

**Chronic Stress as a Causal Contributor to Epilepsy: How Years of Hypothalamic–
Pituitary–Adrenal Activation Lowers the Seizure Threshold**

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Abstract

Stress is the most frequently reported seizure precipitant among people living with epilepsy, but the more consequential question is whether stress sustained over years participates in the development of epilepsy itself. This paper argues that chronic stress lasting five or more years is a causal contributor to epileptogenesis rather than an incidental correlate. Evidence from cellular neuroscience, animal models, and population studies converges on a coherent causal pathway: prolonged hypothalamic–pituitary–adrenal axis activation delivers sustained corticosteroid and corticotropin-releasing hormone signalling to the hippocampus and amygdala, which remodels dendritic architecture, suppresses dentate gyrus neurogenesis, depletes the neurosteroids that positively modulate GABA-A receptors, and primes a microglial inflammatory response that increases blood–brain barrier permeability. Each change shifts the excitation–inhibition balance toward hyperexcitability, and together they resemble the circuit reorganization that defines epileptogenesis. The paper further argues that chronic stress is a uniquely problematic risk factor: unlike a head injury or a stroke, it is cumulative rather than discrete, it is reinforced by epilepsy itself, and it remains largely unaddressed in routine epilepsy care despite being modifiable. Limitations of the causal claim: reverse causation, the confound of functional seizures, reliance on self-report, and the modest effect sizes observed in human cohorts are examined directly.

Keywords: chronic stress, epileptogenesis, hypothalamic–pituitary–adrenal axis, hippocampus, neuroinflammation, seizure threshold

Chronic Stress as a Causal Contributor to Epilepsy: How Years of Hypothalamic–Pituitary–Adrenal Activation Lowers the Seizure Threshold

Ask people living with epilepsy what sets off their seizures and stress is named more often than sleep deprivation, missed medication, or alcohol. It is the single most commonly self-reported precipitant in the clinical literature (Gunn & Baram, 2017; Novakova et al., 2013). Clinically, that observation is usually filed under the heading of triggers: factors that determine when a seizure occurs in a brain already capable of producing one. The framing is convenient, and it quietly sets aside a harder question: whether stress that persists not for an afternoon but for years does something to a brain that was not previously epileptic.

That question turns on the difference between precipitation and epileptogenesis. Precipitation is the unmasking of an existing capacity for seizures. Epileptogenesis is the latent process through which neural tissue is progressively converted into tissue that generates spontaneous, recurrent seizures: a process that typically unfolds over months or years between an initial insult and the first unprovoked seizure. A precipitant changes timing; an epileptogenic factor changes the brain.

This paper argues that chronic stress sustained over five or more years belongs in the second category. Persistent activation of the hypothalamic–pituitary–adrenal (HPA) axis delivers a continuous corticosteroid and corticotropin-releasing hormone (CRH) load to the hippocampus and amygdala, and that load remodels dendritic architecture, suppresses neurogenesis, strips away the neurosteroid support that GABAergic inhibition depends on, and primes a microglial inflammatory response that breaches the blood–brain barrier. These are not four separate risks but one convergent mechanism that lowers seizure threshold and drives the circuit reorganization that defines epileptogenesis, which makes prolonged stress a genuine causal contributor to

epilepsy rather than a background correlate. Chronic stress is problematic in a way that other epilepsy risk factors are not, because it is cumulative rather than discrete, because epilepsy itself feeds back to sustain it, and because it is almost entirely absent from the standard diagnostic workup despite being one of the few epilepsy risk factors that can actually be modified.

What a Causal Claim Requires

Calling chronic stress causal is a strong claim, and it should meet a high standard. Four things would need to be true. There must be a biological mechanism capable of producing epileptic tissue, not merely of provoking a seizure. That mechanism must operate on a timescale that matches the exposure, meaning it must produce changes that outlast the stressor. Experimental animal work, where exposure can be randomized and temporal order guaranteed, must show that stress exposure alters the development of epilepsy and not only its expression. And human populations must show that stress exposure precedes epilepsy onset rather than following it. The sections below take these in turn. The evidence satisfies the first three strongly and the fourth partially: a distinction worth stating plainly rather than smoothing over.

The Endocrine Pathway

The acute stress response is, in isolation, adaptive. A stressor triggers CRH release and a downstream surge of cortisol in humans or corticosterone in rodents, and these mediators act on the brain in a deliberately biphasic sequence. Corticosterone binding at membrane mineralocorticoid receptors increases neuronal excitability within minutes, while slower genomic actions at glucocorticoid receptors normalize function over the following hours; CRH itself rapidly enhances excitatory transmission and reduces inhibitory currents, while neurosteroids provide a compensatory inhibitory brake at GABA-A receptors (Gunn & Baram, 2017). The design is a pulse followed by a recovery.

Chronic stress is pathological because it removes the recovery arm. When the stressor does not end, the excitatory phase renews before normalization completes, and the system settles into sustained hypersecretion. Cortisol hypersecretion decreases seizure threshold, and abnormal cortisol reactivity is associated with epilepsy independently of the psychiatric conditions that often accompany it (Jhaveri et al., 2023). In animal models, the effect is unambiguous: prolonged physical restraint produces a long-lasting elevation in corticosterone and a corresponding reduction in seizure threshold, and socially isolated rats have been reported to seize at rates many times higher than socially housed controls (Espinosa-García et al., 2021). Critically, these hormones act most powerfully on the hippocampus, which is the same structure most implicated in temporal lobe epilepsy, the most common form of focal epilepsy in adults (Joëls, 2009).

Structural Remodelling of the Hippocampus

Sustained stress signalling does not leave the hippocampus as it found it. Prolonged exposure triggers dendritic spine loss and impairs long-term potentiation (Gunn & Baram, 2017), and stress hormones inhibit neural stem cell proliferation in the dentate gyrus, disrupting normal circuit formation and promoting the incorporation of aberrantly positioned neurons into developing networks (Jo & Nam, 2025). The dentate gyrus matters disproportionately here because it functions as a gate, filtering excitatory input arriving from the entorhinal cortex. Stress-induced dysfunction at that gate substantially increases the probability that excitation will propagate rather than be contained (Gunn & Baram, 2017).

The result is a feed-forward problem. An epileptic hippocampus already carries mossy fiber sprouting, interneuron loss, and abnormal GABA-A receptor distribution, and these baseline alterations make the circuit more vulnerable to the pro-excitatory effects of stress mediators rather than less (Gunn & Baram, 2017). Stress remodels the circuit toward

hyperexcitability, and the remodeled circuit responds to subsequent stress more strongly than the original one did. Over five years, that is not a series of independent insults; it is a ratchet.

Erosion of Inhibitory Reserve

A third strand concerns what chronic stress takes away. Prolonged stress depletes brain neurosteroids including allopregnanolone, pregnenolone, and progesterone, all of which are potent positive modulators of GABA-A receptors; their loss directly impairs GABAergic inhibition and raises the probability of seizure initiation (Espinosa-García et al., 2021). Similarly, chronic stress reduces GABA receptor expression and glutamic acid decarboxylase activity while permitting glutamate accumulation, tilting the excitation–inhibition balance toward excitation from both sides (Jo & Nam, 2025). This is the mechanistic reason chronic stress should not be treated as merely a stronger version of acute stress. Acute stress transiently increases excitatory drive; chronic stress degrades the inhibitory reserve that would otherwise contain it.

Neuroinflammation and the Primed Brain

The fourth strand is immunological, and it most clearly distinguishes a trigger from a cause. Chronic elevation of stress hormones activates microglia and astrocytes and drives release of pro-inflammatory cytokines including interleukin-1 β , interleukin-6, and tumour necrosis factor- α , which in turn increase blood–brain barrier permeability and facilitate the formation of seizure-generating circuits (Jo & Nam, 2025). Espinosa-García et al. (2021) describe this as a two-hit mechanism: chronic stress constitutes a first hit that primes microglia through glucocorticoid-driven translocation of high mobility group box-1 protein and upregulation of the NLRP3 inflammasome, and a subsequent seizure acts as a second hit that activates the primed inflammasome, producing an amplified inflammatory response and greater brain injury than the

same seizure would otherwise cause. Chronic stress also makes the blood–brain barrier leaky, allowing peripheral immune cells to infiltrate and sustain central inflammation.

Priming is a durable state rather than an event, which is why exposure duration is the variable of interest. A brain that has been inflammatorily primed for years responds to its first seizure with more damage, and that damage contributes to the substrate for the next one.

Why Five Years Is Not an Arbitrary Threshold

The relevant distinction is not between mild and severe stress but between stress that resolves and stress that does not. Single stressors produce changes that the glucocorticoid receptor arm of the HPA axis is built to reverse. Multi-year exposure is pathological because reversal never occurs, the neuroendocrine set point shifts, and inflammatory and structural consequences accumulate faster than repair mechanisms can address them. The epileptogenesis literature reinforces this timescale from the other direction. Epileptogenesis is a latent process, and effects of stress exposure may not surface as seizures for years. Koe et al. (2009) argued that early life stress may contribute to mesial temporal lobe epilepsy even though seizures often emerge only in adolescence or adulthood, on the grounds that early stress produces enduring structural and functional change in exactly the regions where that epilepsy syndrome originates. Stress exposure and seizure onset are separated by a latency, which means cross-sectional studies looking for a contemporaneous association will systematically underestimate the relationship.

Evidence From Animal Models

Animal work provides what human studies cannot: randomized exposure, guaranteed temporal order, and outcomes assessed in brains with no psychiatric comorbidity to confound interpretation. Early life stressors such as maternal separation have been shown to aggravate epileptogenesis in both status epilepticus and kindling models of limbic epilepsy (Koe et al.,

2009). Reviewing this literature alongside human evidence, van Campen et al. (2014) concluded that early-life stress functions both as a seizure precipitant and as a risk factor for epileptogenesis: the dual role at the center of this paper's argument. Kindling models are especially instructive, because kindling is itself a model of progressive, cumulative lowering of seizure threshold through repeated subthreshold stimulation. That chronic stress accelerates kindling suggests it acts on the same progressive substrate rather than alongside it.

The obvious limitation is translational. A restrained or maternally separated rodent is not a human being enduring five years of caregiving strain, financial precarity, or an abusive relationship, and rodent epilepsy models capture some human syndromes far better than others. Animal evidence establishes that the mechanism is real, and that exposure alters epilepsy development; it does not by itself establish the magnitude of the effect in humans.

Evidence From Human Populations

Human evidence is necessarily observational and more suggestive than decisive. Population-level work has increasingly examined whether severe or sustained stress exposure precedes epilepsy onset. In a nationwide longitudinal study, Chen et al. (2017) examined the risk of subsequently developing epilepsy among individuals diagnosed with posttraumatic stress disorder, a condition defined by chronic dysregulation of the stress response and found an elevated risk relative to matched comparison participants. Danish registry research has tested the pathway at its earliest possible point, following offspring of mothers who experienced severe bereavement during pregnancy and reporting a modest elevation in later epilepsy risk (Li et al., 2008). In adults already at risk, Baldin et al. (2017) found that stress was associated with an increased likelihood of recurrent seizures following a first unprovoked seizure or a new epilepsy diagnosis. Novakova et al. (2013), synthesizing human and animal evidence, concluded that the

role of stress as a seizure trigger is well supported and that the animal literature points toward an additional role in the development of epilepsy.

Taken together, the human findings are consistent in direction and modest in magnitude. They establish temporal precedence in several independent populations, which is the epidemiological requirement that matters most, while leaving the size of the contribution genuinely uncertain.

Why Chronic Stress Is a Particularly Problematic Risk Factor

Suppose the causal contribution is real but moderate. Chronic stress would still warrant more clinical attention than it currently receives, for three reasons.

First, it is continuous rather than discrete. A traumatic brain injury, a stroke, or a febrile status epilepticus episode is a bounded insult after which the brain begins some form of recovery. Five years of unremitting stress provides no such interval; the injurious signal and the repair process compete continuously, and the mechanisms described above, such as dendritic remodelling, suppressed neurogenesis, neurosteroid depletion, and inflammatory priming, all favour the injurious side when exposure does not end.

Second, the relationship is self-reinforcing. Epilepsy is itself a potent chronic stressor: seizure unpredictability, driving restrictions, employment consequences, and stigma constitute exactly the kind of uncontrollable, long-duration adversity that sustains HPA dysregulation. Jhaveri et al. (2023) emphasize that the relationship between epilepsy and stress-related psychiatric conditions is bidirectional, likely reflecting shared pathogenic mechanisms that simultaneously elevate seizure risk and produce mood impairment rather than a simple one-way causal arrow. A person who develops epilepsy under chronic stress acquires a condition that generates more of the same exposure.

Third, and most consequentially, chronic stress is largely invisible to standard epilepsy care. It has no place in a routine seizure workup, no imaging correlate, and no laboratory marker in ordinary practice. Antiseizure medications act on ion channels and neurotransmitter receptors; they do not address a dysregulated HPA axis, a depleted neurosteroid pool, or a primed inflammatory state. This matters because stress is one of the few epilepsy risk factors that is modifiable. Cognitive behavioural therapy, mindfulness-based interventions, and biofeedback already target stress in epilepsy, and Jhaveri et al. (2023) argue for developing disease-modifying approaches explicitly aimed at reducing epileptogenesis. A modifiable causal contributor that no one measures is a worse problem than an unmodifiable one that everyone does.

Limits of the Causal Claim

Intellectual honesty requires stating what this argument does not establish. Reverse causation is difficult to exclude in observational data: undiagnosed epilepsy and its prodromal psychiatric features may generate stress before a formal diagnosis is recorded, inflating apparent stress-to-epilepsy associations. Functional (psychogenic non-epileptic) seizures, which are strongly associated with trauma and stress and are frequently misdiagnosed as epilepsy, may contaminate cohorts assembled from diagnostic codes. Self-reported stress is subject to recall bias, and people searching for an explanation of their seizures may over-attribute them to stressful periods. Registry studies capture severe, discrete events such as bereavement more reliably than the low-grade, unremitting adversity this paper is about, and they cannot fully adjust for socioeconomic disadvantage, injury exposure, sleep disruption, and substance use, all which track with chronic stress and independently affect seizure risk. Finally, the strongest experimental evidence comes from rodents, with all the translational caveats that it carries.

What survives those objections is a contributory causal claim rather than a deterministic one. Chronic stress is neither necessary nor sufficient for epilepsy. It is one strand in a multifactorial causal web, alongside genetic susceptibility, structural lesions, and developmental insults, that raises the probability of epileptogenesis through mechanisms that are specified, measurable, and consistent across levels of analysis. That is the standard applied to other accepted contributory causes in medicine, and chronic stress meets it.

Conclusion

The evidence supports treating chronic stress as more than a seizure trigger. Five or more years of HPA-axis activation produces a convergent set of changes, hippocampal dendritic remodelling and suppressed dentate neurogenesis, loss of neurosteroid-supported GABAergic inhibition, glutamatergic excess, microglial priming, and blood–brain barrier compromise, that together constitute a plausible and increasingly well-specified epileptogenic pathway. Animal models confirm that stress exposure alters the development of epilepsy rather than only its expression, and human cohorts show the exposure preceding the outcome, if with modest effect sizes. The practical implication is not that stress management should replace antiseizure medication, but that duration of stress exposure deserves a place in risk assessment, and that stress-targeted intervention deserves evaluation as a candidate disease-modifying strategy rather than as an adjunct to comfort. A causal contributor that compounds itself, reinforces the condition it helps produce, and goes unmeasured in routine care is worth naming as such.

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