloped.

Depression research during the last four decades of the 20th century focused most heavily on the consequences of stress (DeKloet, Joels, & Holsboer, 2005; McEwen, 2007) and brain norepinephrine and serotonin dynamics (from Schildkraut, 1965, to Harro & Oreland, 2001, so to speak). This excellent work has largely neglected why depression feels so bad. It is becoming harder to believe that general brain serotonergic and/or noradrenergic changes, which globally regulate aspects of forebrain arousal and dynamics, will *specifically* explain the morbid moods of depression (Delgado et al., 1990). These amines regulate quite general brain arousal functions that influence all emotions. It is no surprise that SSRIs mildly ameliorate many psychiatric problems, while having modest overall efficacy, as highlighted by disappointing STAR*D findings (Rush, 2007; Rush, Trivedi, & Fava, 2003). Likewise, more recent work on various neurotrophic factor depletions (Koziek, Middlemas, & Bylund, 2008), stress-induced hippocampal shrinkage and CNS inflammation (Miller, Maletic, & Raison, 2009), and underlying genetics (Levinson, 2006), albeit of potential causal significance, provide little understanding of the affective feelings that characterize depression. Affective neuroscience approaches can illuminate the subjective manifestations of depressive affect (e.g., Kroes et al., 2007; Panksepp, 2006; Panksepp et al., 2002.).

AN AFFECTIVE NEUROSCIENTIFIC PERSPECTIVE ON WHY DEPRESSION FEELS SO BAD

In extending the original Bowlby account of depression to depression neurobiology (Watt & Panksepp, 2009), we here focus on how brain affective networks, altered by sustained distress, may explain the psychological pain and dysphoria of depression. Overactivity of brain separation-distress PANIC/GRIEF and underactivity of SEEKING networks may explain how the biggest

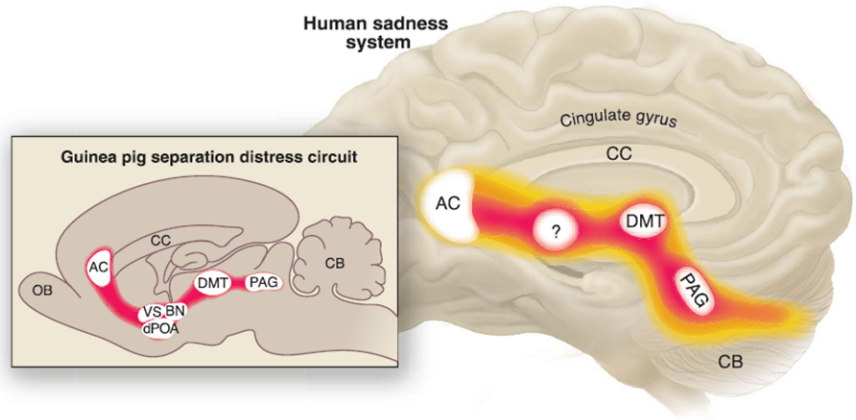

FIGURE 1. Human and animal schematics of sadness and separation-distress systems. Animal data comes from localized brain stimulation mapping of separation distress circuits in guinea pigs (Herman & Panksepp, 1981) and human data from Damasio, et al., 2000 (from Panksepp 2003).

epidemiological stressor, namely social loss, promotes depression (Bowlby, 1980; Heim & Nemeroff, 1999). Depression may feel bad because brain separation-distress systems create psychological pain. As Bowlby recognized, separation distress—the "protest" or "panic" responses that promptly follow social loss, especially in young animals—feels bad in a unique way. Affective understanding of such brain processes, garnered by mapping neuroanatomies and neurochemistries of separation distress, helps clarify the nature of social attachments and loss (Panksepp, 1998). These neuroanatomies are summarized in Figure 1.

The PANIC/GRIEF circuitry starts in midbrain central gray regions, commonly called the periaqueductal gray (PAG), and ascends through medial diencephalic structures, especially the dorsomedial thalamus, and terminates in various basal forebrain nuclei and subcallosal anterior cingulate forebrain regions, which have been targeted for deep brain stimulation (DBS) therapy for treatment-resistant depressions (Mayberg et al., 2005). Key neurochemistries that promote separation calls (protest) are declining opioid and oxytocin chemistries and elevated CRF, combined with increased glutamatergic drive in PANIC/GRIEF circuits of the brain. It is noteworthy that inhibitors of the last two PANIC facilitators have yielded promising antidepressant effects (Holsboer, 2000; Zarate et al., 2006). Likewise, it is to be anticipated that opioid and oxytocin facilitators may alleviate depression. Indeed, opioids were widely used as antidepressants before the modern era (Tenore, 2008), and ultra-lowdoses of buprenorphine are fine antidepressants for individuals not helped by traditional medications (Bodkin et al., 1995). Perhaps oxytocinergic and prolactinergic drugs can be harnessed for similar ends.

BUT SEPARATION DISTRESS IS ONLY THE GATEWAY TO DEPRESSION

The PANIC/GRIEF system probably evolved from general pain mechanisms (Panksepp, 1998, 2003) presumably millions of years ago (birds possess a homologous system). This psychic-pain system promotes social cohesion, forges bonds between infants and caretakers, and fortifies friendships and sexual relationships—in short, promotes social solidarity among group living species. Arousal of this system indexes social attachments, reflecting how much one misses someone else. If someone is never missed,

one does not have an attachment to that individual. The affective consequences of sustained arousal of this system are experienced as painful. This type of psychological suffering, which most humans will avoid at all costs, is a gateway to major forms of depression.

The transition from protest, sadness, grief, and the like to depression proper is still poorly understood. One line of research suggests that immune modulators (e.g., cytokines such as Interleukin 1, IL-6 and TNF-α) may stimulate the sustained despair of depression (Hennessy, Deak, & Schiml-Webb, 2001). Alternatively, perhaps sustained separation-distress cascades into despair because of the ensuing diminution of SEEKING urges. We pursue this line of thought here.

When protest fails to ensure reconnection, a behavioral shutdown (depression) comes into the picture to protect against the consequences of prolonged PANIC, leading to diminished indices of active separation-distress, but not fully diminished internal psychic pain. At this critical transition (from the protest to the despair phase of separation distress), a new form of sustained negative affect, characterized by both lassitude and despair, sets in. This fully developed depressive phenotype may arise when diminished SEEKING activity attenuates the behavioral manifestations of protest. The further elevation of negative affect, contributed to by "giving up" may yield a mixture of the sustained psychic pain of separation being intermingled with the inability to recruit mental energies such as SEEKING-euthymia that characterizes positive "can-do" engagements with the world and the 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 by ways to override the down regulation of dopamine-driven SEEKING urges that characterize depressive despair. Low doses of opioid drugs can do both, yielding dopamine-independent feelings of satisfaction, as well as promoting dopamine-SEEKING urges, through low-dose facilitation of mesolimbic DA arousal. Thus, in the emergence of depressive affect, it is as important to emphasize the lassitude of diminished SEEKING as the psychic pain of separation distress. Anisman and Matheson (2005) found that stressors that promote depressive profiles in animal models are accompanied by elevated thresholds in "brain reward-SEEKING" arousal, which has been replicated and extended by others (Nestler & Carlezon, 2006; Pereira Do Carmo et al., 2009). What causes this reduction in SEEKING urges is a key question for depression research. A primary 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). Additional effects may come from increasing pro-inflammatory cytokines (Miller et al., 2009).

In sum, although negative affective changes in the opioid- and oxytocin-driven attachment and affectional systems may initiate depressive cascades–diminished SEEKING may put "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 all emotions animals exhibit.

Because of the multidimensionality of depression, there are bound to be many variants on these basic themes among the many subtypes of depression, including those with more or less residual grief (PANIC) type process, and differential degrees of SEEKING system shutdown and apathy. In the most common variant of depression, if psychologically desirable outcomes from social protest do not materialize and the psychic pain of separation-distress is prolonged, then additional shut-downs of positive feelings promoted by diminished SEEKING urges change the acute negative affect into deeper and more prolonged phases of sustained

negative despair. Although animal research cannot illuminate the higher-order thought and rumination processes that characterize human depression, it can clarify the primal mechanisms of negative affect.

Beside the neurochemistry 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, Nestler, & Charney, 2009). It is not only the goal of psychopharmacology to counteract and reverse this downward cascade, but also of the psychotherapeutic disciplines. In our estimation, new therapeutic approaches that promote the positive hedonics of social CARE and PLAY systems may substantially improve therapeutic outcomes. Given how higher forms of human empathy may be cognitive enhancements of primary-process emotional systems for maternal CARE/NURTURANCE (Watt, 2007), promotion of these empathic systems in psychotherapy may offer long-term protection against depression and related conditions and may treat acute depression by promoting reconnection and reattachment of disconnected depressed individuals.

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, 2011). It is now clear that the brain changes and affective mental imbalances in psychiatric disorders are two-way neuropsychological streets. On the brain-chemistry-to-affective change side, we can envision direct antidepressant effects with new positive-affect-promoting chemistries. Because of limited space, we will only discuss the antidepressant effects of moderate doses of the relatively safe opioid, buprenorphine. With regard to positive affective psychological approaches, we will highlight the potential chemotherapeutic consequences of playful interactions.

Before the modern era of psychopharmacology, psychiatrists only had opioids for treating mental suffering (Tenore, 2008). Although very effective as antidepressants in the short-term, their addictive potential discouraged long-term use, even though with low prescription dosages of weak opioids, one could probably obtain sustained affective balance. Still, widespread addiction phobias have precluded full empirical evaluation of such ideas. The mixed mu-opioid receptor agonist/antagonist buprenorphine solves most (but probably not all) of these problems, and open-trials have highlighted the high and sustained efficacy of low doses in depressed clients who received no relief from many traditional antidepressants (Bodkin et al., 1995). This "miracle drug" (long off-patent) also has the uniquely desirable effect of blocking despair-promoting dynorphin receptors that are widespread in the brain and counteract the euphoric potentials of the general purpose reward-SEEKING system of the brain. Since high doses of buprenophine block addictive mu-receptors, the drug has a fail-safe mechanism that limits addictive escalations and the ensuing abuse and risk for respiratory depression/arrest of pure opiate receptor stimulants. One reason this medication has been badly neglected in research (e.g., there has been no proper follow-up of Bodkin and colleagues' provocative work on refractory depression) may be because of its seriously diminished profit margin (it is off-patent). Without profits, who will conduct expensive clinical trials needed for medical approval in our materialistic society?

Likewise, the "power of PLAY" in psychotherapy remains almost completely untapped, at least in any systematic way. There are good reasons to believe that recruiting such mental energies could effectively ameliorate various recalcitrant childhood

problems, such as childhood depression and impulsivity (Panksepp, 2007); such pro-social activities promote positive moods and brain maturation. Play promotes various growth factors such as BDNF in the brain (Gordon et al., 2003), which has antidepressant effects, partly by opposing hippocampal dysgenesis that often accompanies depression (McEwen, 2007). Remarkably, animal models have yielded antidepressant-type hippocampal neuronal proliferation as a result of joyful playfulness, as indexed by happy-playful "chirps" (Wöhr et al., 2009). Neural networks for these 50 kHz ultrasonic vocalizations (USVs), especially abundant during the social play of rats, have been mapped to arousal of mesolimbic dopamine-SEEKING networks; these chirpy USVs provide direct readout of positive affective responses (e.g., euphoric eagerness) that may directly counteract depressive affect (Burgdorf et al., 2007). Conversely, diminished chirping, along with elevated 22 kHz complaints, can index depressive affect (Kroes et al., 2007). These are the kinds of direct affective measures that need to be more widely implemented in preclinical work.

The robust effects of play on cortical gene-expression patterns (Burgdorf et al., 2010) have revealed other growth factors that may prove to be affectively positive adjuncts to playful psychotherapy. The largest gene-expression change we have seen is elevation of Insulin Like Growth Factor-1 (IGF-1) expression (Burgdorf et al., 2010). When IGF-1 was evaluated for functional effects on relevant social behaviors, using direct intracerebral injections of an IGF-1 receptor antagonist, as well as siRNA inhibition of IGF-1 brain activity, convergent evidence for elevated positive affect was obtained (Burgdorf et al., 2010). Further research on the positive social-affective chemistries of mammalian brains will surely yield new ways to promote feelings of secure well-being that can help counteract depressive cascades.

In sum, as Bowlby (1980) originally conjectured, depression arises from sustained separation-distress that is eventually followed by chronic depressive despair. Affective neuroscience research has provided abundant data on the brain mechanisms of separation-distress (Panksepp, 1998), and hence the protest mechanisms that promote depression, by gradually diminishing SEEKING that presages depressive despair. The separation-distress mediating PANIC/GRIEF 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) helps explain why depression is almost twice as common in females than males—namely, female brains, because of CARE urges, are intrinsically more responsive to prosocial emotions than male brains.

The pain of depression—arising mostly from social loss and social defeat—may be the price we mammals pay for the evolutionary advantages of social bonds that enrich our lives and promote procreation and survival. Although animal research cannot inform us of the complex cognitive-affective amalgams that emerge in humans during depression (especially depressive ruminations and the "darkening" of most cognitions), preclinical work can inform us of the evolutionarily conserved affective mechanisms that lie at the very heart of depressive despair.

The breadth and depth of our human cognitive consciousness has been widened enormously by the intellectual potentials of our enlarged brains and the resulting cultural supports. But we remain inheritors of ancient biological values that constitute the very ground of affective meaning within our minds. Although this affective groundwork for existence is hard to speak about 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 located subcortical brain regions that all mammals share from common ancestry. These primal powers of the mind get connected to many life

experiences through learning, but their affective intensity is our mammalian evolutionary birthright. A comparative neurophenomenology is critically important for unraveling the affective processes that make depression, and many other emotional problems of the mind, affectively intense. Affective neuroscience strategies have allowed us to envision how John Bowlby's seminal conceptual work on the genesis of depression can finally be linked to specific affective networks that can be studied, in causal detail, only in animal models (Krishanan & Nestler, 2008; Panksepp et al., 1991; Pryce et al., 2005).

DISCUSSION AND CONCLUSIONS

So 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, which encourages us to form *and maintain* attachments, particularly to early caregiving figures, but also with our sexual mates and offspring and supportive social groups; and second, because depression persuades us to give up hope if our attempts to reunite with such figures or groups do not succeed. Thereby, we become psychologically detached from the world. That sustained loss of psychological "energy" and meaning may be intimately linked to diminished SEEKING urges. The fact that such feelings can be easily provoked, and are difficult to erase, leading some individuals to heightened vulnerability to depression and highly maladaptive behaviors, does not contravene the biological forces that selected them into the mammalian genome in the first place. Those forces center around the adaptive nature of social connections (prerequisites for separation distress) and the competing and equally compelling adaptive need to terminate the futility of protracted separation distress, when it would either exhaust the protesting creature or serve as a beacon for predation. Agitated separation distress is normally shut down by a composite of changes, including diminished dopamine arousal, declining mu and delta and increasing kappa-opioids—dynorphins—and various inflammation-promoting cytokines. All these changes may prompt animals to "give up"—to succumb to depressive despair. An understanding of the affective brain may eventually yield emotional endophenotypes that underlie psychiatric disorders (Panksepp, 2005, 2006), knowledge that can be harnessed for therapeutic ends.

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