IN PRESS: CH Ashton and EK Perry (eds) *The Neuroscience of Conscious/Nonconscious Interactions* [working title]

WHY DEPRESSION FEELS BAD.

Mark Solms[1] & Jaak Panksepp[2]

ABSTRACT

We believe that conscious mental phenomena (such as feelings) are not epiphenomenal to the workings of the brain. Feelings evolved for good biological reasons; they make specific, concrete contributions to brain functioning. Notwithstanding all the philosophical complexities, therefore, the non-conscious/conscious interactions that are the focus of this book are, in our view, *causal* interactions. To marginalize consciousness in relation to what is ultimately a dualistic scientific understanding of how the brain works is likely to lead us badly astray. We illustrate this view by trying to address the question: why does depression feel bad?

INTRODUCTION

When Sigmund Freud first argued that the mind is not synonymous with consciousness, he was roundly criticised, mainly on philosophical grounds. Subsequent empirical findings have, however, strongly supported his view that many if not most mental functions do not require consciousness to operate efficiently and effectively. In fact, the evidence for this view is now so overwhelming that the converse question is frequently asked: why do we need consciousness at all? This question deeply haunts contemporary efforts (like this timely book) to explore and explain the many complexities that surround non-conscious/conscious interactions in the brain.

It is therefore interesting to note that in a posthumously-published outline of his life's work Freud (1940, p. 157) acknowledged that consciousness was *the most unique characteristic* of the part of nature that we call the mind -- 'a fact without parallel'. The fact of consciousness, Freud wrote, 'defies all explanation and description'. He continued: 'Nevertheless, if anyone speaks of consciousness we know immediately and from our most personal experience what is meant by it'. He then added a disparaging remark to the effect that 'one extreme line of thought, exemplified in the American doctrine of behaviourism [which was just then coming to prominence], thinks it possible to construct a psychology which disregards this fundamental fact!'.

BEHAVIOURISM

[1] Departments of Neurology & Psychology, University of Cape Town.
[22] College of Veterinary Medicine,Department of Comparative Anatomy, Physiology and Pharmcology, Washington State University

It is well known why behaviourists wanted to construct a science of the mind that disregarded its most unique characteristic. Consciousness cannot be observed externally; it is not amenable to direct objective scrutiny. Consciousness is for that reason an embarrassment to science, the ideal of which is objective fact over subjective experience. The behaviourists, who wanted to treat the mind as if it were no different from any other part of nature, therefore ruled consciousness out of court, and limited scientific psychology to the study of the objectively observable *outputs* of the mind -- to the study of behaviour. Observable experimental manipulations ('stimuli') could then be used to discover the causal mechanisms of behavioural 'responses'. In this way, the intervening variables (conceptualised as the laws of *learning*) became the only valid objects of psychological science.

Not surprisingly, a school of thought predicated on the assumption that the mind consists in nothing but learning, and disregards all the other mental phenomena that we 'know immediately and from our most personal experience', was doomed to failure. To deny the causal influence on behaviour of conscious states (like feelings) is to deny the obvious. If one says: that person committed suicide because he could not stand the pain any longer; one is describing the simple causal power of that person's feelings. If one were to try to re-phrase such causal statements so as to exclude the feelings, one would be doing violence to the obvious facts.

Thankfully, therefore, in the psychology of the last quarter of the twentieth century, realism triumphed over fundamentalism, and consciousness found its way back into science. Even though consciousness still cannot be observed directly, or objectively, today we are nevertheless willing to acknowledge its existence in our experimental subjects, and on this basis to infer the causal mechanisms by which conscious states influence behaviours -- in much the same way as the behaviourists were willing to infer the causal mechanisms of learning.

Or are we?

The mechanisms of consciousness may be ontologically equivalent to those of learning (or anything else) but the *mechanisms* of consciousness differ in fundamental respects from consciousness *itself.* Mechanisms of all kinds are abstractions, derived from experience; they are not experiences themselves. The mechanisms of consciousness, like all other mechanisms, therefore present no special problems for science; they, too, can be described from an objective standpoint, from the third-person point of view. But this excludes the 'fundamental fact' of consciousness, namely that we *experience* it directly. Is consciousness not perhaps still an embarrassment to science; do we not perhaps still think it possible to construct a psychology which disregards the causal role of this uniquely subjective characteristic of the mind – the fundamental aspect of this part of nature?

COGNITIVE NEUROSCIENCE

It is, in our view, no accident that the apparent re-admittance of consciousness to psychology coincided with advances in the neurosciences which made it possible to study the *physiological correlates* of almost any mental state. By shifting the focus of our research efforts to the physical *correlates* of consciousness, we were able to pay

lip service to its existence without having to trouble ourselves too much with its intrinsically subjective nature – with the original source of the embarrassment. Small wonder, then, that so many behaviourists made such a seamless transition to the new paradigm.

As Freud (ibid.) put it:

> 'there would thus be no alternative left to assuming that there are physical or somatic processes which are concomitant with the psychical ones and which we should necessarily have to recognize as more complete than the psychical sequences [… Then] it of course becomes plausible to lay the stress in psychology on those somatic processes, to see in *them* the true essence of what is psychical'.

To seek the essence of what is mental in something which lacks its most unique psychic property is surely to look in the wrong place. But this does not mean that we must abandon reality. Nor does it mean that the brain is the wrong place to seek an understanding of consciousness. It means only that we must admit that consciousness actually exists, that it is a property of nature, that it is a property of the part of nature called the brain, and that this property is no less real and no less causally efficacious than any other natural properties. This in turn means that we must recognise that the brain is not *quite* the same as every other part of nature. The brain has some special properties, and central among these is consciousness. As a consequence of it being conscious, the brain behaves differently from most other things, even from other bodily organs.

As far as we can tell, despite appearances, these views are still not generally accepted, or at least they are not generally incorporated into the current theoretical paradigms of cognitive neuroscience. In fact the very power of cognitive neuroscience seems to be that it treats the organ of the mind as if it were no different from any other bodily organ or piece of matter, indeed from any other complex mechanism – living or dead.

BIOLOGICAL PSYCHIATRY

The baneful consequences of this continued neglect of the 'fundamental fact' of consciousness have been more evident in the field of biological psychiatry than in cognitive neuroscience in general. This is perhaps not surprising, because psychiatry is all about feelings.

In psychiatry today, if one says: the patient committed suicide because he could not stand the pain any longer, one seems to mean: the patient *thought* he was committing suicide because he could not stand the pain any longer, but *really* he was committing suicide because his serotonin levels were depleted (or something like that). The point is: what the patient says, thinks or feels may be left out of our scientific account; the feelings evidently are not really part of the causal chain of events. They are just a layperson's translation of the actual state of affairs in the brain. This, in our view, is doing violence to the facts. In our view, the feelings are a fundamental part of the actual state of affairs in the brain.

We shall now illustrate these principles with reference to a particular problem in modern psychiatry, namely: *why depression feels bad*.

In fact, this problem is not even posed in psychiatry. It is not posed because what depression feels like does not seem to matter in contemporary psychiatric science. This is evidently because feelings in general do not matter. What matters is the physical *correlates* of the feelings. This approach, in our view, is based on a serious misconception of how the brain works, which will almost inevitably lead to equally serious mistakes.

In their haste to avoid the embarrassingly subjective phenomena of depression, psychiatric researchers have in recent decades focused on all sorts of things that correlate with depression, or facilitate it, or contextualise it -- and the neural mechanisms of those things -- rather than the feelings of depression itself.

The main focus of depression research for the past three decades has been the neurophysiological mechanisms of norepinephrine and serotonin depletion (Schildkraut, 1965; Harro & Oreland, 2001), including the neurotrophic effects of this depletion (Koziek et al., 2008), the neuroendocrinological mechanisms of stress (which has similar neurotrophic consequences (De Kloet et al 2005), the neuroimmunological equivalents of these mechanisms (McEwen 2007), their interactions with sleep mechanisms (Zupancic & Guilleminault, 2006), their genetic underpinnings (Levinson 2006), and so on.

These research programmes have evidently been followed because the mechanisms of serotonin depletion (and its cognates) are eminently tractable scientific problems – notwithstanding the fact that they have little to do with actually researching depressive feelings. The reason these programmes have been followed cannot possibly be because anyone seriously thinks that depressive feelings (let alone major depression) are actually *caused* by low levels of serotonin. There is no direct evidence for that notion. In fact, it is well established that experimental depletion of brain serotonin does not cause depression in normal people (Delgado et al, 1990). Nor was there ever any sustained line of research to believe that serotonin *would* play any such specific causal role in depressive mood. Serotonin is an all-purpose modulator of moods and emotions, not only of depressive ones (Berger, Gray & Roth 2009). It is probably for this reason that SSRIs are used to treat not only depression but also a host of other emotional troubles, such as panic attacks and obsessive compulsive disorder. This is also probably the reason why SSRIs do *not* work in so many cases of depression, and why they work only partially or temporarily in the vast majority of cases (cf. STAR*D findings). The same applies to the various cascades associated with serotonin depletion: stress or inflammation or hippocampal shrinkage (Miller, et al., 2009). None of these things has a unique and specific causal relationship to depression. They are too general; 'too much' of an explanation. Their main attraction is only that they are scientifically tractable and therefore scientifically respectable mechanisms.

In summary, it is clear that although the mechanisms of serotonin depletion and its cognates correlate with or facilitate or contextualise depression, something else – something far more specific – must be the actual causal mechanism of depression. We

suggest that this 'something else' most likely has something to do with the brain mechanisms that actually generate depressive *feelings*.

DEPRESSION ITSELF

Our reason for suggesting this is the fact that the clinical phenomenology of depression is characterized above all else by a complex of feelings: low mood, low self-esteem, loss of motivation and energy, loss of pleasure in the world, and so on. Is this feeling complex not the most obvious place to seek the essential nature of depression? And dare we ask whether this constellation of feelings *means* anything? It is after all in the essential nature of feelings that they mean something. It would be entirely normal and reasonable for all of us (even us scientists) to ask -- outside of our scientific work – what it might mean when somebody says that they feel down, bad, defeated, useless; that they have lost all hope for themselves, lost all interest in other people, and so on. *Why* do they feel this?, we should ask. Certainly it is *possible* that the feelings are meaningless epiphenomena of depression -- even though feelings are not normally meaningless -- but it is at least equally possible (and in our view more so) that they are *not* meaningless.

We think the most obvious way of making sense of this complex of feelings is suggested by what the DSM IV definition of major depression describes as diagnostic criterion E:

'*The symptoms are not better accounted for by bereavement'* (emphasis added).

This differential diagnostic criterion suggests that depression may be easily mistaken for bereavement, which in turn suggests that depression is characterized by a complex of feelings that closely resembles those associated with grief. It therefore seems reasonable to infer that depression might have something to do with social *loss*. This reminds us of what the early psychological investigators of depression (who were not embarrassed by feelings and their meanings) concluded on the basis of *talking* to patients about what their feelings might mean to them personally: they concluded that depression was akin to grief, that it seemed in fact to be a pathological form of mourning (Freud 1917).

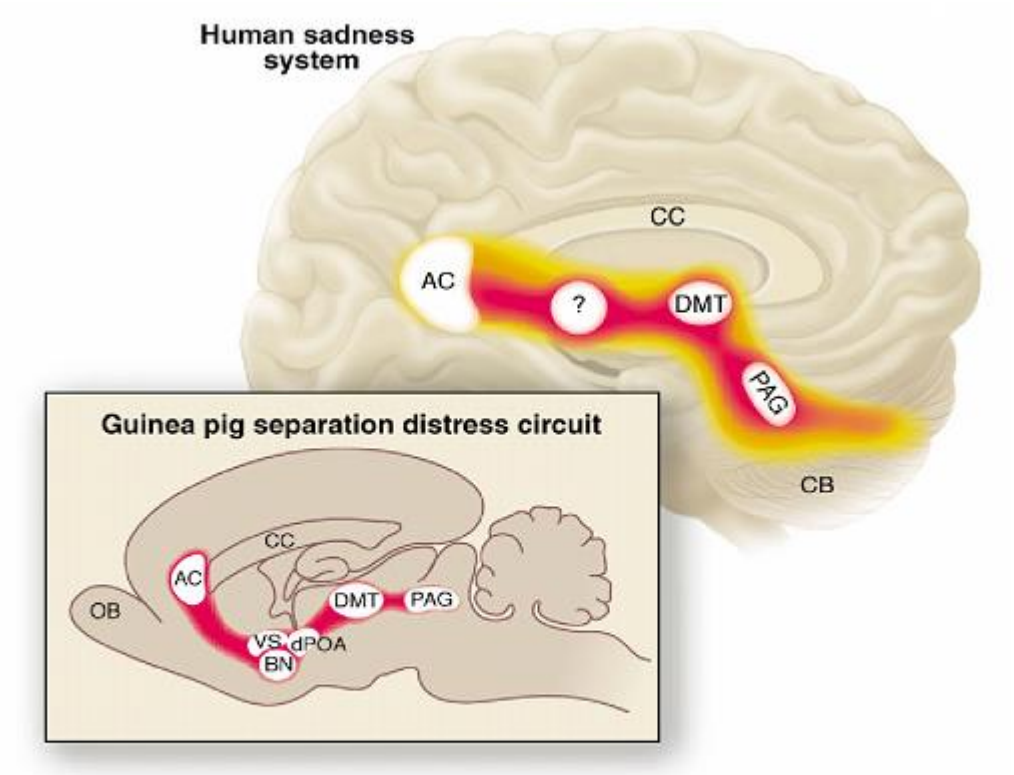
It is in fact well established today that early separation experiences do indeed predispose to depression (Heim & Nemeroff, 1999; Pryce et al., 2005), possibly through mediation of the stress cascades that McEwan (2000) has identified, and possibly also via other 'general sickness' mechanisms (McEwen 2007). We also know that a first depressive episode is most likely to be triggered by social loss (see from Bowlby 1980 to Watt & Panksepp, 2009), and so on.

AFFECTIVE NEUROSCIENCE

In light of such commonplace observations to the effect that depressive feelings are connected with the psychology of attachment and loss, why are we *not* focusing our attention on the mammalian brain systems that evolved specifically for the purpose of mediating attachment and loss, and which produce the particular type of pain associated with these biological phenomena of universal significance, namely

separation distress (also known as 'protest' or 'panic') which, if it does not result in reunion, is typically followed by hopeless 'despair'.

It is likely that a specific mammalian brain system evolved specifically to generate these depression-like feelings (Panksepp, 1998, 2003, 2005). This brain system evolved from general pain mechanisms, millions of years ago, apparently for the purpose of forging long-term *attachments* between mothers and their offspring, between sexual mates, and ultimately between social groups in general. When such social bonds are broken through separation or loss of a loved one, or the like, then these brain mechanisms make the sufferer feel bad in a particular way. This special type of pain is called separation distress or panic. The biological value of this type of pain is that it motivates the sufferer to avoid separation, and to seek reunion with the lost object. However, if this psychobiologically desirable outcome fails to materialize, then a second mechanism kicks in, which shuts down the distress and causes the lost individual to *give up*. This giving up is the 'despair' phase of social loss (Panksepp et al 1989, 1991; Watt & Panksepp, 2009).



[Fig. 1]
(from Panksepp 2003)

This system is embodied in a well-defined network of brain structures [Fig. 1], starting in the anterior cingulate gyrus (about which so much has been said in recent

neuro-imaging studies and DBS treatments of depression; Mayberg et al., 2005), coursing downwards through various medial thalamic, and various basal forebrain nuclei, terminating in the ancient midbrain (pain generating) neurons of the periaquaductal grey. Regulation of this system is fundamentally mediated by opioid receptors. Mu-opioid agonists in particular activate it in such a way as to generate feelings of secure well-being that are the very opposite of depression, whereas mu opioid blockade or withdrawal promotes separation distress. This state is most readily identified in animal models by distress vocalizations (Panksepp 1998). Bowlby (1980) classically described this phenotype as 'protest' behavior, which he contrasted with the more chronic 'despair' behaviours that immediately follow on from it. The transition from acute 'protest' to chronic 'despair' presumably evolved to protect the separated animal from metabolic exhaustion, or alternatively to deflect the attention of predators, or both.

It is the 'despair' phenotype that seems most closely to resemble clinical depression (Harris, 1989).

The separation distress system, which is regulated by the hormonal and peptide releases that precede childbirth and facilitate maternal care (e.g., oxytocin, prolactin), developed early in mammalian evolution. This is why the mechanisms which mediate attachment and separation are much more sensitive in females – who are twice as likely as males to suffer from depression. We have also known for a long time that the chemicals that mediate the brain's separation/attachment mechanism (opioids) have powerful anti-depressant properties (Bodkin et al 1996). If it were not for the addictive risks of opiates, they would almost certainly have formed the front line of anti-depression medications. In fact, there is good reason to believe that the natural brain chemicals – endorphins -- that make us feel good when we are safely and securely attached are themselves addictive; in short, that affectionate bonds are a primal form of addiction. This system apparently provides the elemental means by which mother and infant attach to each other -- the means by which they become addicted to one another.

Although these opioid-driven attachment systems may be the pivotal mechanism in depression, there may of course be many associated mechanisms that mediate the various depressive subtypes. For example, dynorphin-facilitated shutdown of dopamine-driven appetitive systems (when an individual 'gives up' in despair) may form an independent aetiological mechanism in a subset of cases (McLaughlin, et al., 2006; Nestler & Carlezon, 2006).

It seems that the pain of social loss and defeat are the price that we mammals had to pay for the evolutionary advantages bestowed by this system, that is, by mammalian social attachment, the prototype of which is the mother-infant bond. This is an instance of a more general principle: conscious feelings, both positive and negative, evolved because *they enhance survival and reproductive success*. This is their causal role.

CONCLUSION

So why does depression feel bad? It feels bad, on our hypothesis (initially advanced by Watts & Panksepp 2009), for two reasons: firstly, to encourage us to form

attachments, particularly to early care-giving figures, but also with our sexual mates and offspring and social groups and the like; and secondly, to persuade us to give up hope if our attempts to re-unite with such figures or groups do not succeed within a limited time-frame, when we have become detached (or lost). The fact that such feelings can be too easily provoked, or too difficult to erase, etc., in some individuals, is immaterial to the biological forces that selected them into the mammalian genome in the first place.

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 so 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. 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 kappa-opioids), prompting the animal to 'give up'.

Why aren't psychiatric researchers investigating the role of these candidate brain processes in depression? They seem to be the obvious place to start, if we are going to take the phenomenology of depression itself (as opposed to things that correlate with it) as our starting point.

We believe that such obvious starting points are neglected due to an ongoing, deep prejudice against acknowledging the implications for science of the subjective nature of consciousness, and its causal efficacy in the brain. This prejudice is most unfortunate, because subjective consciousness certainly exists, and it almost certainly evolved for a reason (it almost certainly enhanced reproductive fitness). It is accordingly almost certainly a central feature of how the brain works. We therefore ignore it at our peril.

REFERENCES

Berger M, Gray JA, Roth BL (2009). The expanded biology of serotonin. *Annu. Rev. Med.* **60**: 355–66.

Bodkin, J.A., Zornberg, G.L., Lukas, S.E., & Cole, J.O. (1995) Buprenorphine treatment of refractory depression. *J Clin Psychopharmacol*. 15, 49-57.

Bowlby, J. (1980). *Loss: Sadness and depression*. New York: Basic Books.

De Kloet, E., Joels, M. & Holsboer, F. (2005) Stress and the brain: from adaptation to disease. *Nature Rev. Neurosci*. 6, 463–475.

Delgado, P.L., Charney, D.S., Price, L.H., Aghajanian, G.K., Landis, H., & Heninger. G.R. (1990).Serotonin function and the mechanism of antidepressant action: Reversal of antidepressant-induced remission by rapid depletion of plasma tryptophan. *Arch Gen Psychiatry* 47, 411–418

Freud, S. (1917) Mourning and melancholia. *Standard Edition*, 14: 239-258. London: Hogarth Press.

Freud, S. (1940) An outline of psychoanalysis. *Standard Edition*, 23: 144-207. London: Hogarth Press.

Harris, J.C. (1989). Experimental animal modeling of depression and anxiety. *Psychiatric Clinics of North America*, 18, 815-36.

Harro, J. & Oreland, L. (2001). Depression as a spreading adjustment disorder of monoaminergic neurons: A case for primary implications of the locus coeruleus, *Brain Research Reviews*, 38, 79-128.

Heim, C. & Nemeroff, C. (1999). The impact of early adverse experiences on brain systems involved in the pathophysiology of anxiety and affective disorders. *Biological Psychiatry*, 46, 1509-1522.

Koziek, M., Middlemas, D., & Bylund, D. (2008). Brain-derived neurotrophic factor and its receptor tropomyosin-related kinase B in the mechnism of action of antidepressant therapies, *Phamacol Ther.*, 117, 30-51.

Levinson, D.F. (2006). The genetics of depression: A review. *Biological Psychiatry* 60, 84-92.

Mayberg, H., Lozano, A., Voon, V., McNeely, H., Seminowicz, D., Hamani, C., Schwalb, J. & Kennedy, S. (2005) Deep brain stimulation for treatment-resistant depression *Neuron*, 45: 651-660.

McEwen, B.S. (2000). The neurobiology of stress: from serendipity to clinical relevance. *Brain Research*, 172-189.

McEwen, B.S. (2007). Physiology and neurobiology of stress and adaptation: central role of the brain *Physiol Rev* 87, 873-904.

McLaughlin, J.P., Li, S., Valdez, J., Chavkin, T.A, & Chavkin, C. (2006). Social defeat stress-induced behavioral responses are mediated by the endogenous kappa opioid system. *Neuropsychopharmacology* 31:1241–1248.

Miller, A.H., Maletic, V. & Raison, C.L. (2009). Inflammation and its discontents: The role of cytokines in the pathophysiology of major depression. *Biological Psychiatry*, 65: 732-741.

Nestler, E.J. & Carlezon, W.A. Jr. (2006). The mesolimbic dopamine reward circuit in depression. *Biological Psychiatry*, 59, 1151-1159.

Panksepp, J. (1998) *Affective Neuroscience:, The Foundations of Human and Animal Emotion*. New York: Oxford University Press.

Panksepp, J. (2003) Can anthropomorphic analyses of "separation cries" in other animals inform us about the emotional nature of social loss in humans? *Psychological Reviews*, 110: 376-388.

Panksepp, J. (2003) Feeling the pain of social loss. *Science*, 302: 237-239.

Panksepp, J. (2005). Feelings of social loss: The evolution of pain and the ache of a broken heart. In R. Ellis & N. Newton (eds). *Consciousness & Emotions, Vol. 1*. pp. 23-55, John Benjamins, Amsterdam.

Panksepp, J., Lensing, P. and Bernatzky, G. (1989). Delta and kappa opiate receptor control of separation distress. *Neuroscience Abstracts*, 15, 845.

Panksepp, J., Yates, G., Ikemoto, & Nelson, E. (1991) Simple ethological models of depression: social-isolation induced "despair" in chicks and mice. In B. Olivier and J. Moss (Eds), *Animal Models in Psychopharmacology*, (pp. 161-181) Holland: Duphar.

Pryce, C.R., Ruedi-Bettschen, D., Dettling, A.C., Weston, A., Russig, H. Ferger, B., & Feldon, J. (2005). Long-term effects of early-life environmental manipulations in rodents and primates: Potential animal models in depression research *Neuroscience and Biobehavioral Reviews* 29: 649–674

Schildkraut, J. (1965) The catecholamine hypothesis of affective disorders: a review of supportive evidence. *Am. J. Psychiatr.*, 122: 509-522.

Watts, D. & Panksepp, J. (2009) Depression: An evolutionarily conserved mechanism to terminate separation distress? A review of aminergic, peptidergic, and neural network perspectives. (with commentaries) *Neuropsychoanalysis*, 11: 11, 5-104..

Zupancic, M. & Guilleminault C. (2006). Agomelatine: a preliminary review of a new antidepressant. *CNS Drugs.* 20: 981-992.