Limbic Kindling: Hard Wiring the Brain for Hypersensitivity and Chronic Fatigue Syndrome

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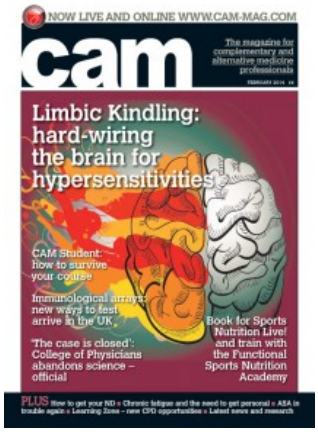
By Niki Gratrix May 17, 2014

It may be the most exciting concept in neuroscience that most people have never heard of. Eric Kandel's Nobel prize in 2000 on 'neuronal learning' in the brain laid the basis for it. It's become a possible model for Multiple Chemical Sensitivity (MCS) and Post Traumatic Stress Disorder (PTSD). Dr Leonard Jason believes it may explain Chronic Fatigue Syndrome (ME/CFS) as well.

It's called 'Limbic Kindling' and CAM magazine contributing editor and Health Rising blogger Niki Gratrix, (BA, Dip ION, mBANT) introduces it here and highlights its possible connections with infection and toxins.



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Limbic kindling is a condition where either repeated neurological exposure to a sub-threshold stimulus (i.e. one that does not produce problems), or a short-term high intensity stimulus (e.g. brain trauma), eventually leads to a persistent hypersensitivity to that stimulus.

Kindling was originally discovered in 1967 by Graham Goddard while studying the effects of electrical stimulation of the amygdaloid complex in the brain on learning in rats.(1) Similar to the work of Eric Kandel, he found that long-term, **low intensity** and **intermittent** electric shocks to their brains caused rats have spontaneous, epileptic-like seizures – **even when no stimulation was given.**

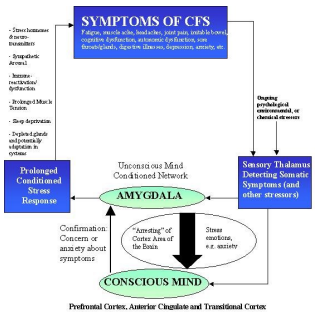
The limbic system regulates the autonomic nervous and endocrine systems and the emotions, memory and even smell. Is it 'on fire' in ME/CFS?

Goddard also found he could create similar reactions using chemical stimulation. In 1970 Gellhorn suggested that prolonged stimulation of the limbic- hypothalamic-pituitary axis, could also cause a lowered threshold for activation.(2) Girdano et. al. proposed in 1990 that excessive arousal could increase in dendrite (nerve endings) increases in the limbic system which further increased limbic stimulation and hypersensitivity to stimuli.(3)

Ashok Gupta was the first to propose a similar theory as the basis for CFS/ME in 2002 (4). (A diagram from his paper is below). Based on the work of Le Doux in the '90s (5), Gupta proposed that an infectious, chemical or psychological stressor could create a "cell

assembly" within the unconscious amygdala that was particularly resistant to extinction. As with Goddard and Gellhorn, Gupta's work implied that people who became "hard wired" to respond more easily to stimuli could find it more difficult to suppress the chronic stress, or "flight and fight" response established by Selye's classic model of stress (3-5)

With the idea that kindling could hard-wire the brain to produce an unhealthy response to stress, the Limbic Kindling hypothesis brought new understanding to the effects of 'stress'. A review of PTSD brain images in the British Journal of Psychiatry in 2002 which indicated that "increased activation of the amygdala after symptom provocation" was present suggested the Kindling hypothesis was accurate. (6)



In 2009, Dr Leonard Jason and his colleagues suggested that chronic long- term hyperarousal of the central nervous system – a form of limbic "kindling" – could lead to **chronic sympathetic nervous system arousal** which cause many of the physiological abnormalities documented in ME/CFS patients.

They include:

- immune system activation and movement from TH1 to TH2 dominance;
- up-regulation of the hypothalamic-pituitary- adrenal axis initially, which over time leads to **reduced** cortisol output and glandular depletion;
- disrupted ion channel transport;
- reduced grey matter in the brain; reduced GABA production; depleted acetylcholine;
- depleted antioxidant levels;
- eventually high levels of oxidative stress, increased opportunistic infections and reactivated latent infections, poor mitochondrial function and cardiomyopathy (7)

Dysbiosis

In addition to the symptoms Jason et. al. cited, chronic sympathetic nervous system activation is also known to cause dysbiosis (gut flora dysregulation). Pre and post-natal stress, for instance, causes dysbiosis in infant monkeys (8, 9) and several papers suggest CFS patients often have gut dysbiosis and leaky gut.(10)

Methylation and Detox

Stress was identified as a primary cause of pyrroluria (compromised haemoglobin synthesis) by the late great Dr Carl Pfeiffer, one of the co-founders of orthomolecular psychiatry. McGinnis et al have shown that pyrroluria may also be linked to leaky gut appears able to induce porphyria – a "downstream" cousin of pyrroluria that is associated with dysfunctional heme-producing enzymes. This in turn down-regulates the CYP450 liver enzymes (11). Many patients with MCS have been found to have porphyria (a topic covered in CAM in October 2012).

Has an activated sympathetic nervous system impaired the ability to detox as well?

Pyrroluria also results in excessive vitamin B6 and zinc excretion, which would slow the methylation cycle, again reducing the ability to detoxify.

The Lymph Connection

Also of great interest is the possible link between chronic stress and lymph stasis. Dr Raymond Perrin, an osteopath specializing in ME/CFS, hypothesizes that cranial lymph flow becomes dysfunctional in states of chronic stress (12). The cranial lymph flow is stimulated by a rhythmic pump governed by the sympathetic nervous system.

Perrin has developed a form of deep lymphatic massage called the “Perrin Technique” specifically for ME/CFS (13) and has published two studies on his work with ME/ CFS patients.(14, 15) A 2010 UK survey of more than 4,217 patients by the ME Association found that the Perrin technique ranked number three (after pacing and relaxation) out of 25 types of treatment (16).

A Vicious Chronic Stress Cycle

The limbic kindling model explains how multiple types of stressors (psychological, electrical or chemical) all result in the same outcome: chronic sympathetic nervous system activation that reduces the body’s ability to “rest, digest and detoxify”, and often results in allergies and hyper-sensitivities.

Limbic kindling could also explain electro-hypersensitivity. The biochemical changes resulting from chronic sympathetic nervous system activation include increased oxidative stress, inflammation and toxin build-up, which in turn, causes more limbic kindling and could explain how illnesses like ME/CFS and MCS become chronic.

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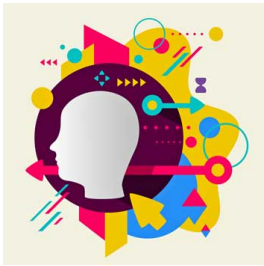
The fact that limbic kindling can both cause and be caused by stressors, reflects the bi-directional relationship between the brain and the body, and the fact that the human body is a complex adaptive system where everything essentially affects everything else.

The initial underlying causes of environmental sensitivities and illnesses like Chronic Fatigue Syndrome may therefore come from stressors directly acting on the brain and triggering biochemical changes downwards in the body, or via factors acting directly on the body triggering changes upwards in the limbic system through chronic inflammation.



The bi-directional nature of limbic kindling means what was set in motion by the body can be exacerbated by the mind.

Physical factors which can lead to chronic inflammation and thus limbic kindling include chronic infections, type IV delayed hypersensitivity to toxins, and food and gut inflammation. In a second paper by Jason et. al. on kindling theory and ME/CFS in

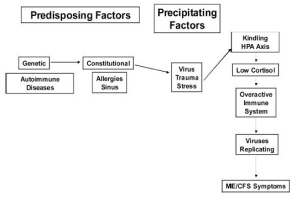
Niki proposes a multi-factorial mind and body approach to limbic kindling.

2011, the authors argued that inflammation from chronic infections could also cause limbic kindling.

Factors linked to psychology which may help perpetuate limbic kindling or accentuate sympathetic nervous system activation in ME/CFS could include personality issues such as proneness to being an over-achiever, anxiety, or being an excessive “helper” type (16-19). Emotional trauma in childhood is a well-established risk factor for the onset of Chronic Fatigue Syndrome (and other inflammatory/autoimmune disorders) in later life (20-23). Effective management of the emotional stressors associated with chronic illness (which is traumatic in itself) can be a major factor in recovery for some patients (24, 25).

Commonly used psychological or energetic techniques for CFS and other disorders of sympathetic nervous activation include NLP, CBT, EMDR, yoga, Qi Gong, Mickel Therapy and meditation (16).

The diagram here summarizes Jason’s conclusion that “we need studies based on systems biology that explain the illness, in combination with more details about the environmental contributors to the illness as well as validation of findings with functional studies.” (27)



Heavy metals may also be involved in limbic kindling. Dr Stejskal, the researcher involved with developing the Melisa test for type IV hypersensitivity to heavy metals has completed numerous large studies confirming metal sensitivity in ME/CFS patients (discussed in CAM , November 2013).

In Neuroendocrinology Letters in 1999 Dr Stejskal discussed studies linking inflammation to heavy metals accumulation and concluded: “Chronic metal-induced inflammation may dysregulate the HPA-axis and contribute to fatigue”(28). The authors went on to state that xenobiotics such as formaldehyde and isothiazolinones would have a similar inflammatory impact and that the genetic ability to detoxify xenobiotics, together with the **individual susceptibility to the toxin**, are probably the most important factors in whether a person develops sensitivity.

Other sources of chronic inflammation can include delayed type IV hypersensitivity to foods, especially gluten (CAM , September 2013). An extensive referenced discussion of the links between gluten sensitivity, gut inflammation and CFS can be found on this website HERE.

Physical Interventions for Detoxification

A key point to take away from the limbic kindling model is that a nervous system that has become sensitized/programmed to overreact to toxins and other substances may require different interventions.

Mind/body approaches may help to reset the neural reprogramming found in some people with sensitivity to toxins. Other approaches include sauna, chelation and nutritional supplementation.

While the intervention for type IV delayed immune system sensitivity to a toxin entails testing for and removing the toxin from the environment of the patient, and the intervention for genetic polymorphisms affecting methylation and other detox pathways may entail recommending a “nutritional bypass” to modulate and improve detoxification, sensitivity to toxins due to **neurological reprogramming** may be served better by **interventions to reset the unconscious amygdala** – such as NAET therapy, a form of non-invasive acupuncture therapy, or similar energy-psychology techniques such as EFT (tapping).

Other physical treatment interventions which should be accompanied by concurrent psychological support commonly include the Perrin technique for lymph stasis, cleanses such as **sauna and chelation** therapy, as well as **nutritional support** for metabolic imbalances including pyrroluria, porphyria, poor mitochondrial function, leaky gut, low adrenals and thyroid, chronic infections and immune system imbalances.

Conclusion

Practitioners – and researchers – would be wise not to downplay or ignore either environmental or psychological factors that could help perpetuate the limbic kindling found in complex chronic illnesses like ME/CFS and MCS. Treatment interventions should ideally be concurrent and multifactorial. A comprehensive physical and psychological history and multi-faceted approach to treatment may yield the highest rates of success.

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