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The psychobiology of stress, depression, adjustment disorders and resilience

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ABSTRACT

Objectives: This paper focuses on the psychobiology of stress, depression, adjustment disorders (ADs), and resilience. Since the ADs fall under the rubric in DSM-5 of *Trauma and Stressor-Related Disorders*, essentials of the psychobiology of stress-response syndromes will be reviewed.

Methods: A narrative review of the psychobiology of stress-response syndromes is undertaken, and the implications for our understanding of ADs are discussed.

Results: Advances in our understanding of the psychobiology of stress-response syndromes provide an important foundation for understanding ADs, and for conceptualizing their diagnosis, as well as issues of resilience.

Conclusions: Future investigations of the psychobiology of trauma- and stressor-related disorders may shed additional light on ADs, and ultimately improve their treatment.

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Adjustment disorder; stress-related disorder; psychobiology of stress; allostatic load; stress response

Introduction

This paper will discuss the psychobiology of stress, depression, adjustment disorders (ADs) and resilience. The psychobiology of depression and its relationship with the central nervous system will be presented. An approach to the problems of researching the psychobiology of the ADs will be outlined. Since the ADs are one of the diagnoses considered under the rubric in DSM-5 of *Trauma and Stressor-Related Disorders* and which by definition have the requirement that a stressor be a precipitant and key element of the diagnostic algorithm, essentials of the psychobiology of stress will also be elucidated (APA 2013). And, finally, the psychobiology of resilience will be discussed, since recovery from stressor-related and other disorders are in part dependent upon resilience.

The psychobiology of stress and major depressive disorders

In an attempt to understand stress and its role in depression McEwen and Rasgon (2018) present their ideas in an important discussion of the *Brain and Body on Stress: Allostatic Load and Mechanisms for Depression and Dementia* and emphasise the key role of the brain: 'Depression and other mental health disorders involve not only dysregulation of neuronal architecture and function but also systemic physiological dysregulation.'. McEwen and Rasgon (2018) further state that the brain and body are in continuous communication through the neuroendocrine, autonomic, metabolic and immune systems. 'Stress is a major factor in psychiatric illnesses, and the brain is the key organ of the stress response because it determines what is threatening and, therefore stressful, and also controls the behavioral and physiological responses'.

McEwen and Rasgon (2018) argue that the concept of allostatic load describes the consequences of dysregulation of brain–body communication by life experiences and health-related behaviours that lead not only to systemic pathophysiology, but also to brain changes that underlie psychiatric disorders. Allostatic load refers to the wear and tear on the body that result from either too much stress or from inefficient management of allostasis, e.g. not turning off the response when it is no longer needed. The authors emphasise in their review that one of the biological consequences of early life adversity is the prolonged elevation in inflammatory cytokines as well as poor dental health, obesity, elevated blood pressure in children and young adults (Miller and Chen 2010; Danese and McEwen 2012; Tomasdottir et al. 2015). Sterling and Eyer (1988) used 'allostasis' to refer to the active process by which the body responds to daily events

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and maintains homeostasis (allostasis literally means 'achieving stability through change'). And, McEwen and Rasgon (2018) state: 'Because chronically increased allostasis can lead to disease we introduced the term "allostatic load" to refer to the wear and tear that results from either too much stress or from the inefficient management of allostasis, not turning off the response when it is no longer needed'. Other forms of allostatic load involve 'not turning on an adequate response in the first place or not habituating to the recurrence of the same stressor and thus dampening the allostatic response'. The authors continue: 'a good example of the biphasic actions of stress, i.e. protection versus damage', is in the immune system in which an acute stressor activates an acquired immune response via mediation by catecholamines and glucocorticoids and locally produced immune mediators; and, yet chronic exposure to the same stressor over several weeks has the opposite effect and results in immune suppression (McEwen 1998; Dhabhar 2009).

The hippocampus is an important player and a target for glucocorticoids and stress (Dhabhar et al. 2012). It is obviously outside the hypothalamus. This central nervous system organ is involved with insulin resistance, cognitive impairment, depression and Alzheimer's disease and, via the 'glucocorticoid cascade hypotheses', contributes to our understanding of allostatic load. There are many entities involved in managing stress: adrenaline and noradrenaline, glucocorticoids, pro- and anti-inflammatory cytokines and they may affect each other as well. At times these agents may be enhanced and at other times suppressed by stress. The parasympathetic system may oppose the sympathetic system, e.g. can slow the heart and have anti-inflammatory effects (Borovikova et al. 2000; Sloan et al. 2007; McEwen et al. 2015b). McEwen et al. describe the biphasic actions of stress, i.e. protection versus damage. There can be immune activation or immune suppression and depending upon which functions is needed it can be helpful, e.g. wound healing or hurtful as in auto-immune illnesses. McEwen et al. (2015a) have also shown that the hippocampus undergoes adaptive changes in response to acute and chronic stress via cellular and molecular mechanisms. McCarthy and Arnold (2011) demonstrated that acute and chronic stressors are responded to differently by males and females, and this involves epigenetic effects of hormones along with genetic mechanisms governed by the sex chromosomes.

Although it is commonly understood that adrenaline and noradrenaline are common mediators of stress, glucocorticoids outpouring from the adrenal cortex response to hypothalamic-pituitary-adrenocortical (HPA) activity is another major stress hormone. Furthermore, as McEwen and Rasgon (2018, p. 3) emphasise, pro- and anti-inflammatory cytokines regulate each other and are in turn regulated by glucocorticoids and catecholamines. Inflammation and stress has been an active area of research and offers suggestions for important investigative efforts that can be undertaken to understand the effects of stress on the brain and the body and adumbrate and unravel the psychobiological effects that may accompany stress and depression. The hippocampus atrophies with chronic stress, in major depression, type 2 diabetes, post-traumatic stress disorder, chronic inflammation and lack of exercise: it increases in size with anti-depressant therapy, regular exercise and intense learning (McEwen and Rasgon 2018). McEwen also has reported that the peptide/protein hormones: insulin-like growth factor 1 (IGF-1), insulin, ghrelin and leptin are able to enter the brain and affect the hippocampus (McEwen and Rasgon 2018).

Finally, depression appears to disrupt the neuroimmune axis that interfaces the immune system and central nervous system to effect behaviour (McCarthy and Arnold 2011). Studies examined the peripheral immune system's effects on the brain, its response to stress and an individual's vulnerability to mood disorder. Inflammation has been suggested as a possible mechanism for depression (Hodes et al. 2015). 'Neuropsychiatric research has pivoted from investigation of monoaminergic mechanisms to novel mediators, including the role of inflammatory processes. Subsets of mood disorder patients exhibit immune-related abnormalities, including elevated levels of proinflammatory cytokines, monocytes, and neutrophils in the peripheral circulation; dysregulation of neuroglia and blood–brain barrier function; and disruption of gut microbiota. The field of psychoneuroimmunology is one of great therapeutic opportunity, such as peripheral cytokine targeting antibodies, microglia and astrocyte targeting therapies, producing findings that identify therapeutic targets for future development' (McCarthy and Arnold 2011, p. 1). Are these mechanisms involved with major depressive disorder (MDD) and AD accompanied by depressive mood, one of the most common AD subtypes?

Post has proposed that depression is a recurrent, progressive illness and in need of long-term prevention (Plau et al. 2018) of the important questions for researchers studying the AD sub-type depression is whether the depressive sub-type tends to be recurrent, come more frequently in time without treatment or spontaneous recovery, and with the passage of time occur without the precipitation of a stressor, as is

the case with a MDD. In time without treatment does the sub-type follow the pernicious course of the inadequately or poorly treated MDD? To date, the long-term course of AD with depressive mood has not been reported.

For the MDD progression to more frequent occurrences one mechanism is the 'wear and tear' that comes with inflammation, HPA, adrenal over activity, oxidative stress, etc. 'The second type of mechanism is the increasing reactivity or sensitization that occurs upon recurrence of depressive episodes (episode sensitization); stressors (stress sensitization); and, psychomotor stimulant-induced behavioral sensitization' (Post 2018). Post also reports having multiple prior depressive episodes places an individual not only at greater risk of recurrence, but treatment refractoriness and cognitive dysfunction. Does this formulation help the conceptualisation of AD with depressive mood over time and point to the need for a longitudinal examination of this psychiatric disorder?

Psychobiology of adjustment disorders

The dilemmas of diagnosis of AD

The major limitation for essential research with regard to AD stems from the conundrums of its diagnosis. There is at times great difficulty distinguishing normality from pathology, and no place in the psychiatric lexicon is this greater than in those disorders that have been regarded as sub-threshold. Although it has been argued that the ADs should be considered a full-fledged psychiatric diagnosis (see Maercker et al. this issue), there is still uncertainty when trying to establish the reliability and validity of this class of disorders. This remains the most important issue in finding cohorts that are consistent across institutions for research purposes, and avoiding using diverse groups of patients to attempt to understand the psychobiology of the ADs. Furthermore psychiatric and medical comorbidity need to be eliminated in the cohorts under study to ensure that there is a homogeneous diagnostic profile in the patients under investigation. The three components to make the diagnosis of ADs are subjectively and phenomenologically derived without metrics which further complicates the comparability of study samples (Casey 2016; Strain and Casey 2016; Tyrer 2016).

(1) There is no valid measure of the degree of severity of the stressor or an individual's reaction to the stressor, and obviously an individuals' reaction to a stressor differs and is related to culture. Loss of a job can be regarded as a relief or a threat to one's financial integrity. One's capacity to cope can neutralise the pernicious effects of stressors. And, in fact, most individuals who experience a stressor or even a traumatic stressor do not go on to develop pathological states, e.g. posttraumatic stress disorder (PTSD), acute stress disorder (ASD), dissociation disorder (Strain and Casey 2016). No metric guidelines in the DSM-5 are given for the AD diagnosis except that the patient's reaction to the stressor is out of keeping with the degree of the stressor or with those beliefs held by the patient's culture and social context.

Furthermore, as Casey (2016) has argued there are no 'zones of rarity' when the ADs are examined; this contrasts for example with diabetes mellitus, where an A1C of 6 or more is considered to place the patient in a diabetic range (zones of rarity imply that there is a distinction between those who are ill and those who are not, with few in the intermediate zone). Hypertension has guidelines as does the prostatic serum antigen levels for prostate pathology. This lack of zones of rarity which places an individual into a normal range or in a potentially pathological range does not occur for many psychiatric diagnoses, but it remains a particular issue for the ADs in that there are no metric guidelines to assess symptoms, e.g. stressor, dysphoria, dysfunction, which makes it difficult for researchers to be in agreement with either the presence of or the severity of this disorder. Furthermore, all symptoms are given the same weight, and many psychiatric illnesses have the same symptoms. And all symptoms in the algorithm may not be required for the diagnosis (actually this is an example of the polythetic approach to diagnosis) (Casey and Strain 2016). The length of time a symptom is present also contributes to the variability in diagnostic certainty resulting in samples of patients under investigation to not be comparable.

(2) The second characteristic to make the diagnosis of AD requires that the patient have distress beyond that expected in their cultural or social context. Again, there are no guidelines in how to assess this 'distress' and when is it excessive enough to warrant being a component to make the diagnosis of AD?

(3) The third dilemma is the element of dysfunction which could be viewed in performance at work, school and/or in relationships. The fact is that for the ADs there are few check lists or valid and perhaps even reliable measures to assess the three constituents of the diagnosis. Succinctly, there is no measure to assess normality versus pathology with reliable or valid instruments for the ADs. To further complicate the accuracy of diagnosis there are two schools of thought in regard to dysphoria and dysfunction: American

(DSM-5) (APA 2013) and European (International Classification of Disease-11) (2018).

Maercker et al. (2007), drawing on the formulation of Horowitz, have proposed a different set of criteria than that stated by DSM-5, and which are to be included in the International Classification of Diseases-11 (ICD-11) in 2018: that the diagnosis of AD should include intrusive symptoms, e.g. involuntary stressful reminders, or excessive worrying/ruminating about the event, *and* avoidance behaviour, e.g. avoidance or repression of feelings and thoughts about the stressful event. This constructs the algorithm for ADs to be much closer to the symptom requirements for PTSD where both items were central in its diagnosis for DSM-III (APA 1987). Furthermore, Maercker and Einsle ascribe to the position that, in addition to the precipitation by a stressor, the individual being assigned the AD diagnosis must have *both* dysfunction and dysphoria, not *either/or* (Maercker et al. 2007).

The American position that it could be *either/or* emanates from a generalisable evidence base of research findings that are lacking to support the change proposed for the ICD-11. European workers feel strongly that the diagnosis should demand both dysphoria and dysfunction to qualify for the AD diagnosis (ICD-11 2018; Maercker et al. 2007). Still, other researchers argue that the AD subtypes are misleading, unnecessary and should be eliminated.

Therefore, psychobiological research is compromised if the researcher cannot be certain that they have an authentic diagnostic group or that their sample will be comparable to that of another researcher. There is no guarantee that researchers will be examining the same cohorts of patients. The diagnostic uncertainty is intensified when there is psychiatric and medical comorbidity. These confounds are major impediments to the psychobiological study and the advancement of understanding of this most important diagnosis. In fact, AD is one of the most commonly employed diagnoses in the DSM-5. It is the most frequently used diagnosis in the military, in children, and is frequently employed in the consultation–liaison psychiatry setting. However, it remains situated between normality and pathology and in essential need of further study.

Psychobiology of the ADs

As inferred from the preceding, the psychobiology of ADs may best be understood by examining stress effects on the central nervous system. The stress-related psychiatric disorders have been placed together whether they are associated with a traumatic or a non-traumatic stressor in the *Trauma and Stressor-Related Disorders section of the DSM-5 (2013)*. Strain and Friedman (2011) have reviewed the psychobiology that might apply to the ADs in an earlier publication. A useful biological context within which the pathophysiology of ASD, PTSD, anxiety disorders and ADs may be better understood is that proposed by Hans Selye (1956) based on his classic work on the key role of the HPA system in the human stress response. Such work has been updated by current, more sophisticated understanding of the neurocircuitry and psychobiological systems that mediate and moderate this response. Stress-induced alterations in HPA function are known in depression, PTSD, ASD and in other anxiety disorders (Maercker et al. 2007; DSM-III [APA 1987]; Maercker 2013; Maercker and Perkonigg 2016; Strain and Friedman 2011). Expanding on the suggestion by Maercker et al. (2007) to consider AD as a stress response syndrome, it would be important to know how the HPA system operates in the AD, and whether each AD subtype exhibits similar psychobiological alterations, or whether their psychobiology is more similar to the parent mood state, e.g. depression, anxiety.

With extensive research (Strain and Friedman 2011) on stress-related HPA reactions, it is likely that (at least some) AD subtypes are associated with altered HPA mechanisms, as is seen in the parent affective and anxiety disorders, e.g. MDD, generalised anxiety disorder. Since HPA changes are commonly found in chronic stress syndromes, depression, PTSD and anxiety disorders, overarching constructs such as allostatic load and cumulative physiologic effects of repeated, even minor stressors are a useful heuristic in these cases and may be important to understanding the psychobiology of the ADs.

And does the stress response that accompanies and precipitates ADs affect the hippocampus as McEwen et al. (2015b) have discovered in animal studies as another target for exploring the psychobiology of the ADs? That is glucose regulation, cognition, insulin resistance and the hippocampus? And, as mentioned above, McEwen et al. have also reported that the peptide/protein hormones (insulin-like growth factor 1 (IGF-1), insulin, ghrelin and leptin) are able to enter the brain and affect the hippocampus. Is this an effect seen in the psychobiological changes in the ADs?

In summary, in considering the ADs it remains to be determined if the psychobiological abnormalities seen in major depressive and anxiety disorders will also be found in the AD depressive and anxiety subtypes. Therefore, two important approaches to the psychobiological study, e.g. the HPA axis function of the ADs are: (1) to compare the subtype with its

Table 1. Critical elements of human resilience (Dennis Charney, MD, Dean, Icahn School of Medicine at Mount Sinai, New York, NY, Psychiatric Grand Rounds January 2009).

Character strengths and virtues
Altruism
Optimism
Moral compass/a code of honour
Faith/spirituality
Humor
Role models
Social supports
Facing fear/out of one's comfort zone
A life's mission
Training (in all its forms)

parent (e.g. AD with depressive mood with MDD); and (2) the subtypes with each other, e.g. AD with depressive mood against AD with anxiety. This would provide important psychobiological information in that if the AD with depressed mood had a similar psychobiology to MDD, treatment targeted for the latter may be applicable to the former (Selye 1956).

Chrousos and Gold (1992) and McEwen (2004) have examined the psychobiological differences between depression and chronic stress syndromes. Friedman and McEwen (2004) have done the same with respect to PTSD, as have others with regard to anxiety disorders. Overarching constructs, such as allostatic load, are useful in all cases. Furthermore, there is considerable overlap between depression, PTSD and certain anxiety disorders with regard to some associated biological abnormalities (e.g. endocrine, cardiovascular, metabolic, immunological, etc.). McEwen and Stellar (1993) hypothesised that the cumulative impact on health risk from modest dysregulations in multiple systems can be substantial, even if they individually have minimal and insignificant health effects. Thus, they defined allostatic load as a cumulative measure of physiological dysregulation over multiple systems. These relationships are far from simple and there may also be some differences between specific Axis 1 psychiatric disorders and chronic stress with regard to these findings. Extending this argument to ADs, it is not fully known whether psychobiological abnormalities associated with depression will be seen in the AD depressive subtype, and whether alterations found in anxiety disorders will be found in the AD anxiety subtype.

Psychobiology of resilience

Current genetic findings regarding individual differences with regard to vulnerability and resilience may be another research avenue to consider. Kilpatrick et al. (2007) have demonstrated that individuals with the short allele of the serotonin transporter gene (5-HTT LPR) who had high hurricane exposure and low social support were at greater risk for developing PTSD than a matched cohort with the long allele of this gene. This study replicates several trials regarding gene × environment interactions in depression (Dienstbier 1989; Friedman and McEwen 2004; McEwen 2004), and raises the critical question of post-stress/traumatic/depressive vulnerability versus resilience. It has been shown that most people exposed to traumatic events or stressors, e.g. losses, do not develop PTSD, depression or anxiety disorders (Kessler et al. 1995). Although data are lacking, it is reasonable to suggest, by extension, that most people exposed to traumatic or non-traumatic stressful events do not develop AD or another psychiatric disorder. This raises a number of questions. Do the same genetic differences determine vulnerability versus resilience in depression, PTSD, other anxiety disorders, and the ADs?

Southwick and Charney (2012) have described in great detail, using several paradigms, the psychological tools for enhancing resilience and the biological correlates which are affected with acute stress (Tables 1 and 2). They further relate in their tables how these biological correlates are affected by resilience. This paradigm of elucidating the psychological variables that can enhance resilience and their accompanying biological correlates is instructive in considering how the ADs may be aided and abetted with treatment or self-improvement. If it is assumed that the ADs are caused by traumatic or non-traumatic stress, and that these biological phenomenon are then consequences of the stress(ors), then psychological treatment and pharmacological agents may have the outcome of restoring psychological well-being, and a return to normal of the dysphoria and dysfunction as well as the various biological processes affected by stress, e.g. cortisol, dopamine, serotonin, etc. Southwick and Charney (2012) offer a seminal contribution to human resilience (Tables 1 and 2). These authors described the important biological dimensions that were altered with stress and the changes that needed to occur with resilience.

Conclusion

Are the same psychobiological mechanisms involved in resilience seen in ADs and other psychiatric conditions (Southwick and Charney 2012; Haglund et al. 2007)? Does AD exhibit shared neural substrates, familiarity, genetic risk factors, environmental risk factors, biomarkers, temperamental antecedents and/or abnormalities of cognitive or emotional processing as people with depression, PTSD, ASD or anxiety disorders? Finally, will treatments that effectively produce clinical

Table 2. Neurochemical response patterns to acute stress (Dennis Charney, MD, Dean, Icahn School of Medicine at Mount Sinai, New York, NY, Psychiatric Grand Rounds January 2009).

	Key functional interactions	Resilience	Psychopathology
Cortisol	Increases amygdala CRH Increases hypothalamic CRH	Stress induced increase constrained by negative feedback via GR and MR receptors	Unconstrained release leads to hypercortisolemia, depression, hypertension, osteoporosis, insulin resistance, coronary vascular disease. Over constrained release leads to hypercortisolemia – seen in some PTSD patients
DHEA	Antiglucocorticoid actions	High DHEA cortisol ratio may have preventive effects regarding PTSD and depression	Low DHEA response to stress may predispose to PTSD and depression and effects of hypercortisolemia
CRH	CRH-receptor-1 anxiogenic CRH-receptor-2 anxiolytic Increases cortisol and DHEA Activates LC-NE system	Reduced CRH release adaptive changes in CRH-1 and CRH-2 receptors	Persistently increased CRH may predispose to PTSD and major depression, may relate to chronic symptoms of anxiety, fear and anhedonia
Locus coeruleus norepinephrine system	Activates sympathetic nervous system and HPA axis, inhibits parasympathetic outflow, stimulates hypothalamic CRH	Reduced responsiveness of LC-NE system	Unrestrained LC-NE system leads to chronic anxiety, hypervigilance and intrusive memories. Some patients with PTSD, panic disorder and major depression show evidence of heightened LC-NE activity
Neuropeptide Y	NPY reduces CRH related actions at amygdala, NPY reduces LC firing rate	Adaptive increase in amygdala NPY is associated with reduced stress-induced anxiety and depression	Low NPY response to stress associated with increased vulnerability to PTSD and depression
Galanin	Galanin reduces the anxiogenic effects of LC-NE system activation	Adaptive increase in amygdala galanin is associated with reduced stress-induced anxiety and depression	Hypothesized low galanin response to stress associated with increased vulnerability to PTSD and depression
Dopamine	Reciprocal interactions between cortical and subcortical DA systems	Cortical and subcortical DA systems remain in optimal window of activity to preserve functions involving reward and extinction fear	Persistently high levels of prefrontal cortical and low subcortical DA activity associated with cognitive dysfunction and depression. Persistently low levels of prefrontal DA associated with chronic anxiety and fear
Serotonin	High levels of cortisol decrease in 5HT1A receptors	High activity of postsynaptic 5HT1A receptors may facilitate recovery	Low activity of postsynaptic 5HT1A receptors may predispose to anxiety and depression

remission in anxiety disorders, PTSD, ASD or anxiety disorders also be effective for the respective subtype of AD? Hopefully, the HPA heuristic may provide a useful psychobiological context within which to encourage both basic research and clinical trials that will enhance our general understanding of the relationship between stress response syndromes, depression, PTSD, anxiety disorders, and the ADs. In addition, such investigations should also provide a theoretical context within which to investigate different therapeutic approaches for the different AD subtypes including psychotherapies and pharmacological interventions.

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No potential conflict of interest was reported by the author.

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