Panksepp's SEEKING System Concepts and Their Implications for the Treatment of Depression with Deep-Brain Stimulation

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Panksepp, as the true founder of the field of affective neuroscience, has predicted that the understanding of the emotional systems of animals will lead to understanding on the nature of human feelings. The Target Article that we comment on most convincingly shows a careful analysis of impaired SEEKING function for the clinical entity of major depression. It becomes increasingly clear that certain affective imbalances of this and other disorders (e.g., addiction) converge on a common subcortical emotional system, the very SEEKING system that Wright & Panksepp discuss. We conclude our comment with the first report of actual medial forebrain bundle (SEEKING system) stimulation results in humans, treated for therapy refractory depression and performed by our group.

Keywords: appetitive motivation; depression; deep-brain stimulation; diffusion tensor imaging; reward system

> There are now electrical appliances with the main unit so sealed in that it cannot be got at for repair. There have always been human beings like that.
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> Mignon McLaughlin, *The Neurotic's Notebook* (1960)

Sigmund Freud developed in the late nineteenth century a theory attempting to describe and explain what exactly drives human emotion, behavior, experience, and cognition. This theory of psychoanalysis—in its three applications: as a *science* of unconscious driving factors, as a *methodology* to assess human thinking and behavior, and as a *treatment* method for disordered behavior—quickly developed into the leading paradigm guiding psychiatry. A criticism of psychoanalysis has always been that it had not been developed by careful and deliberate study following the classic principles of scientific observation, hypothesis, and experimentation in animals and man but, rather, by interpretative phenomenology (Webster, 1996). Freud started his career as a neuroscientist but probably quickly realized that convincing scientific explanations for complex human behavior could not be found with the methods available to neuroscience in the nineteenth century (Freud,1940). Already in 1998, Panksepp asserted that "the failure of psychology to deal effectively with the nature of the many instinctual systems of human and animal brains remains one of the great failings of the discipline. The converse could be said for neuroscience." This statement can be seen as a formulation of a goal that is addressed in Jason Wright and Jaak Panksepp's Target Article.

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In their *tour de force,* Wright & Panksepp indeed develop a *neuroevolutionary framework* and a truly neurobiological framework for some key aspects of human behavior by broadly discussing the germane importance of the SEEKING system for understanding normal and disordered affective functions in humans. Their article integrates, in a bold conceptual framework, findings from neurobiology, neurophysiology, neuroanatomy, and ethology on a system in the mammal brain that might be responsible for the psychoanalytic concept of motivational "drives." They thereby take advantage of the wealth of data on substrates of appetitive motivation that has been accumulated since the beginning of the twentieth century and, more originally and perhaps somewhat controversially, integrating wrongly ignored results from animal research.

Panksepp, the founder of the field of affective neuroscience, has for a long time made the point that studies of emotional and other affective systems of animals will shed a profound light on the nature of our own feelings (Panksepp, 2005). It is assumed that so-called primal emotions, such as fear, are associated with ancient parts of the brain and evolved among our premammal ancestors and that social emotions evolved among social primates. However, this is an assumption and "As long as psychology and neuroscience remain more preoccupied with the human brain's impressive cortico-cognitive systems than subcortical affective ones, our understanding of the sources of human consciousness will remain woefully incomplete" (Panksepp, 2004). The authors are to be commended for the masterful integration of their research on affective consciousness in animals with human drives as posited but not biologically explained by the psychoanalytic method. From a conceptual standpoint, probably most convincing is their careful analysis of impaired SEEKING function for the clinical entities of depression and addiction, as it becomes increasingly clear that certain affective imbalances of both disorders converge on a common subcortical emotional system, the very SEEKING system they discuss (Coenen, Schlaepfer, Maedler, & Panksepp, 2011).

The concept of the hedonic principle says that we are motivated to approach pleasure and to avoid pain; prototype disorders associated with dysfunction of the reward system—or, more correctly, the SEEKING system—are substance abuse and depression. Indeed, the opioid-withdrawal syndrome is an integral diagnostic part of opioid dependence and is characterized by both behavioral and physiological responses that reflect actions opposite to those of the acute effects of opioids. Withdrawal from a drug of abuse induces symptoms of negative affect such as dysphoria, depression, irritability, and anxiety; dysregulation of the SEEKING systems involves some of the very same neurochemical pathways implicated in the drug's acute reinforcing effects, but in this case they represent an opponent process (Koob & Le Moal, 2001, 2008). For depression, it has been demonstrated, that modulation of activity of a substructure of the SEEKING system (the nucleus accumbens) may modulate neural activity in other emotion and motivation centers of the brain. Indeed, bilateral stimulation of the nucleus accumbens results in acute anti-anhedonic and antidysphoric effects (Schlaepfer et al., 2008) and longer-term antidepressant effects in extremely treatment-resistant patients suffering from major depression (Bewernick et al., 2010).

In their article, Wright and Panksepp posit several hypotheses that, given today's level of methodological refinement, are testable. Indeed, during the development of hypotheses for a new understanding of depression and its therapy with deep-brain stimulation (DBS) in very treatment-resistant patients, the analysis of experimental DBS targets that have been used to date (nucleus accumbens septi, subgenual cingulate gyrus) with modern sophisticated imaging and electric-field modeling techniques (among others, diffusion tensor-imaging-based tractography) led to the discovery by our group (Coenen, Panksepp, Hurwitz, Urbach, & Mädler, in press) that a structure that has long been associated with euphoric drive and anticipation of reward (appetitive motivation), and not so much reward itself, might be an important protagonist that probably can play a key role in the treatment of major depression. This structure—the medial forebrain bundle (MFB)—was stimulated by our group in an experimental setting for the treatment of very treatment-resistant depressive patients in a study under the prerequisites of a local ethics committee permission in $n = 7$ patients.

As a concept it was proposed that a dysbalance between two dichotomic systems—the SEEKING system, promoting positive euphoric drive and anticipation of reward, and the PANIC system, promoting the feeling of separation distress—plays a major role in the clinical syndrome of depression (Coenen et al., 2011). Very likely, the two systems that promote these opposite affects can be described, using the diffusion tensor imaging–FT (magnetic resonance fiber tracking) technique (Coenen, Panksepp, Hurwitz, Urbach, & Mädler, in press). With the help of the same technique, the area of the most densely packed MFB fibers was aimed for, implanted stereotactically and effectively stimulated. The acute effects that were seen intraoperatively with

unilateral high-frequency stimulation are very reminiscent of acute activation of the SEEKING system: All 7 patients showed clear effects of increased appetitive motivation. All patients showed explorative behavior. They visually searched the room instantaneously after initiation of test stimulation. They reported motivational behavior such as an increased interest in travel or other activities they would not have performed for years. In our understanding, these are clear signs of what is best explained as "SEEKING behavior." However, none of the patients reported any sign of hypomania/mania or altered mood, indicating that acute stimulation induces anticipation of reward and not reward itself, as has been defined in Panksepp's description of the action of the SEEKING system (euphoric drive—Panksepp, 1998).

In summary, we believe that the article by Wright & Panksepp has the potential to be viewed as one of the most important contributions to thoughts on psychiatry for some time to come, provided that some of its basic tenets are substantiated by future research. At the very least, it provides a convincing logical and in many points testable framework elucidating the inner workings of the "electrical appliances with the main unit so sealed in that it cannot be got at . . .," insights that will potentially lead to therapeutic approaches for humans suffering from the most horrible disorders there are.

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