

DEPRESSION AND SEPARATION DISTRESS

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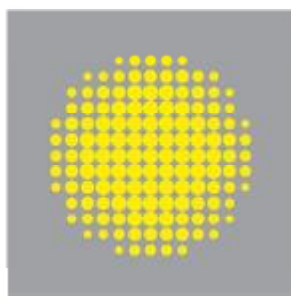
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I would like to thank the organizers, not only for inviting me to speak at this important meeting, but also to venture 'out of the box' - to present novel and challenging ideas. By responding in this spirit to your invitation, I am well aware that I talk as an outsider, with comparatively little experience of depression research; and I know only too well from my years of English education that it would normally be considered bad manners to offer critical opinions under these circumstances.

I was invited to speak here as a representative of the Hope for Depression Research Foundation (HDRF), one of the sponsors of this meeting [SLIDE 1]. My job as Research Co-Director of HDRF (together with Jaak Panksepp) is to advise the Board on how best to utilize its limited resources in order to maximize its chances of making an impact on depression research today. When I speak of limited resources I do not mean to underestimate the resources of the Foundation or the generosity of its founder, Audrey Gruss. She has already expended many millions of dollars on research into the causes, mechanisms and treatment of depression since 2006, which is when she established HDRF, together with the Institute for the Study of Affective Neuroscience (ISAN) in Israel. I mean only that by comparison with the statutory research funding agencies and big pharmaceutical companies, HDRF's resources are limited; so we have to think carefully about our strategy if we are going to make a difference.

Jaak and I were, therefore, inclined to 'think out of the box' from the start. In fact we were probably appointed precisely because Audrey Gruss had been told that we took an unconventional approach to our fields, Jaak as an experimental neurobiologist working mainly with animals, and I as a human neuropsychologist working mainly with clinico-anatomical methods. What set us apart is that we are opposed to what might be termed 'ruthless reductionism'. We believe that mental phenomena (such as feelings) are not epiphenomenal to the workings of the brain. We believe that feelings evolved for good biological reasons - that they make specific, concrete, causal contributions to brain functioning. To marginalize this unique property of the brain in our understanding of how it works is likely to lead us badly astray.

This appears to have happened in recent attempts to understand the brain mechanisms of depression ... so much so that as we surveyed the state of the art of your field during the past two days, it was only the aforementioned considerations of manners that prevented me from changing the title of my talk to: '*Are We Studying Depression Yet?*'.



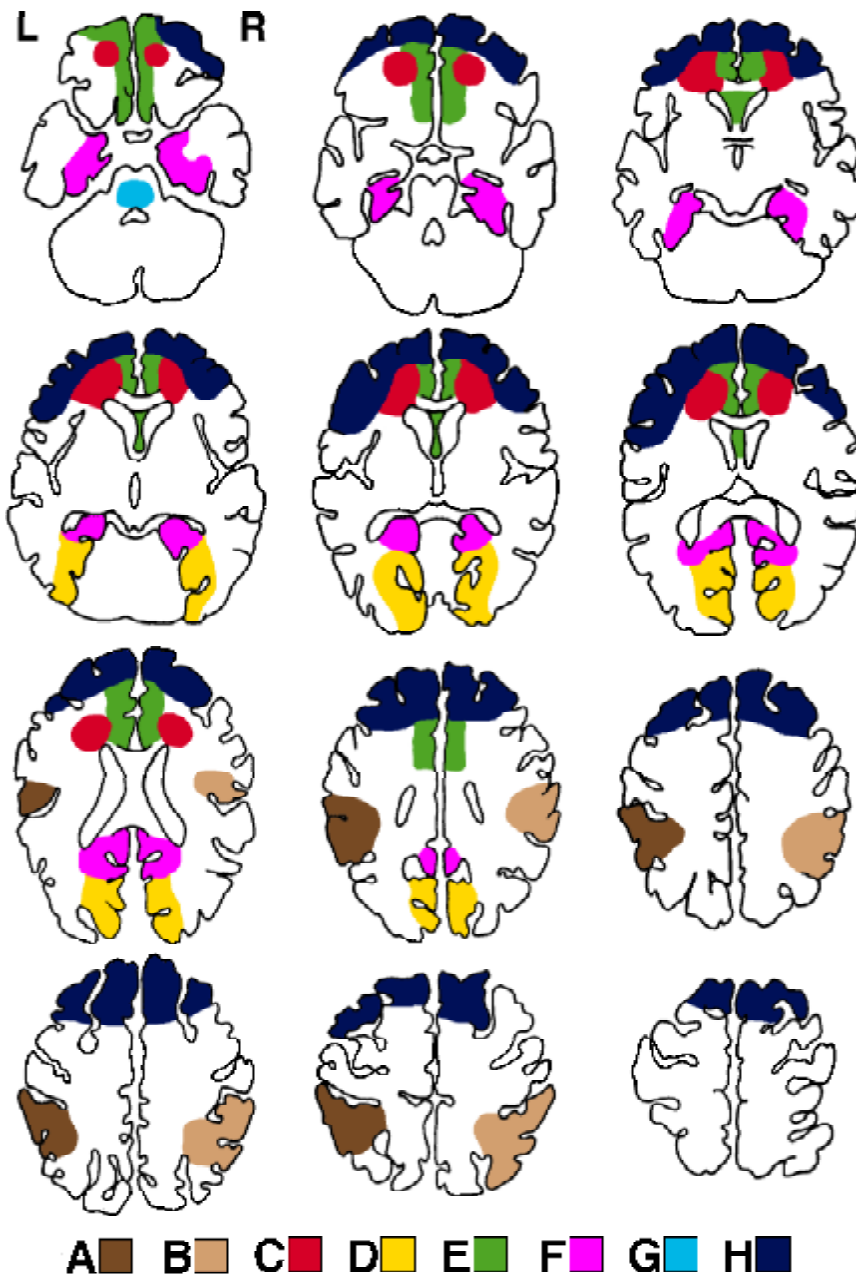
HOPE FOR DEPRESSION RESEARCH FOUNDATION

[SLIDE 1]

Allow me to explain by means of a parable, drawn from my own field of research, namely the neuropsychology of sleep and dreaming. We once took the psychology of dreaming very seriously. As is well known, Freud (1900) claimed that behind the apparently random perceptual imagery of the explicit dream lies a complex, implicit cognitive process with specific motivational content. The method by which he reached this conclusion was highly problematical, relying as it did on retrospective, subjective reports and his knack for tracing semantic associations in them. Subjective states are such fleeting and fugitive things, so difficult to manipulate experimentally, especially if one wants to determine their meaning – what philosophers call their ‘intentionality’. Leaving aside the troublesome fact that things like intentionality do exist in nature, indeed the possibility that such things may be fundamental to what we call the mental, one would still rather exclude such things from science if one could. This applies even to the science of the mind, to what today we call cognitive neuroscience.

It is therefore not surprising that my predecessors leapt at the opportunity to replace dreams with their physiological correlates - the physiological constituents of REM sleep - just as soon as these were discovered in the mid 1950s. The aim of thus grounding dream research on a proper scientific base was greatly facilitated by the development of animal models, since homologues of human REM sleep – the objective markers of dreaming - were clearly identifiable in most other mammalian species. By the mid 1960s already, therefore, we knew that dreaming was generated at a rather low level in the neuraxis, namely in the pontine brainstem, and by the mid 1970s we had a good understanding of its fundamental mechanism, namely cyclical

forebrain activation by cholinergic pontine neurons accompanied by reciprocal demodulation by serotonergic and noradrenergic ones (McCarley & Hobson 1977).

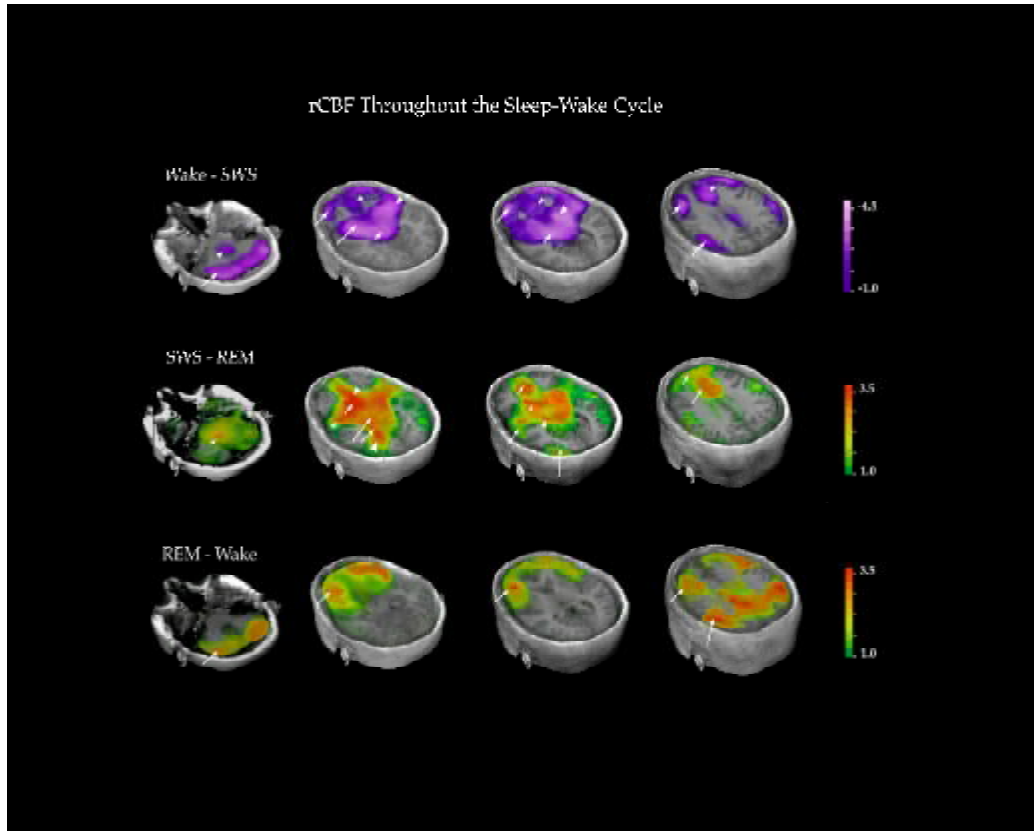


[SLIDE 2]

[C = site of lesion producing cessation of dreaming]

Given this background, you can imagine my surprise when I conducted the first systematic investigation of the differential effects on subjective dreaming of focal brain lesions in humans (Solms 1997) and found that mesolimbic forebrain rather than pontine brainstem lesions cause loss of dreaming [SLIDE 2]. We had gone so far in our quest to replace the psychological phenomena of dreaming by their more tractable physiological correlates that, although it was well established that pontine lesions cause loss of REM sleep in humans no less than in other mammals, nobody had ever

thought to ask the humans with loss of REM sleep whether they still dreamed or not. The equation 'dreaming sleep = REM sleep' turned out to be a fallacy, which had led us down a blind alley for more than 20 years (Solms 2000). This could have been avoided if, in our haste to jettison the subjective phenomena, we had remembered one of the most basic rules of science - namely that correlation does not imply causation, let alone identity of mechanism.



[SLIDE 3]
[from Braun 1997]

Dreaming turns out to be generated not by brainstem cholinergic mechanisms but rather by dopaminergic mesolimbic ones. This was revealed initially by the finding that deep ventromesial frontal lesions produce cessation of dreaming (accompanied by loss of motivation), and buttressed by the finding that dopamine agonists increase dream frequency, duration and intensity independently of any effects on REM sleep (Hartmann 1980), while dopamine antagonists have the opposite effects (Yu, unpublished). The fact that REM sleep merely contextualizes and facilitates dreaming - the actual mechanism of which is an unrelated brain system located in the mesolimbic dopamine system, known loosely as the 'reward' system - is further supported by converging lines of evidence, from functional neuroimaging studies which reveal massive activation of this system in REM sleep [SLIDE 3], through single-cell recordings which reveal phasic bursts of activity in VTA dopamine neurons during REM sleep, analogous to that seen in feeding behavior (Dahan et al., 2007) to microdialysis studies which reveal greater release of dopamine in the nucleus

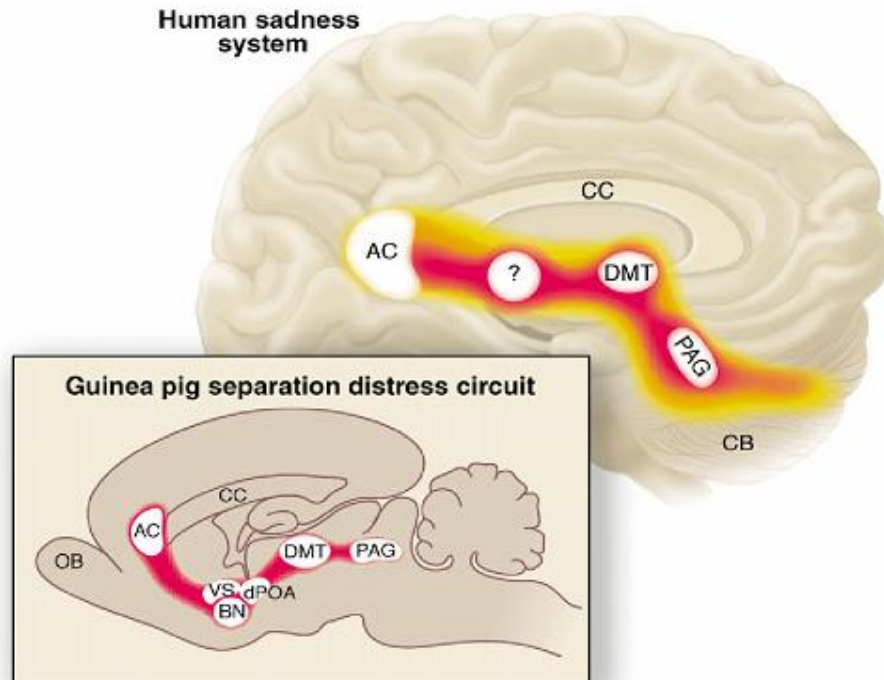
accumbens during REM sleep than at any other point in the sleep/waking cycle (Lena et al, 2005).

What is most interesting about the finding that the mesolimbic ‘reward’ system is the actual linchpin of dreaming is the fact that it brings us full circle back to the original psychological findings, to the effect that dreaming appears to be driven by implicit motivational mechanisms. There is something reassuring about such a convergence between the psychological and neurological lines of enquiry.

I worry that something similar to what happened in dream research is happening now in depression research. In our haste to avoid the messy psychological phenomena of depression, we may be focusing on all sorts of things that correlate with it or facilitate it, and the neural mechanisms of those things, rather than the mechanisms of depression itself. The neurophysiological mechanisms of monoamine depletion, their neurotrophic consequences, the neuroendocrinological mechanisms of stress, their neuroimmunological equivalents, the interactions between sleep mechanisms and mood, and even the contributions of certain genetic variations; all of these things appear to contextualize and facilitate depression, but none of them is even nearly specific enough to explain depression itself. The mechanisms you are focusing on might, therefore, have no closer relation to depression than REM sleep had to dreaming. The linchpin mechanism of depression apparently lies elsewhere.

The clinical phenomenology of major depression is characterized above all by a complex of *feeling* states: low mood, low self esteem, loss of motivation and energy, loss of pleasure in the world, and so on. What seems to bind this complex of feelings together is revealed by what DSM IV describes as diagnostic criterion E: ‘The symptoms are not better accounted for by *bereavement*’ (emphasis added). In other words, depression is characterized by a complex of feelings that closely resembles bereavement. It therefore must have something to do with social loss. This brings us back, as with dreaming, to something the early psychological investigators of depression surmised, namely that depression is akin to mourning, that it seems to be a pathological form of mourning (Freud 1917).

It is well established today that early separation experiences do indeed predispose to depression, possibly through mediation of the stress cascades that Bruce McEwan has identified, and we also know that a first depressive episode is most likely to be triggered by social loss. But I have already said that the HPA stress mechanisms provide, as it were, ‘too much’ of an explanation of depression - too general a mechanism. In light of the observation that depression is intimately connected with the dynamics of attachment and loss, why are we not focusing our attention on the mammalian brain system that evolved specifically for the purpose of mediating attachment and loss, and which produces the particular type of stress associated with them, namely *separation distress*?



[SLIDE 4]
 (from Panksepp, 2003)

This system comprises a well-defined network of structures, starting in the anterior cingulate (about which so much has been said at this meeting), coursing downwards through various thalamic, hypothalamic and other basal forebrain nuclei, terminating in the ancient midbrain (pain generating) neurons of the peri-aqueductal grey [SLIDE 4]. Activation and deactivation 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 well-being that are the very opposite of depression, whereas mu opioid blockade or withdrawal produces separation distress. (This state is most readily identified in animal models by distress vocalizations.) John Bowlby (1969) classically described this phenotype as 'protest' behavior, which he contrasted with the more chronic 'despair' behaviors 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 to deflect the attention of predators.) It is the 'despair' phenotype that seems most closely to resemble clinical depression.

The separation distress system, which is greatly sensitized by the hormonal and peptide (prolactin, oxytocin) releases that precede childbirth and facilitate maternal care, developed early in mammalian evolution. This system apparently provides the primal means by which mother and infant 'attach' to each other - the means by which they become 'addicted' to one another. (Here, incidentally, we also have the basis of the sex bias in depression that was mentioned so often during this meeting.) It seems

that the pain of social loss is the price that we mammals have had to pay for the evolutionary advantage bestowed by this system, that is by social attachment, the prototype of which is the mother-infant bond.

It seems reasonable to hypothesize that the linchpin of depression is none of the things we have discussed at this meeting, but rather the brain mechanisms that normally mediate the transition from 'protest' to 'despair'. In other words, it seems reasonable to hypothesize that the core mechanism 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 we investigating the role of these brain mechanisms in depression? They seem the obvious place to start, if we are going to take the phenomenology of depression itself (as opposed to the many things that facilitate, contextualize and otherwise correlate with it) as our starting point.

It is for this reason that Jaak and I, when searching for an 'out of the box' research funding strategy for HDRF that is likely to make a difference to the field, alighted on these mechanisms. Accordingly, since 2007 HDRF and ISAN have funded approximately 60 colleagues to undertake research that may shed light, directly or indirectly, on the role of the separation distress system in depression. We would like to invite all of you to consider doing likewise, or at least to consider undertaking research into the relationship between the brain mechanisms that you are studying already and the mechanisms that I have just outlined. That should not require too great a departure from the path you are on already. I am sure you can see how the research paradigms and findings presented at this meeting over the past few days all have points of contact with this hypothesized core mechanism.

We are particularly interested in funding studies that also include a direct psychological component, to complement the conventional behavioural and physical measures. For example, it would be particularly interesting to follow up in a systematic way on the anecdotal observations made by Helen Mayberg regarding her DBS patients, who spontaneously reported that they felt, not so much as if something had been added by the DBS, as that something had been taken away. Is this 'something', in reverse, the global shutdown process that we are looking for?

The procedure for applying for HDRF funding is very simple, and deliberately so. In the first instance you merely send a 200 word abstract of your proposed study to Jaak Panksepp and/or me. We will revert with some suggestions as to how the study might be more fully aligned with our funding strategy, and then provide you with the formal application form. This is not a very onerous document to complete at all – just a two page description of your proposed research is required, with a brief CV and a budget. We typically give \$110,000 per project, usually over two years, but these are not hard-and-fast limits.

We are also willing to fund seminars like this one, where leading depression researchers discuss and integrate their results across different methodologies and paradigms. We would be especially interested in funding an ongoing seminar, perhaps one devoted to a consideration of the sorts of issues that I have raised here, in the light of the ongoing findings, including those of the researchers that we are funding.

Thank you for your kind attention and, once again, for the permission to discuss novel and challenging ideas. I hope that I have given you food for thought, without transgressing the bounds of good manners!

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