Evolutionary Aspects of Depression, Stress and Subordination

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Abstract

An evolutionary approach to depression, aims to understand psychopathological phenomena that arise from evolved molecules, emotional value systems, brain structure, and social strategies, interacting with the modern social world. I hope to show how this approach may help us, to make sense of the differing symptoms and forms of major depression and make valid empirical predictions. This suggests that core depressive symptomatology may be rooted in emotional systems, evolved to nurture, dominate, adapt to loss and defeat and be sensitive to threats and safety. It focuses on the consequences of failure to turn off the threat/defence system (HPA- axis) as the final common pathway to depression. The key role of serotonin in these processes is explored. Finally this paper offers suggestions for therapeutic interventions, based on an understanding of these interactions.

Introduction

On the face of it the neurovegitative (sleep, appetite, circadian rhythm, libido), motivational (arousal, expectancy), cognitive (low self esteem, guilt, pride, shame), social (anxiety, withdrawal) and stress vulnerability of depressed people appears maladaptive. Why has the potential for this 'maladaptive ' pattern not been selected out by natural selection? Why is depression associated with an elevated stress response? Why do losses of loved ones as well as loss of status or power trigger depression? This paper explores some possible answers to these questions concentrating on social attachment, social hierarchy and stress response systems- psychophysiological mechanisms deeply rooted in our phylogenetic ancestry.

Natural Selection and Evolutionary Conservation

1. Let us begin by reminding ourselves of the basic tenets of natural selection:

* Diversity of variants,
* Selections by the environment and
* Differential amplification or reproduction of variants or individuals that best match the environment.[1]

The power of Darwinian selection is demonstrated by its utility in very diverse fields. For example, within immunology, selectionism has been used to explain the capacity of the immune systems to generate the appropriate antibody to unique antigens that have never existed in the history of the universe.[2] In consciousness studies, there is increasing interest in neural selectionism within the cortico-thalamic system as shifting alliances of neurons compete in a process similar to natural selection.[3]

2. Another basic evolutionary tenet is its essentially conservative nature. At a molecular level, conservation of function (or adaptation) is seen with respect to the peripheral and central effects of neuropeptides.[4] For example evolution utilises the more ancient peripheral effects of oxytocin (birthing, milk let down) by later conserving its function centrally (brain changes towards nurturance, care, reciprocity, friendships and mothering in both sexes), that is, a utility harmonious with its previous function. We shall return later to the importance of self-nurturance, forgiveness and acceptance. Peripherally, vasopressin produces water retention and male sexuality, and centrally, memory retention, aggression and interestingly, jealousy.
3. The highly conserved HPA stress response system is mediated in all mammals by adrenalin and cortisol, both of which are linked to the challenges we call 'stressors'. But both are also linked to basal physiological processes involved in many other aspects of daily life, including sleep, activity, food intake, and day-night diurnal cycles.[5] So diet, exercise, quantity of sleep, smoking and alcohol all influence the secretion and levels of the same mediators that are activated by stressful experiences.

'Allostasis' or achieving homeostasis through change,[6] represents an adaptive response to stress. 'Allostatic load' in contrast refers to the damaging response or price the body pays for adapting over long periods to challenges. It reflects 'wear and tear' on the body produced by the need to adapt to an ever-changing world. This terminology emphasises that protection and damage are linked to each other physiologically.[7]

HPA arousal (fight/flight response) is also active in circumstances of conflict, heat, cold, pain, abuse or separation[8] as well as in defeat or when criticism is seen to be unjustified.[9] Chronic elevation of glucocorticoids are well known to lead to failure of the negative feedback loop controlling cortisol secretion through hippocampal cell fatigue and death.[10] Sustained high levels of glucocorticoids compromise growth, reproduction, wound healing and disease resistance, a high price for sustained overactivity of an adaptive threat/ defence system. The 'inverted U' shape of the Yerkes-Dodson law[11] illustrates how performance declines in states of overarousal. (Figure 1).
4. Emotions serve as value systems, communicating, detecting and assigning salience to biologically useful events and resources.[12] (food, mates, territory, threat, loss etc). Striking is the conservation of these homologous, subcortical systems in all mammals that sustain on-going behaviour patterns and anticipate survival needs. Panksepp has detailed with remarkable precision, the neurobiol-

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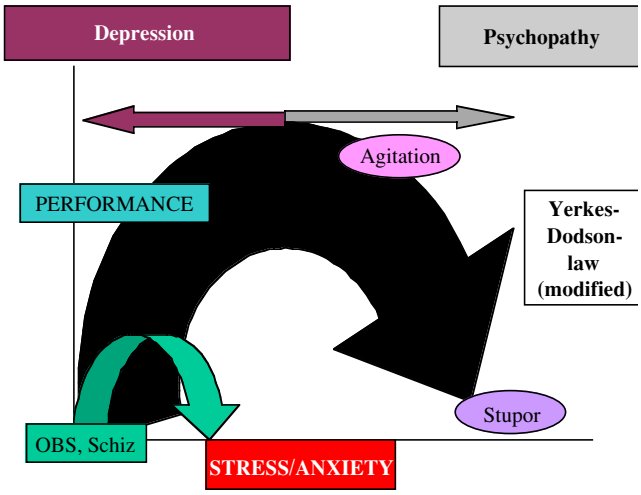

Figure 1: The Stress/Performance Response (adapted from Yerkes Dodson)
With increasing stress/anxiety, performance becomes dysfunctional at a critical point, followed by agitation (sustained elevation HPA-axis, ?CRF receptor sensitivity) and finally stupor/retardation (hippocampal cell fatigue, ?CRF receptor down-regulation,). It is hypothesised that depression would tend to shift the peak of the graph to the left, indicating an already aroused HPA axis, and consequent rapid development of agitation. Psychopathy would represent a contrary position. Organic brain syndromes (OBS) and schizophrenia are diagrammatically represented as a smaller green arrow, indicating the relative ease with which the stress response system is overridden in these patients and their consequent relative intolerance to stress/arousal (?via cortical disinibition via DA pathways).

ogy of several basic emotional systems. These include seeking (find and anticipate survival needs), rage (bodily surface irritation or frustration of expectation), aggression (inter-male, predatory etc), fear (bodily threat or damage), lust, panic (related to separation anxiety), nurturance (the capacity for attachments, altruism, self-nurturance), rough and tumble play.[13] There is now increasing evidence for the existence of rank systems of subordination and dominance[14] (social competition).

5. The Triune brain. At a macro level, Maclean's concept of the Triune brain[15] illustrates successive ordering of new layers upon old reptilian parts- ie diencephalic –reptilian, limbic- palaeomammalian, cortical – primate. It is useful to conceptualise instinctive behavioural routines of reptiles as 'closed' circuits that require minimal learning. The more 'open' circuits of the neo-cortex require much learning in order to instantiate. The emergence of laterality later expanded cortical abilities hugely with minimal increase in size. The right hemisphere is more closely linked to emotional centres, providing the greater depth to our emotional narratives and has a more lugubrious or doleful mood than the left.[16] The left is perhaps a specialist in emotional repression, projecting an image of positive desirability into the world.[17]

The anterior cingulate cortex receives the richest dopaminergic innervations of any cortical area. It appears to play a critical role in emotional self-control and on-line problem solving (error detection). Environmental stress appears to interfere with the competence of this system.[18] The higher reaches of limbic areas, as they interface with the neocortex, provide the playground for our primate Machiavellian intellegences of hiding out intentions, deceit, deception, and ultimately self-deception. The capacity to deceive oneself may interfere with a coordinated response to competitive defeat.[19] Maclean's Triune brain raises fundamental issues such as the effectiveness of more recent cortical controls over more ancient subcortical emotional systems, dysregulation and functional isolation of component parts, matters to which we shall return later. (Figures 2 & 3).

The Attachment and Rank Systems.

The two great emotional systems that concern us here are those of attachment and rank. The attachment system itself has more ancient evolutionary roots in pain circuitry, place attachment and thermoregulation.[20] These roots account for our capacity to experience the emotional pain of separation from people as well as from places we love. The musical 'chills' or shivering in response to profoundly moving music (usually sad) seems to evoke the thermoregulatory response to hearing separation calls of the young (loss and redemption).

Infants when placed in situations marked by potential threat, illness and distress, experience physical and emotional arousal exceeding a level they can modulate. They therefore depend on their caregiver's capacity to read their cues and respond in a manner that will restore the equilibrium.[21] The attachment system fulfils the pri-

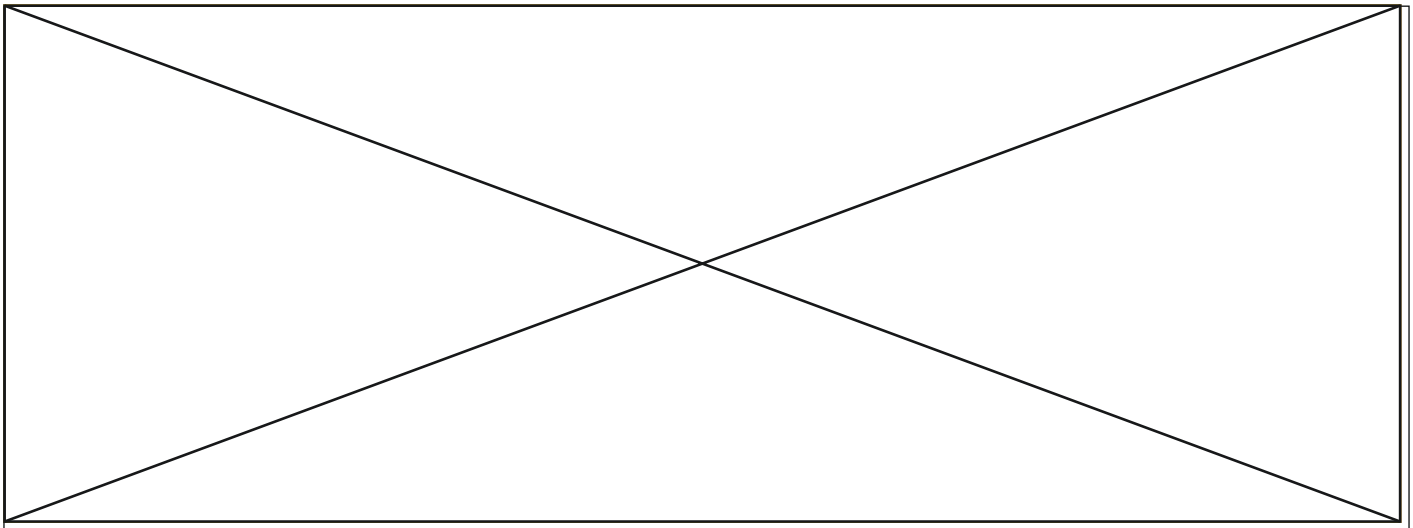

Figure 2&3 Maclean's concept of the Triune Brain
The emotions or value systems are diencephalic and diagrammatically represented as an orchestra. The reason is that these value or salience systems (via DA, 5HT, NA), project to all areas of the brain, changing sensitivities of sensory systems and leading to better adaptive choices. The conductor here represents a coordinating locus or primitive 'self'. Panksepp (1998) gives compelling reasons for a putative site of this structure lying in the region of periaquaductal grey (PAG), close to primitive motor centres and through which every emotional system funnels. The fronto-striatal-limbic loops as well as cortico-thalamic system, are also indicated.

mary function of keeping the dyad in close proximity to increase the probability of survival.[22] Secure attachments are able to successfully utilise others for emotional support and affect regulation. The insecurely attached may be successful in maintaining proximity to a carer but not successful in regulating affect, so that high arousal levels are maintained following competitive or social losses.[23]

Panic is an integral symptom of depression. There is increasing evidence that separation distress emerges from the panic system (although fear and panic systems operate synergistically) and represents a young animal's attempt to search for its mother,[24] and therefor not sleep or eat. (Lack of sleep in depression may relate to phase advancement of the sleep-wake cycle induced by stressing the HPA axis, experimentally replicated in animals). Separation distress is relieved by opiates whereas anticipatory anxiety is relieved by benzodiazepines. Panic and separation distress are relieved by imipramine, clomipramine[25] and certain SSRI's (paroxitine). The antikindling effects of carbemazepine relieve anxiety and anger associated with PTSD.[26]

The rank system (subordination and dominance displays) underlies social competition, a critical element of hierarchy formation. Hierarchies stabilise groupings and effectively organise resource distribution. Success in competition for power or attractiveness brings more access to food, territory or mates, therefore rank is heavily defended and animals evolved to seek higher rank.

We are programmed to respond to initial perception of loss with a series of stress responses (HPA activation), that is, protest or panic, despair-demobilization and detachment.[27] Protest serves in order to maximise chances of winning or drawing mother's attention to the infant's needs. However when defeat is inevitable, or if mother does not return, it is generally best to stop protest, conserve resources or disengage expeditiously. The despair-demobilization serves to stop the infant wandering and also to elicit care from a potential mother surrogate. This requires a rapid change in orientation from protest/belligerence to freezing/conciliation or flight. The subordination system thus serves a harm-avoidance function by protecting the child from predators,[28] as well as bringing conflict to an end and preserving the stability of the group as a whole.

Sloman and Gilbert [29] have termed the subordination response the Involuntary Defeat Strategy (IDS). Designed to achieve a rapid change in orientation, it is involuntary and therefor outside consciousness (dienchephalic) and triggered by the perception of the inevitability of defeat. The IDS is characterized by feelings of helplessness, hopelessness, tiredness, weakness, inadequacy and inferiority. These features seem exquisitely designed to discourage the individual from continuing the conflict and promote submission and acceptance or flight. A feeling of mild disappointment may be indicative of a mild IDS. The term 'strategy' refers to its genetic programming. When the individual has submitted and accepted defeat, the IDS is switched off, leaving the individual free to face other challenges.

When the IDS functions effectively it is appropriate to circumstances, appropriately timed (not prematurely activated or terminated), successful in triggering submission or flight and successful in turning off the dominance system, thereby precluding the simultaneous activation of dominance and subordination or their rapid cycling.

Therefore the individual with an effective IDS better accepts defeat and can move on. If effective these qualities represent affect regulation.

It has been argued that low self esteem is a manifestation of the IDS and because the IDS is associated with negative affect, those with an activated IDS may be preoccupied with how to avoid the pain of further loss that would trigger an even more powerful IDS.[30] Simultaneous activation or rapid cycling of dominance and subordinate systems may result in the individual continuing a fruitless interpersonal struggle. This is revealed by an inability to admit any weakness or error or by the tendency to use put-downs. The avoidance of confrontation prevents resolution and issues are addressed in indirect ways.[31] Struggles that are motivated by anticipation of pride and joy on the other hand are associated with success or a real struggle over resources.

Affect regulation is achieved by the reassurance and warmth of secure attachments and by recognition of high status. Insecurely attached children experience anxiety and are less likely to feel they have a stable ally. They are more likely to trigger their IDS prematurely in any potential confrontation and it is likely to become more intense. This may manifest in depression and victimisation and or bullying in an attempt to regulate affect. Children with insecure attachments are more likely to become either bullies or victims [32].

Following major defeat, support from someone with whom there is secure attachment may alleviate anxiety and reduce arousal sufficiently to allow the individual to accept defeat and move on. Thus if activation of either the attachment or social rank system fail to regulate painful affect, this may lead to a triggering of the other system. For example insecurely attached individuals may utilise submission signals (helplessness) or dominance (control others or inflation/grandiosity/tantrums) in order to regulate affect and maintain proximity.[33]

Social Rank, Defeat and the HPA axis

Competitive encounters are also known to mobilize the HPA axis.[34] This is nowhere more graphically illustrated than in the case of the Tree shrew. When these animals were placed in a confined territory, resulting in fighting. The victor became dominant. Defeated losers adopted two different strategies. Some animals (called 'subdominants') adopted typical submissive patterns. They continued with activities but in a rather timid and cautious way. They showed an elevated stress response. However other defeated animals (called 'submissives') were quite different. These animals became seriously demobilised with greatly elevated cortisol and corticosterone responses and died within 14 days of the confrontation.[35] Even separating victor and loser with wire mesh placed between them did not save these animals. The presence of the dominant was enough to have a major biological impact.

Low ranking baboons show increased cortisol and DST resistance. Following a fight, a fall in cortisol is seen in winners, the loser remaining highly aroused. This arousal is protective in agonic hierarchies where lower ranking males are exposed to unpredictable attacks.[36]

Thus competitive encounters mobilize the HPA axis. Prediction of loss triggers the IDS which if effective, de-escalates behaviour and restores normal HPA axis function. This in turn leads to successful escape, submission, acceptance of loss and a new social status. The IDS is terminated.

Failure to turn off Adaptive Fight/Flight mechanisms

Depressed patients frequently experience a state of chronic overarousal, as evidenced by elevated CRF, and blunted ACTH response to CRF.[37] Suicide victims with a history of major depression show down-regulation of hippocampal glucocorticoid receptors.[38] Antidepressants have been shown to normalise cortisol and restore DST suppression.[39] In addition, maladaptive competitive defeat responses are more vulnerable to major depression ie less stress is needed to precipitate depression. This state of overarousal may contribute to the physiological features of major depression. (Figure 4)

A successful IDS following defeat enables the HPA axis to be switched off and the individual comes to feel safe. This may involve

fight/flight, escape, submission/freeze, eliciting help or accepting one's social position - if only temporarily, to fight another day. If the IDS is unsuccessful, the threat/defence system remains activated. Conditions likely to bring this about include:

* failure which is unexpected or not accepted, [40]
* an IDS which is inappropriate to the circumstance or inappropriately timed (premature triggering of the IDS may underlie rejection sensitivity).
* conditions of entrapment or blocked escape, [41]
* failure to elicit help,
* being unable to accept one's social position
* or simply because the loss or failure are too enormous, or because one has all 'one's eggs in one basket'. [42]

Anger causes HPA arousal and this context deserves special mention. Rage is triggered in proportion to in-built expectations (frontal lobe), and is enhanced by testosterone, hunger and pain. [43] The greater our expectations are the greater will be rage in response to unexpected losses or failure. Anger or protest is the first stage of disengagement from loss described by Bowlby. Anger therefore could be seen as a winning response or an attempt to recover what one has lost. The appearance of the second stage described of despair/withdrawal does imply the dawning of the reality of the loss, painful though this may be. Grief work following losses of loved ones commonly focuses on giving up anger and validating the pain of grief in order to move to a stage of acceptance.

When anger or humiliation that is concealed for fear of further humiliation (eg child sexual abuse), it may become chronic and later distort personality development. Gilbert [44] has usefully applied the term 'shame' to this situation. Shame frequently involves violation of social norms. Continuing anger may also follow defeat in which the competition is seen as unfair. Thus, anger arises from perceived violations of social expectations and is resolved by restoration of propriety or equity. [45]

Our more recently acquired cortical expansions have less control over subcortical emotional responses such as rage, than the converse. The uniquely expanded human memorial capacity and fronto-limbic-striatal loops, allow us to nurture and ruminate upon past hurts and grievances, transforming them into prejudice and hatred. This may explain why it is seemingly so difficult for us to give up anger.

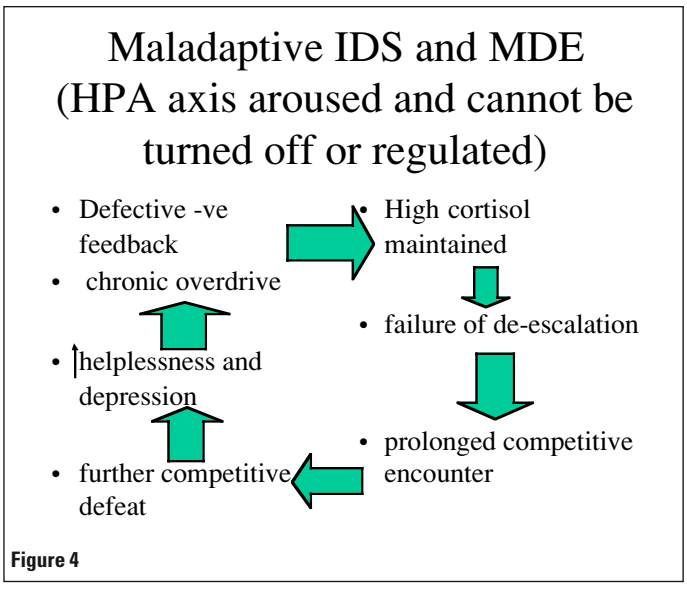

Figure 4

Serotonergic Mechanisms in Primate Social Behaviour and Major Depression

The IDS plays a crucial role in stabilizing primate hierarchies by de-escalating competitive behaviour. Serotonin appears to play a key role in this process, at many levels.[46]

Dominant rhesus monkeys have peripheral 5HT levels 1.5–2 times the levels of low-status or subordinate males, as well as a greater 5HT responsivity. When CNS responsivity is high, these dominant animals are less aggressive and more relaxed. If the frequency of submissive displays by subordinate males declines (through the use of one-way mirrors), peripheral 5HT levels decline among dominant males. Should a subordinate male become dominant, or a dominant male become subordinate, their behaviour and physiological measures change to those characteristics of their new social status.[47]

In primates, maladaptive aggression and risk taking, most often occurs in impulsive low-ranking subjects with low CSF serotonin metabolites. Female rhesus monkeys with low CSF HIAA exhibit higher rates of spontaneous aggressive wounding and are more likely to be expelled from their social groups. Females with above average CSF HIAA were able to attain and maintain a high social dominance within their social group.[48] Serotonin therefore, plays a critical role in social affiliation and de-escalation by controlling impulses that regulate aggression and promote competent social behaviour.

Several other studies have found primates with high CSF HIAA are more likely to engage and spend time in positive social interaction. [49] Pharmacological intervention that increases brain serotonin can increase the frequency of positive social interaction and improve social rank and the opposite is true when serotonin activity is pharmacologically reduced.

Human findings are consistent with non-human primates. Serotonergic dysfunction and low CSF 5HIAA have been associated with deficient impulse control, [50] violence,[51] personality disorder characterised by impulsivity and poor social affiliation,[52] and bulimia nervosa,[53] and dysthymic disorder.[47]

The serotonin system appears therefor to have important effects on impulsivity and hostile mood and affiliative behaviour in both humans and primates. For example the SSRI paroxetine, reduces hostility and enhances affiliative behaviour in such subjects.[54]

Thus low serotonin or abnormal modulation increases impulsivity and hostility, and decreases social affiliation, thereby preventing de-escalation, submission and acceptance. The encounter is prolonged enhancing the experience of defeat and depression.

IDS, Serotonin and the Triune Brain

At a neuroanatomical level the IDS can be thought of as a pre-programmed neural circuit linking the striatum, limbic system and prefrontal cortex, which mediates the behavioural, emotional and cognitive components of the IDS. [55] If competitive loss appears inevitable these components trigger submissive gesturing/flight (striatal), anxiety (limbic), and deflation/pessimism (cortical) respectively.

If submission signals are successful there is concomitant decrease in HPA arousal, anxiety and a new cognitive set of acceptance mediated at the prefrontal cortex.

Serotonin pathways link the limbic system, prefrontal cortex and striatum [56] and therefore modulate this functional circuit as well as HPA axis activity at both the hypothalamic [57] and pituitary [58] levels, ensuring adaptive regulation. It appears therefore that abnormal serotonin modulation of these circuits leads to chaotic, disorganised activity, preventing a normal unfolding of the IDS in a co-ordinated fashion.

Functional isolation or dysregulation of component parts may

therefore explain the diverse symptomatology of depression. Overactivity can be experienced subjectively as intense anxiety or panic (limbic), pessimistic rumination (prefrontal) and agitation (striatal). Further overactivity, (see Figure 1) might be experienced as apathy (limbic), paucity of thought/indecisiveness (prefrontal) and psychomotor retardation/stupor (striatal). The outcome is presumably heavily influenced by individual genetic as well as phenotypic factors.

In summary, the biological treatments involving serotonin-enhancing agents:

* decrease impulsivity, hostility and increase affiliation and status in primates and humans
* improve social anxiety in humans [59]
* normalise communication of fronto-striatal-limbic circuits enhance de-escalation by normalising HPA activity and preventing chronic CRH/cortisol release.

Conclusions

The HPA axis/arousal system is activated to defend against losses of attachment as well as social rank. Sustained arousal of this system is the final common pathway toward depression and increased mortality especially if these losses have long term implications. [60] Previous experience of depression would tend to lower the threshold of this response. This evolutionary approach is consistent with what is known of the predictive factors of recurrent depression, namely: frequent or multiple episodes, 'double' depression, pre-existing dysthymic disorder, longer duration of individual episodes, a family history of affective disorder, incomplete resolution of symptoms and co-morbid anxiety [61] as well as the need to treat each episode vigorously. [62]

However the quality of grief/separation distress is distinct from shame, and grief does not necessarily involve subordination.[63] Oxytocin relieves separation distress, but does not relieve low rank. [64] Further, grief and separation distress involve the cingulate gyrus, [65] whereas pride and shame seem to be localized in the orbitofrontal cortex. [66] Separation distress arises in the first year of life, whereas pride and shame arise in the third year.

Further, many life events, such as divorce and physical illness, involve complex losses- of attachment (to goals and ideals such as one's myth of personal invulnerability), physical pain and disability, isolation, as well as status effects (financial, self esteem).

However, this emerging evidence could help to clarify the traditionally confusing debates around classifying depression,[67] and offer richer and more focused treatment implications.

Treatment Implications

An evolutionary approach fosters a true integration of the bio-psycho-social model. Decreasing arousal of the HPA axis or allostatic load and preventing an escalation of the IDS may be achieved by interventions at any level. For example, antidepressants and psychotherapy may act synergistically,[68] and there is strong evidence for the physiological benefits of care and support. [69] D2 blockade reduces agitation and stupor empirically, as well as increasing tolerance to stress.

Decreasing stress and anxiety has far-reaching brain effects such as on cingulate spindle cell function, potentially improving on-line error-detection and problem-solving following defeat or loss. Recognising self-deceit strategies, evolved in order to deceive others (eg refusing to consciously accept defeat), might enhance acceptance after loss.

The following are some psychotherapeutic tools in depression, informed by these principals:

* Recognition of internally generated hostile-attacking-critical-dominant sub-personalities or 'voices' and evoking a counter voice of forgiveness, nurturance, compassion and care. In other words, giving a face and narrative to the archetypal core of various evolutionary evolved propensities. This enables the patient to depersonalise, externalise and exert control over the archetypal pattern.[70,71,72]
* Identifying and giving up fruitless struggles, unrealistic goals, ideals and expectations that may hamper acceptance of defeat and thereby the fulfilment of new possibilities.
* By using effective-self assertion or challenging 'self-downing', if the individual submits or gives up too readily.
* By the appropriate use of flight in situations of genuine entrapment in critical or abusive relationships or environments.
* By avoiding 'all one's eggs in one basket' scenarios through developing other hierarchies, roles, interests and neglected personal aspects.
* Recognising therapeutic relationships as powerful and soothing and therefore able to deactivate defence.
* Countering the effects of social isolation or feeling 'out-group'.
* Dealing with shame, by allowing for the expression of past hurts, anger and humiliation in an environment of valuing reassurance and mutual respect.
* Forming a secure base that affords the possibility of experiencing healthy attachments, without the need to control others via aggression and appeasement.
* Acknowledging the pain as well as the value of grief is a co-ordinated adaptive response that connects us all to each other, and to our ancient mammalian heritage.

Acknowledgements

I am deeply grateful to Leon Sloman and Jaak Panksepp for their enormous generosity and assistance. I would like also to express sincere appreciation to Vivian Russell at the Department of Physiology, UCT who took time to discuss some issues central to this paper.

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SAPR

COMMENTARY

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This paper attempts to establish a causal link between stress, subordination and depression drawing evidence from Darwinian theory, ethology, psychology, sociology and neurobiology. The central hypothesis is that loss of attachment or social rank failure leads to chronic hypercortisolemia via hyperarousal of the hypothalamic pituitary adrenal (HPA) system. The clinical syndrome known as depression surfaces when chronic hypercortisolemia is combined with a hypo-functioning serotonergic system.

Dr. Kibel views his approach as evolutionary as the disturbances are taking place in those systems that would otherwise serve survival functions such as healthy attachments and adaptive responses to success or failure in the search for the highest level of social status and rank. Dr. Kibel asks why natural selection has not eliminated the potential for what is clearly a maladaptive pattern. Two evolutionary explanations that come readily to mind are that depression, like Huntington's disease, is not lethal at a young age nor prevents reproduction in most cases. Dr. Kibel's hypothesis that depression arises from a chronically overaroused HPA axis with resultant hypercortisolemia is more simply described as a biological hypothesis since HPA arousal has multiple causes other than attachment loss and rank failures.

Much of the paper describes some of the background neurobiology, psychology, sociology and ethology. Dr. Kibel borrows central concepts from Panksepp and Sloman and Gilbert. Panksepp's classification of emotional systems may however cause cognitive dissonance in practicing clinicians. Panic to clinicians is a form of severe anxiety. According to Panksepp it is the panic system that is activated by separation and loss. This system is better described as a bonding system where loss of attachment activates the psychic distress known as sadness or depression. This distinguishes depression from anxiety. That separation with the threat of loss also causes anxiety (Panksepp's fear system) should come as no surprise. Threats of any kind including that of loss activate anxiety.

Dr. Kibel describes Sloman and Gilbert's involuntary defeat strategy (IDS). The IDS is an unconscious system whose purpose is to respond adaptively to defeat and struggle for dominance within a social hierarchy. Defeat in such a struggle activates the HPA system. More specifically it is the loss of the struggle for rank that does this as reflected in the elevated serum cortisol in the losers not the winners. It is therefore unclear to me why it is not loss per se that is the critical variable under consideration. This would link it symbolically to the attachment system and also explain why losses of many kinds, as recognized by Dr. Kibel, may cause depression such as the losses that occur in divorce, physical illness, financial mishaps and to one's self-esteem.

From this perspective depression is the emotional response to loss. The archetypal loss is that which may take place between the mother – offspring attachment. Then as with many flexible neurobiological routines, this attachment system extends to or co-opts other biological resources or symbolic representations that are essential for or augment survival.

Dr. Kibel's final common pathway is a chronically overactivated HPA system with consequent hypercortisolemia. Hypomodulation of the serotonergic system is the other ingredient. Is hypercortisolemia the final common pathway? Light upon this hypothesis can be shed from clinical practice. Pharmacological doses of corticosteroids are standard therapy for a variety of immunological and inflammatory conditions. Depression, mania and

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psychosis are the most common psychiatric complications. Prospective studies have documented affective symptoms in up to one third of patients. Euphoria is more common than than depression[1]. Depression is thus not a predictable consequence of hypercortisolemia. The aroused HPA system is more likely a consequence not a cause of depression representing an energized and activated organism mobilized to respond to the threat that depression poses to existence.

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REPLY TO COMMENTARY

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I wish to express my thanks to Dr Hurwitz for his concise and useful commentary. A central idea of this paper has been that whilst depression may be maladaptive, its origins can be traced to ancient neural mechanisms, which channel an orchestrated response to losses and defeat all kinds. That is, losses of social rank, status, as well as attachments, alliances and social bonds. The HPA axis becomes activated because loss is threatening and carries meaning. The greater the meaning the greater is the threat. These mechanisms appear to operate within an adaptive range, of duration and intensity. When this range is exceeded there follows overactivation of the threat/defense system, with ensuing psychobiological effects, including depression. The remarkable evolutionary conservation of a coordinated subordination system as well as the HPA axis itself attests to the utility and stability of these systems over countless millennia. Clinical depression then it would seem, is the result of an exaggerated or distorted derivative of these evolved mechanisms.

Single gene defects such as Huntington's disease as Dr Hurwitz justifiably points out, are hidden and manifest themselves after reproductive age and so avoid selection pressures against them. There is no need to evoke an adaptive mechanism to account for their continuation.

To my knowledge CRF remains elevated in chronic stress but is reduced in response to exogenous corticosteroids. Moreover in clinical practice, mania not infrequently seen in exposure to corticosteroid use is often followed by depression. This raises the important though unresolved issue of whether there are evolutionary advantages or precedents to bipolar predisposition. Gardener[1] has attributed the features of mania to excessive triggering of the dominance system. Rapid switching from subordination to dominance in propitious situations (or visa versa) could conceivably have been of value. Brain mechanisms tracking dominance and defeat could share a final common regulatory pathway.[2] Defects in these circuits could then open the door to random activation of either or mixed states.

Dr Hurwitz urges, *'Panksepp's classification of emotional systems may however cause cognitive dissonance in practicing clinicians. Panic to clinicians is a form of severe anxiety.'* Panksepp sites evidence for the distinction between the basic emotional systems of panic (arising in response to separation anxiety or attachment loss), and fear (a general threat to bodily integrity), stemming from differing pharmacological responses as well as detailed microanatomy of these circuits. Losses of allies and attachments would certainly have profound implications for bodily integrity in animals whose survival critically depends on close group affiliation and support. It is postulated therefor that the basic emotions fear, panic, rage, care, lust, dominance/submission etc, are recruited in the service of higher order emergent emotions such as embarrassment, shame, guilt, sadness, frustration, contempt (eg jealousy is also tinged with separation distress and anger).[3] Further, complex social strategies such as encountering competitive defeat or loss as well as all the emotional disorders have multiple determinants. The prospect of new psychopharmacological agents such a neuropeptides, targeting specific emotional circuits highlights the importance of a differentiated understanding of these emotional systems.

In the fluidity of constantly changing social life, emotions are readily projected into the world of sensory-perceptual affairs. In 'A Primate's Memoir'[4], Robert Sapolsky describes with riveting often hilarious detail, the stress effects on baboons in the wild who have lost social rank. Frequently, the fallen alpha male is subject to ongoing persecution, torment, and humiliation by former adversaries. It seems that even baboons have long memories. With the rise of an expanded frontal lobe, memorial capacity and receptive neuro-symbolic field in humans, it is now possible to visit this kind of persecution upon oneself.

Dr Hurtwitz argues 'the aroused HPA system is more likely a consequence not a cause of depression representing an energized and activated organism mobilized to respond to the threat that depression poses to existence'. *Whatever the direction of causality it is as well to remind ourselves that we proceed at our peril if we do not rise to the developmentalist challenge. In the words of Panksepp: "structure-function relations do not simply emerge from DNA codes, but as much from the many interactions between genetic information, environmental information, and the ontogenetic experience of individual….genes do not directly control mind or behaviour, but only the proteins and developmental patterns that help construct specific types of brains".*[5]

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