

STRESS AND EPILEPSY: FACT OR FICTION, AND WHAT SHOULD YOU DO ABOUT IT?

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ABSTRACT

People with epilepsy report stress as the most common trigger for their seizures and some believe it caused their epilepsy in the first place. The link between stress and epilepsy has been studied in extensively in preclinical, epidemiological and clinical studies with at times confusing results, and clinical studies in particular fraught with confounders. However there is little doubt that stress is bad for health in general, and there is now a substantial body of pre-clinical evidence suggesting that chronic stress can worsen seizures in established epilepsy, in selected cases may even be a causal factor in epilepsy. Taken together it is surely time for healthcare professionals working with people with epilepsy to pay more attention to stress in clinical practice, in which context some practical advice and guidance for screening and management are provided

INTRODUCTION

It is increasingly recognized that providing good care for people with epilepsy is about much more than ensuring optimal seizure control and minimizing side effects of antiepileptic drugs, particularly so in those who have on-going seizures despite our best efforts¹. Psychological and psychiatric comorbidities in particular have consistently been shown to be strongly associated with health-related quality of life and costs in epilepsy² but remain frequently undetected and undertreated. Stress is the most commonly reported trigger for seizures in people with epilepsy, and sometimes put forward as the cause of their epilepsy. Stress is not a new phenomenon of course, experienced by all (**Figure 1**) at some point, and increasingly portrayed in the media as a plague of modern life, as any quick internet search will illustrate. How often have you had a patient report that their recent seizure was triggered by stress and responded with simple reassurance or an increase in medication? Or dismissed the claims of a patient that their epilepsy is as a result of a difficult childhood, concentrating instead on the MRI result? Unless you can honestly say never to both, this article is for you. The following is based on a comprehensive review of all articles identified from a search the terms “stress” together with “seizure” and/or “epilepsy” on PubMed and Web of Science databases, together with hand searches of the articles cited there in.

WHAT IS STRESS?

Stress is defined as the physiological and/or behavioural response to an event or events that are interpreted as threatening to the individual. The psychology and biology of stress are now well understood (**Figure 2 and Box 1**). Stress occurs when environmental demands exceed an individual's adaptive capacity resulting in psychological and biological changes. Stress is a process that involves stressors, stress appraisal and stress responses³. Physiological stressors (e.g. pain) are appraised by brainstem and hypothalamus, whereas complex emotional and experiential stressors are appraised in multiple limbic forebrain structures with inputs from higher order sensory processing and memory⁴. Both systems activate the paraventricular nucleus of the hypothalamus and the brainstem via direct projections and the limbic system indirectly. The paraventricular nucleus releases corticotropin-releasing hormone which activates both the sympathetic adrenergic pathway of the autonomic nervous system and the hypothalamic-pituitary-adrenal axis. Sympathetic activation increases both circulating adrenaline (primarily from the adrenal medulla) and noradrenaline (primarily from the sympathetic nerves). The resultant behavioural changes include the largely protective fight or flight reactions, but can become maladaptive including increased eating, smoking, drug use, and increased vigilance leading to anxiety and worrying. In the hypothalamic-pituitary-adrenal axis, both corticotropin-releasing hormone and vasopressin released into the portal system stimulate the anterior pituitary to produce adrenocorticotrophic hormone. This in turn stimulates the adrenal cortex to release cortisol which promotes the mobilization of stored energy, and potentiates several sympathetically mediated effects. Thus both systems are working in a complementary fashion, with additional feedback loops to terminate the response, and influence appraisal and thus adaptation.

Box 1: Stages and terminology of stress

STRESSOR: events or experiences objectively associated with threat. Physical (e.g. pain, fatigue), psychological (e.g. fear, sadness), environmental (e.g. temperature, noise). Most stress reported by patients is psychosocial.

APPRAISAL: The assessment of threat in the context of individual coping resources/adaptive capability. This may involve conscious and subconscious mechanisms.

RESPONSE: The resultant biological and behavioural changes involving activation of autonomic and endocrine pathways. These can be adaptive ('fight or flight'), but can become maladaptive including e.g. increased eating, smoking and hypervigilance leading to anxiety

The time course of the stress and our response is crucial (**Figure 3**). The acute stress response evolved as adaptive process to allow the body to maintain a constant internal state in the face of a changing environment (allostasis), and in moderation is beneficial. However, when stress is excessive, the cost of reinstating homeostasis can become too high with potentially harmful consequences. This inappropriate stress response, or "allosteric load"⁵ produces a vulnerable phenotype and leaves genetically predisposed individuals at increased risk of chronic diseases, both psychiatric and physical. Chronic stress can be created by different situations e.g. stress event sequences e.g. fired from job, chronic intermittent stressful events e.g. conflict with neighbours or ongoing chronic stress conditions including living with disability.

DOES STRESS CAUSE SEIZURES/EPILEPSY? CLINICAL EVIDENCE

In retrospective studies, stress is consistently identified as a major seizure trigger in between 10-83% of people with epilepsy from across the world including UK, USA, Australia, Singapore, Brazil and Scandinavia, in both tertiary and community settings⁶⁻⁸. Stressful life events have also been described as trigger for new onset seizures⁹, and patients with epilepsy who report stress as a seizure trigger are more likely to have early life stress from childhood traumatic experiences, particularly emotional abuse¹⁰. However such studies are inherently dependent on patient perception and memory, and often have inherent selection biases, so methodologically unreliable. Loss of self-control is the most disturbing psychosocial consequence of epilepsy and trying to find connections between their seizures and external or internal events that give a feeling of predictability is a natural likely coping mechanism¹¹.

Seizures and epilepsy have also been studied following traumatic events. For example as reviewed elsewhere⁶ people evacuated due to flooding in the Netherlands had more seizures compared to controls; Similarly a study of children with epilepsy during and after the 1991-1992 Croatian War showed that those from directly affected areas had more seizures than before the war and those from unaffected areas. The actual numbers, however, are small (between 30 and 60 per group), the studies are retrospective, and stress is inferred rather than confirmed/measured. Furthermore, disasters on this scale are very prone to confounding factors such as non-adherence with medication and sleep

deprivation as was found during a study in Persian Gulf War. A large Danish population based national registry showed 50% increased risk of developing epilepsy in bereaved parents and this could not be explained by sociodemographic factors, and is truly population based, though the effects of potential lifestyle confounders such as alcohol and substance abuse, and misdiagnoses could not be excluded. A retrospective analysis of medical information and duty assignments (combat, maintenance or administrative) from over 300,000 compulsorily drafted Israeli Defence Forces males followed for 30 months showed that the risk of new onset seizures was slightly higher in the “high stress” combat than other units. However, in those with previous or current epilepsy there was no effect on risk of seizure recurrence.

In terms of prospective studies, these are few and hampered by a lack of clear definitions and standardized assessment tools. Stressful verbal stimuli presented to healthy controls has been shown to produce subtle EEG changes (narrowing of the bandwidth and regional changes in frequency) of sufficient magnitude that a blinded reviewer could correctly identify 92% of stress stimuli on EEG alone¹². Similarly in people with a variety of epilepsies, stressful interviews induced changes (exaggerated spiking, paroxysmal activity or epileptiform complexes) in the majority¹³ and there are case series of stress inducing audio/video recordings inducing seizures in patients with temporal lobe epilepsy in particular¹⁴. There are few larger or longer term truly prospective studies some of which show increased risk of seizures with stress¹⁵ and some where the effect of stress could not be separate for the effects of confounders such as sleep deprivation, alcohol and missed medication¹⁶.

Thus, although there is reasonable support from clinical studies that stress might lower seizure thresholds, it is difficult to separate the effects of stress per se from confounders such as sleep deprivation, alcohol and missing medication or to separate cause from effect. In addition, as highlighted by one of the most recent prospective studies, it is often difficult to disentangle between the subjective perception of stress and other premonitory sensations preceding seizures or mood disorder symptoms¹⁷. In fact, changes in the brain preceding a seizure might increase patient perceptions of stress and anxiety rather than the converse.

DOES STRESS CAUSE SEIZURES/EPILEPSY? NEUROBIOLOGICAL EVIDENCE

It is interesting to note that evidence from pre-clinical animal studies suggests that acute stress is anticonvulsant and protects from seizures although results vary in different models¹⁸. The largest group of experiments is in rodent models exposed to swim stress creating both physical and psychological stress. If the seizures were induced by a gamma-aminobutyric acid-A antagonist, acute stress was anticonvulsant, but exacerbated electroconvulsive shock seizures, and had no effect on various other models. The anticonvulsant effects are most likely mediated via neuroactive steroids acting at gamma-aminobutyric acid-A receptors, that change subunit expression following acute stress, increasing inhibition and decreasing seizure activity¹⁹. Conversely, as we will go on to discuss chronic stress, either in early life or over time in adulthood, has been shown consistently to influence brain excitability and seizure susceptibility at all stages in the development of epilepsy (**Figure 4**) in a broad range of models, acting as an initial insult, decreasing the latent period and increasing seizure frequency in established epilepsy¹⁹⁻²¹. There are a range of mechanisms which may underpin this association (**Figure 5**), which we will go on to discuss.

Early life stress

Pre-clinical studies clearly show that early life stress predisposes the brain to provoked seizures and to later epilepsy. For example, if pregnant female rodents are stressed (e.g. by restraint, bright lights or injections), it is easier to induce seizures several weeks later in the pups in response to kindling, audiogenic stimuli and chemoconvulsants. Similarly, postnatal stress induced by separation of pups from their mother renders the pups more susceptible to later seizures with kindling and chemoconvulsants²⁰. Possible mechanisms underlying the link between early-life stress and epilepsy are:

- (i) Changes in connectivity, function and structure of neuronal circuitry that acts as a first hit and lowers the insult needed in later life to trigger epileptogenesis e.g by hyperexcitable neurotransmission due to decreased gamma-aminobutyric acid inhibition, changes in neural structure due to corticotropin-releasing hormone elevation, damage from inflammation, decreased brain derived neurotrophic factor or delayed white matter development²².
- (ii) Impaired stress response due to a hyperactive hypothalamic-pituitary-adrenal axis with abnormal negative feedback, as reviewed in²⁰. The hippocampus normally acts to shut off the hypothalamic-pituitary-adrenal axis but excessive exposure to glucocorticoids can cause the hippocampus to shrink, disinhibiting the hypothalamic-pituitary-adrenal axis and resulting in a vicious cycle of unopposed allostatic load. There is evidence of HPA axis dysfunction with epilepsy in rodent models with acutely provoked (kindled) seizures as well as in clinical studies of status epilepticus, although antiepileptic drug treatment is a potential confounder in all the clinical studies. Functional imaging studies in humans are also now starting to examine the link between cortical and physiologic responses to stress and the relationship between seizure control in epilepsy and both the hypothalamic-pituitary-adrenal axis and functional MRI signal reactivity²³.

Chronic stress in adulthood

Animal models consistently show an increase in seizure risk²¹ during and following chronic stress. Chronic stress may render the brain more susceptible to unprovoked seizures, or at risk of more severe or frequent seizures in the event of an additional trigger.

This may occur by two possible mechanisms:

- (i) Decreasing the latent period of epileptogenesis. Many of the processes thought to underlie epileptogenesis are potentiated by chronic stress including inflammation²², abnormal neurogenesis and synaptic plasticity²⁴.
- (ii) Increasing brain excitability via an increase in excitatory glutamatergic transmission, in intrinsic neuronal excitability and/or shift in gamma-aminobutyric acid-ergic inhibition²¹²⁵, likely mediated via neurosteroids¹⁹. This phenomenon would increase the baseline excitability and therefore would keep the brain activity closer to the seizure threshold.

IF STRESS IS IMPORTANT, CAN WE TREAT IT?

UK guidance highlights the importance of ensuring people feel supported to manage their condition, and improved functional abilities as key areas for enhancing quality of life, and specifically includes stress as a topic that patients should receive information on²⁶. Guidelines also recommend that both psychologists and psychiatrists are part of a multidisciplinary epilepsy team at least at tertiary centres, but there is little clarity beyond that, and of note no psychiatric/psychological outcomes in proposed USA²⁷ or UK²⁸ quality standards for epilepsy care.

In this context, it is important to recognize that the management of stress can be both distinct from that of comorbid anxiety, depression or other psychiatric disorders, but that there are also complex multidirectional relationships between stress and these disorders. It is well known that stressful events can precipitate depression or anxiety, but attempting to dissect out the causal relationships between seizures, stress, anxiety, depression and other confounding factors such as sleep deprivation has yielded sometimes conflicting results. A longitudinal cohort study of over 400 community recruited patients using a range of validated scales applied retrospectively at two time points looked in detail at the interaction of anxiety, depression and perceived stress on seizure frequency and concluded that depression underpinned the relationship²⁹. In contrast, two cross sectional studies, both of over 200 patients attending an epilepsy centre⁷³⁰, 50 – 80% respectively of whom reported stress as a seizure trigger, concluded that anxiety was the most important factor. Others have shown a high correlation between stress, sleep deprivation and fatigue³¹, though others³² including a more methodologically robust multivariate analysis of prospective paper diaries collected over up to 1

year¹⁵, albeit in smaller numbers (n=71), concluded that sleep deprivation, anxiety and stress were all independent predictors of seizure occurrence. It should go without saying (but we will say it anyway) that active treatment of any comorbid psychiatric disorder is strongly recommended, and of established importance both to seizure control and quality of life¹. What we will now discuss is the evidence base for treating stress per se.

NON PHARMACOLOGICAL TREATMENTS

Stress is a fact of life, and often the result of non-modifiable factors, so the treatment of stress primarily relies on psychologically based treatments to restore a sense of control over emotions, and down regulation of the biological response mechanisms. Stress is universal but there is variability in source, quality of experience, and acceptability of various treatment methods according to cultural influences. Western culture has a mechanistic explanation of stress reflected in relaxation, biofeedback and cognitive techniques. Asian cultures have a somatic expression of stress giving a somatic focus with treatments such as with yoga and mindfulness. There are a broad range of techniques many of which have been studied in epilepsy with positive results (BOX 2).

BOX 2: PSYCHOLOGICAL AND MIND-BODY TREATMENTS OF POTENTIAL BENEFIT FOR STRESS IN EPILEPSY

- **COGNITIVE BEHAVIOURAL THERAPY:** A range of techniques which essentially involves teaching and reinforcing self-monitoring of thoughts and emotions, identifying automatic thoughts that accompany distressing emotions, learning about different types of cognitive distortions, and working towards reducing intrusive thoughts, and/or separating them from the anxiety that they produce
- **BIOFEEDBACK** is a process that enables an individual to learn how to change measured physiological activity such as EEG or galvanic skin responses for the purposes of reducing seizure frequency. Rapid and accurately feedback physiological data is presented in conjunction with identifying changes in thinking, emotions, and behaviour
- **MINDFULNESS** is simply paying attention to moment-by-moment experience in an open and non-judgemental way-practising awareness of sensory and mental experiences as they happen
- **YOGA** is an ancient Indian, non-religious, mind–body approach that has components centring on meditation, mindfulness, breathing, and activity or postures
- **ACCEPTANCE AND COMMITMENT THERAPY** is an empirically-based psychological intervention that uses acceptance and mindfulness strategies mixed in different ways with commitment and behaviour-change strategies, to increase psychological flexibility

There are numerous challenges to undertaking intervention studies in this area including in relation to blinding, sham controls and powering when the potential effect size is unknown, but as has been reviewed in more detail elsewhere³³, evidence of potential benefit is now beginning to accumulate. For example, a recent assessor-blinded randomised control trial (n=60) demonstrated that 4 week bi-weekly mindfulness compared to social support was associated with clinically important improvements in quality of life, and reductions in seizure frequency in drug-resistant epilepsy³⁴. A Cochrane review of Yoga³⁵ in epilepsy found yoga treatment was better than no intervention or interventions other than yoga (postural exercises mimicking yoga). Also that acceptance and commitment therapy was of comparable efficacy to Yoga, though as pointed out by the authors all the studies included are open and small (18-32 participants), so no reliable conclusions can be drawn. A meta-analysis of EEG-biofeedback studies in drug-refractory patients³⁶, extracting data from 10 of at that time 63 such studies which had been undertaken, found that 74% of patients (n=87) responded, with significant (61%) reduction in median seizure frequency overall. More recently, a small study (n=11) using skin conductance biofeedback has shown promising initial results, with an almost 50% reduction in seizure frequency over 12 sessions³⁷. Although a 2008 systematic review³⁸ of psychological treatments in epilepsy found no evidence of benefit, this largely reflected methodological deficiencies and the limited number of studies included. In more recent studies cognitive behavioural therapy approaches have been associated with significant (>50%) reductions in seizure frequency (37%) in a uncontrolled retrospective studies (n=60)³⁹, and in a small (n=37) open randomised control trial compared to relaxation⁴⁰, though an also small (n=27) single blinded randomised control trial of cognitive behavioural therapy versus counselling and wait list showed no significant change in seizure frequency⁴¹. In all the above the study interventions are often time intensive (1-2 sessions/week over 4-8 weeks, sometimes with daily home-programs), with subsequent follow up for only a few weeks, although one long term follow up study, 10 years after a biofeedback intervention demonstrated sustained benefit in the responders, albeit with only 19 of the original 41 participating in the later study⁴².

Neither hypnosis nor stress inoculation therapy, widely used in other contexts have been studied in terms of effects on seizure frequency in epilepsy. Similarly for eye movement desensitization and reprocessing, a psychotherapy that emphasizes disturbing memories as the cause of psychopathology and often used in the treatment of post-traumatic stress disorder, there is very limited evidence for its utility in epilepsy with only case reports and some caution must be used as there is the report of reactivated seizures⁴³.

PHARMACOLOGICAL TREATMENTS

There is of course no pharmacological treatment of stress per se, though psychoactive agents are often indicated in the context of stress-related psychiatric conditions. The Diagnostic and Statistical Manual of Mental Disorders, fifth edition identifies a specific category named "Trauma and stressor-related disorders" and major diagnostic categories are represented by acute stress disorder, post-traumatic stress disorder, adjustment disorder and reactive attachment disorder. The treatment of these conditions is obviously not part of the aims of this review. However, it is worth mentioning that although several antiepileptic drugs have been tested in post-traumatic stress disorder and related disorders, the majority of such studies are uncontrolled leading to a low level of evidence⁴⁴. If we consider the broad chapter of anxiety disorders in general, Pregabalin is the only antiepileptic with good clinical evidence and currently licensed also for the treatment of generalised anxiety disorder⁴⁴.

IMPLICATIONS FOR CLINICAL PRACTICE

So what does this all mean for clinical practice now? Whatever the mechanisms and uncertainties about strength of association, stress clearly matters to patients, can impact on mood and quality of life, and there is biological plausibility in terms of potential influence on seizure control. At the very least we should actively acknowledge this. A range of validated screening tools can detect relevant symptoms and be easily incorporated into routine practice, for example with short questionnaires

completed in the outpatient waiting room prior to appointments¹, and this sort of proactive attention to symptoms of than seizures has been shown to be of benefit to patients⁴⁵. Stress is also something which in our experience patients often readily volunteer, yet may be disregarded in a busy clinic, perhaps also influenced by the clinician helplessness in the face of weak evidence, and lack of resources for psychotherapeutic or behavioural support. There are however a wealth of self-help resources in this field, and many people will anyway seek complementary therapies privately. We suggest as a starting point any service could at least compile a list of local resources and recommend reading/self-help website about stress management to offer to those in whom stress is identified as a potential issue. In this context, particularly if the patient will be expending time or money on any intervention we recommend offering support in defining outcome measures and time frames for that individual as a “trial of treatment”, just as is routine practice when changing antiepileptic drugs. However, patients and providers may have very different perspectives, and recognizing individual goals and patient input when negotiating any program requiring self-management is of fundamental importance to success⁴⁶. On the other hand, it is already well established that chronic stress is bad for health and quality of life, and improved by stress reduction strategies so perhaps we should stop trying to prove the benefits in epilepsy, and start by promoting what is known in more general terms as part of holistic care.

WHAT NEXT FOR STRESS AND EPILEPSY?

There has already been an increasing emphasis on individualized therapy for epilepsy in recent years, recognizing that the epilepsies are diverse with multiple genetic and structural/metabolic causes. Brain connectivity and responses to stress are likely to vary in different epilepsy types. For example, stress is thought to be of particular importance in temporal lobe epilepsy, and the decreased functional connectivity in this group⁴⁷ might reflect underlying network abnormalities resulting in epilepsy that also affect their response to stress. In support, one recent case control study (n=23 each group) in left-sided temporal lobe epilepsy has shown a significant relationship between seizure control and both the hypothalamic-pituitary-adrenal axis and functional MRI signal reactivity to acute psychosocial stress⁴⁸. The very nature of psycho-behavioural treatments requires some personalization to reflect individual stressors, appraisal and response patterns and coping resources which will also vary considerably from person to person. Designing and delivering good clinical studies in the face of these challenges is a daunting prospect, even before issues relating to blinding, cost effectiveness and cost-utility are taken into account. Potential new pharmacological treatments seem a more attractive prospect on this background. Neurosteroids, specifically ganaxolone and allopregnanolone which are potent allosteric modulator of gamma-aminobutyric acid-A receptors are currently under investigations as antiepileptic drugs¹⁹, with parallel studies underway in post-traumatic stress disorder and severe postpartum depression. It is also worth mentioning that vagal nerve stimulation, an established treatment for epilepsy with known effects on the autonomic nervous system is also likely to also influence stress. Non-invasive transcutaneous vagal nerve stimulation in healthy individuals during functional MRI has been shown to cause widespread decreased activation to high threshold stimulation in emotional/stress related regions of the limbic system, associated with significant improvements in well-being afterwards compared to sham stimulation⁴⁹, so perhaps we have been treating stress in our vagal nerve stimulation patients for some time without realising it.

Box 3: Key points

- Stress is the most commonly reported trigger for seizures in people with epilepsy
- Clinical and especially pre-clinical evidence supports an association between stress and epilepsy, though clinical studies are often confounded by factors such as sleep deprivation, alcohol and missing antiepileptic medication
- Acute stress is anticonvulsant, but chronic stress in early life or adulthood promotes epileptogenesis and seizures. An imbalance of the autonomic nervous system and hypothalamic-pituitary-adrenal axis dysregulation is believed to lead to dysfunction in limbic gamma-aminobutyric acid and glutamate pathways
- Subgroups of people with epilepsy are likely sensitive to stress as a result of a combination of genetics, early life stress exposure and syndrome specific brain connectivity
- A range of psychological and mind-body behavioural treatments for stress have a potential role in improving seizure control and quality of life in epilepsy, though large well controlled studies are lacking.

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'Why the modern world is bad for your brain'
www.theguardian.com 18 Jan 2015

'Modern life means stress can hit before you even leave the bedroom' The average Brit experiences 14 bouts of stress every day, research reveals' www.express.co.uk 12 Aug 2014

'How to beat stress: a complete and relaxing guide' www.telegraph.co.uk 29 Oct 2015

'That foggy feeling the "new epidemic of modern life"' www.irishnews.com 28 Oct 2015

'Stress and fatigue hit one in three workers as modern life wears us out' www.mirror.co.uk 23 Sept 2015

Figure 1: Stress at work and in life
 Stress authors working on this paper (top), and a selection of headlines from recent UK newspapers.
 170x192mm (300 x 300 DPI)

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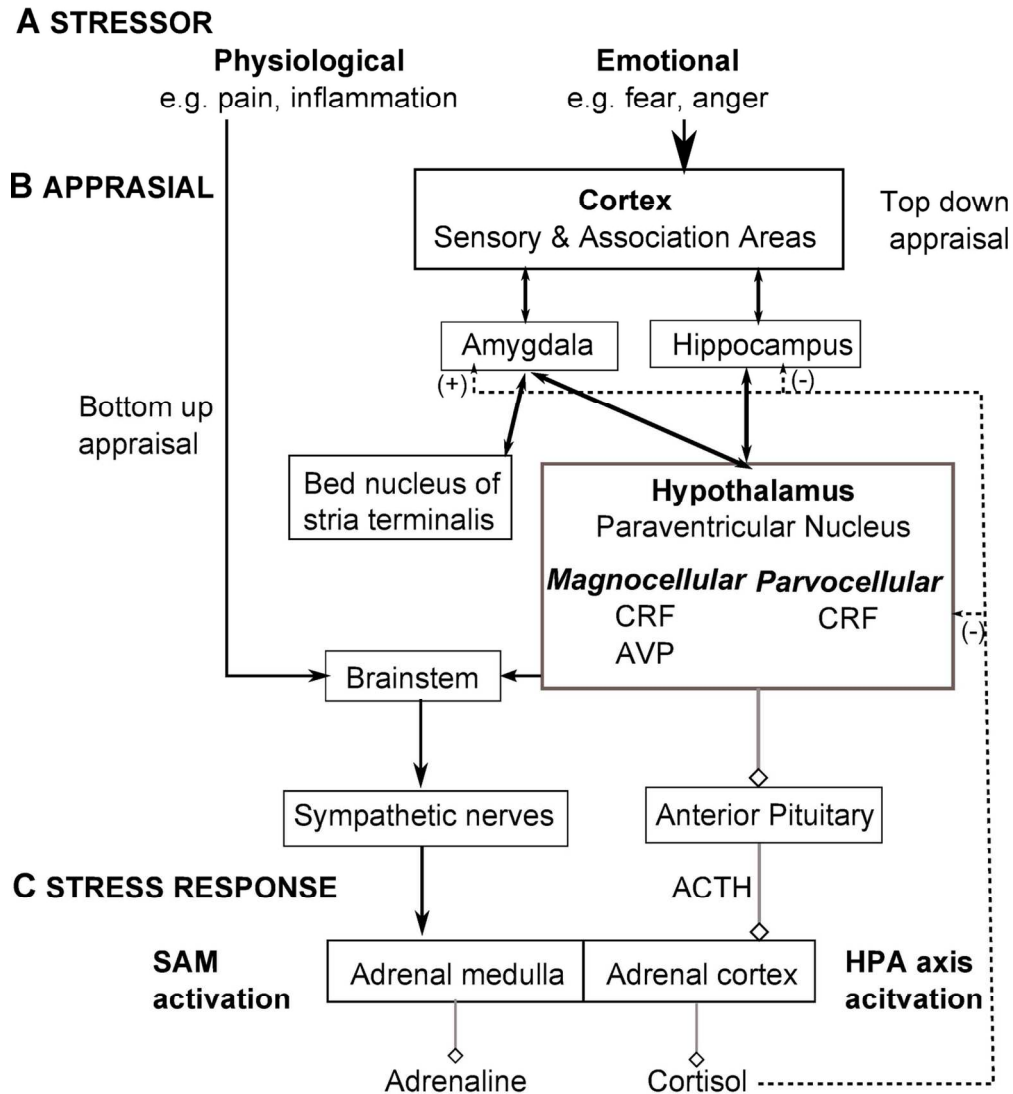


Figure 2: Anatomy and Physiology of Stress

Stress is the non-specific response of the body to any demand for change, and has multiple components.

PVN = paraventricular nucleus of the hypothalamus; CRH = corticotropin-releasing hormone; CRH1 and CRH2 receptors; SAM = sympathetic adrenergic pathway of the autonomic nervous system; HPA = hypothalamic-pituitary-adrenal axis; AVP = vasopressin; ACTH = adrenpcorticotrop hormone. For other definitions and examples see box 1. Reproduced with kind permission from Springer International:

Neuropsychiatry of Epilepsy, Chapter 15 Stress and epilepsy, 2016, Galtrey CM and Cock HR, figure 15.2 © Springer International Publishing Switzerland 2016.

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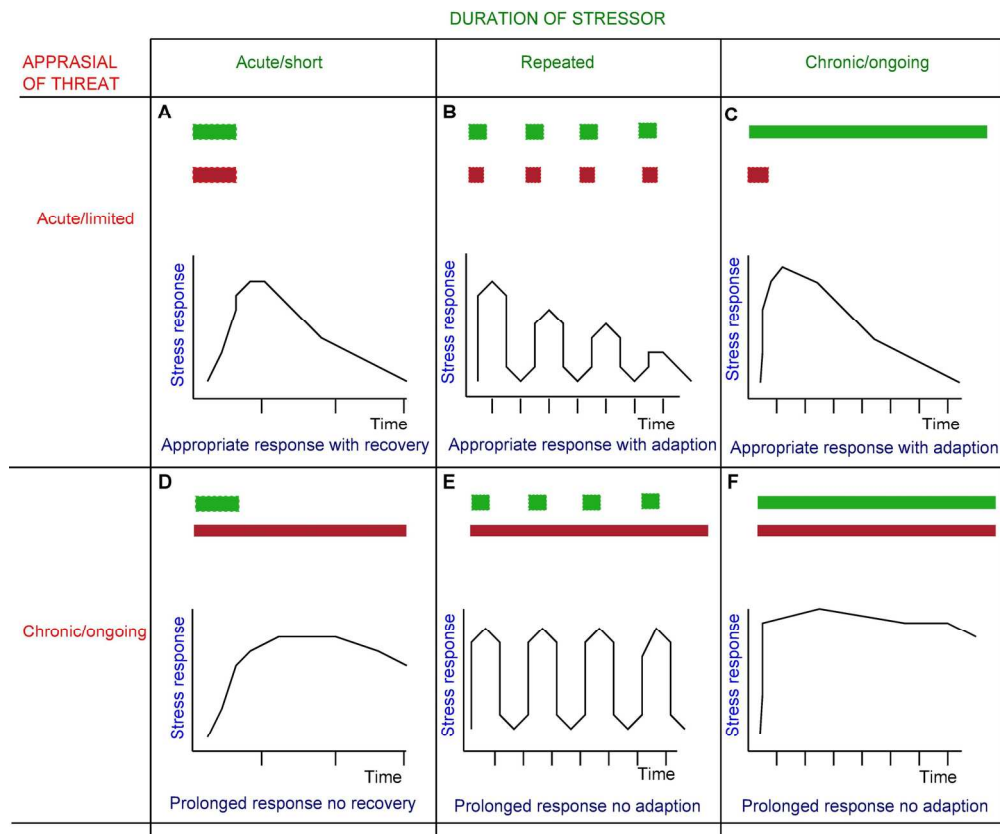


Figure 3: Normal and maladaptive responses to acute and chronic stress
 The combination of acute (A and D), repeated (B and E) or chronic (C and F) stressors (green) with an appraisal of either acute or limited (A to C) or chronic (D to F) threat (red) can produce differing stress responses (blue) which can be acute with appropriate recovery (A) or adaption (B and C) or chronic and maladaptive with no recovery or adaption (D to F).
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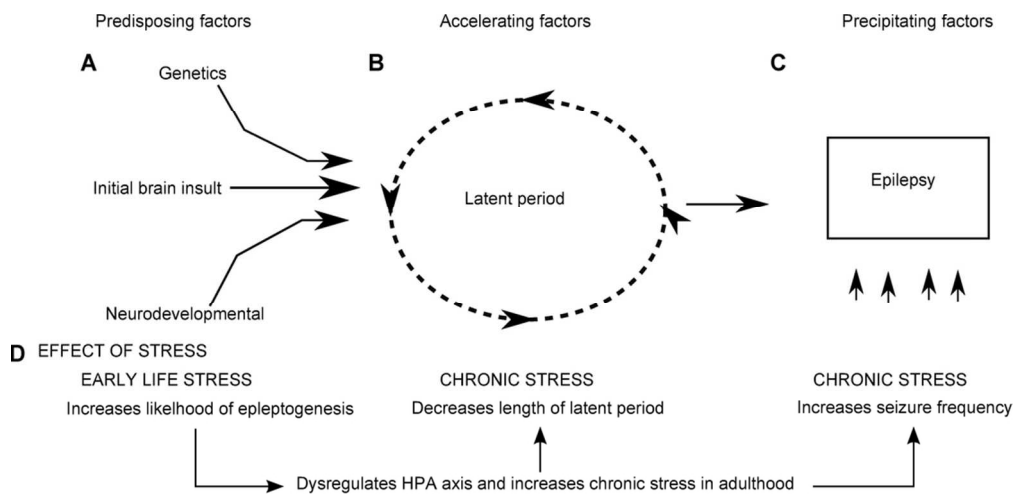


Figure 4: Stress and epileptogenesis

Epileptogenesis is the process by which the previously normal brain is functionally altered and biased towards the generation of the abnormal electrical activity that subserves chronic seizures. The initial predisposing brain insult (e.g. genetic, neurodevelopmental, trauma, infection or stroke), may itself seizures (e.g. febrile convulsions or prolonged status epilepticus). This is followed by a latent period during which the brain is altered by progressive cellular and network changes to create an epileptic brain. The latent period may last days or years, or in some instances be indistinguishable from the insult. Stress can affect each of these stages.

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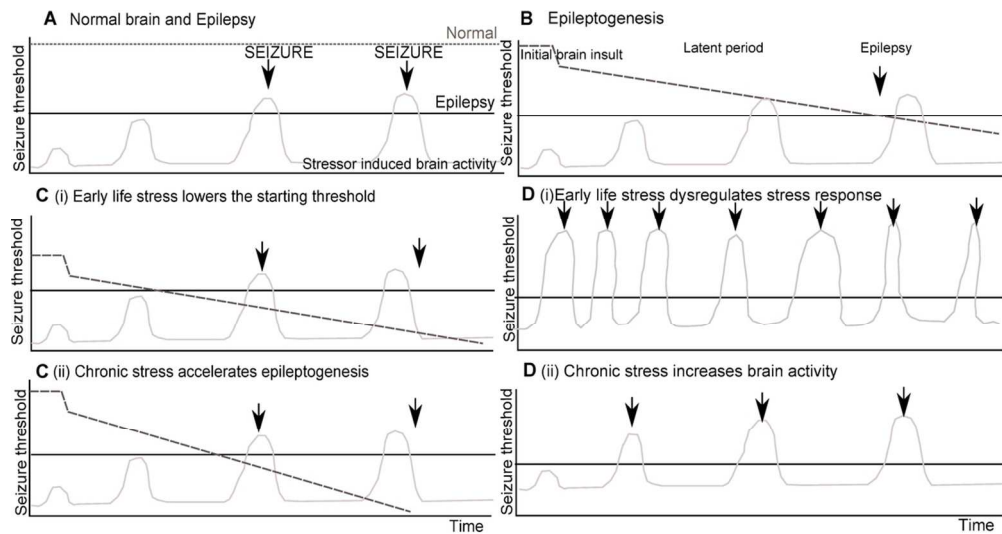


Figure 5: Potential mechanisms by which stress promotes seizures

_____ seizure threshold at which unprovoked seizures may occur (= epilepsy)

----- seizure threshold in an individual over time

_____ brain activity fluctuations in response to stress ↓ seizure

A. Normal brain and stable epilepsy: Extreme physiological challenges (e.g. hypoxia, hypoglycaemia) may trigger in a "normal brain" (acute symptomatic seizures, not shown). In a person with epilepsy, seizures occur at a lower threshold and are by definition unprovoked, though may be triggered at this lower threshold by lesser events, which may include stress.

B. Standard model of epileptogenesis: Following an initial predisposing insult and latent period an individual's seizure threshold decreases to a point where previously tolerated stressors now trigger seizures. This threshold may continue to decrease after the onset of epilepsy.

C. (i) Early life stress lowers the starting threshold or (ii) Chronic stress accelerates epileptogenesis resulting in a vulnerable phenotype that develops seizures/epilepsy earlier or in response to milder stressors.

D (i). Early life stress dysregulates stress response: Early life stress has minimal effect on the background threshold, but alters the HPA axis so that background and/or stress responses, and their effects on brain activity are exaggerated resulting in seizures.

D(ii) Chronic stress increases brain activity increases background brain activity such that seizures are triggered more readily, including by fluctuations that would not previously have been ictogenic.

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