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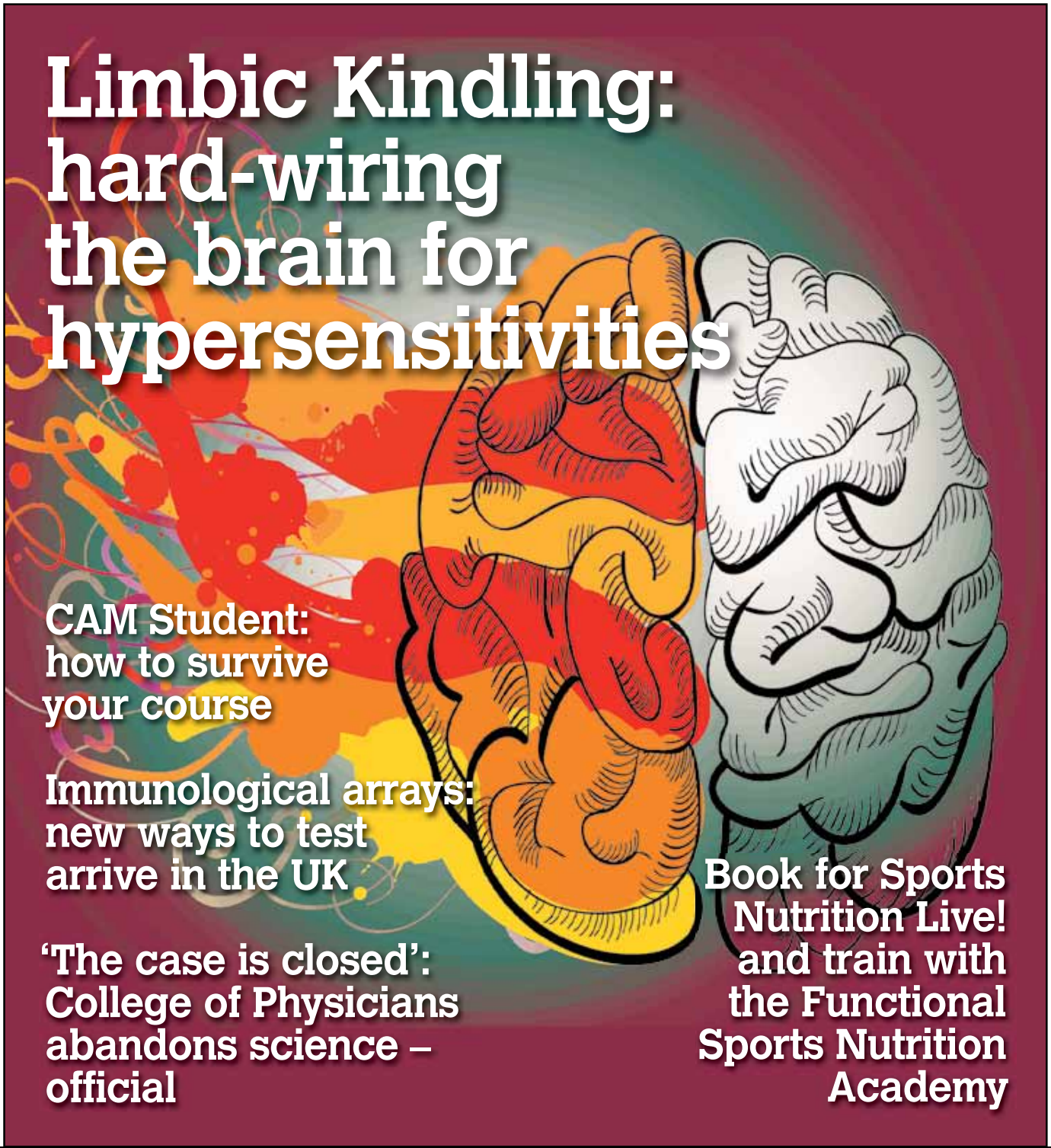
Limbic Kindling: hard-wiring the brain for hypersensitivities



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Limbic kindling: hard-wiring the brain for hypersensitivity

It's one of the most exciting concepts in neuroscience you've never heard of. And it's becoming a key model being examined as a possible theoretical basis for Multiple Chemical Sensitivity (MCS) and Post Traumatic Stress Disorder (PTSD). Recently, a leading researcher in CFS/ME, Dr Leonard Jason, has argued it provides a comprehensive model to explain CFS as well. *CAM* contributing editor **Niki Gratrix**, BA (Hons), Dip ION, introduces the idea and highlights the connections with infection and toxins.

Limbic kindling is a condition where either repeated neurological exposure to initially chronic sub-threshold stimulus, or a short-term high intensity stimulus (eg brain trauma), can eventually lead to persistent hypersensitivity to the stimulus.

Kindling was originally discovered in 1967 by Graham Goddard, who was studying the effects of electrical stimulation of the amygdaloid complex in the brain in learning in rats.(1) He found that after long-term, low intensity intermittent stimulation from electric shocks to their brains, the rats began to have spontaneous, epileptic-like seizures – even when no stimulation was given. Goddard also found he could create similar reactions using chemical stimulation.

In 1970, Gellhorn suggested that under prolonged stimulation of the limbic-hypothalamic-pituitary axis, a lowered threshold for activation could occur.(2) Girdano et al in 1990 proposed that the excessive arousal could lead to an increase in dendrites of the limbic system, which can further increase 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 suggested that an infectious, chemical or psychological stressor could create a "cell assembly" within the unconscious amygdala and that these cell populations are particularly resistant to extinction. As with Goddard and Gellhorn, this again implied that people could become "hard-wired" to respond more easily to stimuli and in turn find it more difficult to suppress the chronic stress, or "flight and fight" →

→ response established by Selye's classic model of stress.(3-5)

Where limbic kindling takes our understanding of stress to new levels is the idea that this kindling leads to "hard-wiring" in the brain for an unhealthy response to stress. This was boosted by a 2002 paper in the *British Journal of Psychiatry*, where a systemic review of brain images of patients with PTSD found "increased activation of the amygdala after symptom provocation".(6)

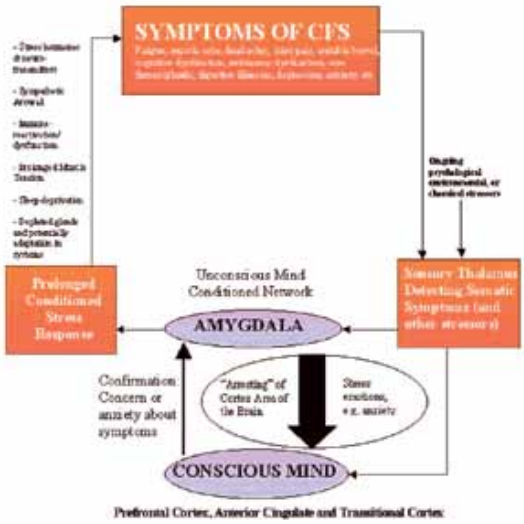
In 2009, Dr Leonard Jason and colleagues suggested that chronic long-term hyperarousal of the central nervous system – from this "kindling" – leads to chronic sympathetic nervous system arousal and will in turn result in the physiological abnormalities documented in ME/CFS patients. This includes:

- immune system activation and movement from TH1 to TH2 dominance;
- up-regulation of the hypothalamic-pituitary-adrenal axis initially, which over time leads to reduction of cortisol output and glandular depletion;
- disruption in ion channel transport;
- reduction of grey matter in the brain;
- reduction of GABA;
- depletion of neurotransmitter acetylcholine;
- depletion of antioxidants;
- and eventually the oxidative stress, opportunistic infection and reactivation of latent infections, poor mitochondrial function and cardiomyopathy.(7)

In addition to those symptoms Jason et al cited, chronic sympathetic nervous system stress is also known to cause dysbiosis; for example pre- and post-natal stress causes dysbiosis in infant monkeys (8, 9) and numerous papers now show CFS patients often have gut dysbiosis and leaky gut.(10)

Methylation, detoxification

Stress has been 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. This is important, as McGinnis et al have explained that pyrroluria may also be linked to leaky gut and it appears to also induce porphyria – the "downstream" cousin of pyrroluria, in which heme-producing enzymes are dysfunctional. This in turn down-regulates the CYP450 liver enzymes (11 – and covered in *CAM* in the October 2013 issue). Many patients with MCS have been found to have porphyria (a topic covered in *CAM* in October 2012). Pyrroluria also means the patient excessively excretes vitamin B6 and zinc, 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 specialising in CFS, has theorised that lymph flow is stimulated by a rhythmic pump governed by the sympathetic nervous system, which becomes dysfunctional in states of chronic stress.(12) Perrin has developed a form of deep lymphatic massage called the "Perrin Technique" specifically for CFS (13) and has published two studies on his work with CFS patients.(14,15) In a UK study of more than 4217 patients in 2010 by the ME Association, ranking how helpful different treatments are for ME/CFS, after pacing and relaxation techniques, the Perrin Technique ranked as number three above at least 22 other types of treatment.(16)

The vicious cycle of chronic stress

The limbic kindling model explains how multiple types of stressors, which can be psychological, electrical or chemical, can all result in the same outcome: chronic sympathetic nervous system stress which reduces the body's ability to "rest, digest and detoxify", and often results in allergies and sensitivities to all these types of stressors as well. Limbic kindling may also explain electro-hypersensitivity.

The biochemical changes which result from chronic sympathetic nervous system stress include oxidative stress, inflammation and toxin build-up, which in turn, causes more limbic kindling and explains how illnesses like CFS and MCS become chronic.

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 essentially everything affects everything else.

Initial underlying causes of environmental sensitivities and illnesses like CFS 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.

Factors linked to psychology which create limbic kindling in CFS include personality issues such as proneness to being an achiever, anxiety, or being an excessive "helper" type.(16-19). Emotional trauma in childhood is a well-established risk factor for CFS onset in later life.(20-23) Emotional stress related to how patients cope with becoming ill with CFS (which is traumatic in itself) has also been found to be a major factor in recovery.(24, 25) Emotional stress is also a well-established trigger for onset of the illness.(26) Commonly-used psychological or energetic techniques for CFS include NLP, CBT, EMDR, yoga, Qi Gong, Mickel Therapy and meditation.(16)

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 2011, the authors argued that inflammation from chronic infections could also cause limbic kindling. The diagram here summarises their 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)

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 CFS patients (discussed in *CAM*, November 2013). →

→ In Neuroendocrinology Letters in 1999, Dr Stejskal discussed studies linking inflammation to heavy metals and concluded: "Chronic metal-induced inflammation may dysregulate the HPA-axis and contribute to fatigue".(28) The authors went on to state that other 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.

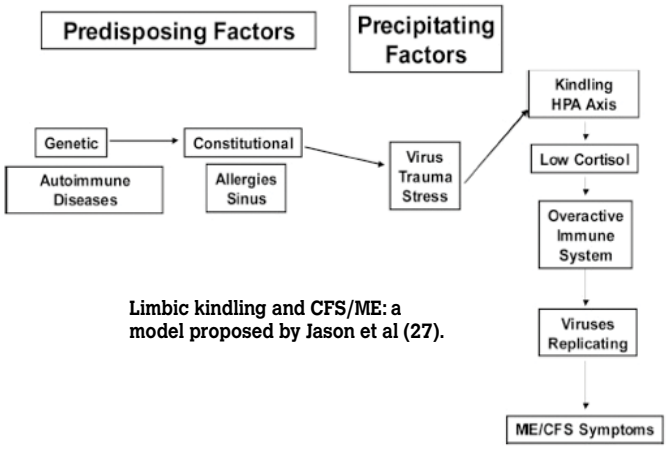
Other sources of chronic inflammation can include delayed type IV hypersensitivity to foods, especially gluten (*CAM*, September 2013). An extensive referenced discussion of the links between gluten sensitivity, gut inflammation and CFS can be found on Cort Johnson's CFS advocacy site; www.cortjohnson.com.(29)

Physical treatment interventions for detoxification

A key point to take away from the limbic kindling model is that the nervous system can become sensitised to toxins and become "programmed" to react to them.

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 programming 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.



Limbic kindling and CFS/ME: a model proposed by Jason et al (27).

Conclusion

Practitioners – and researchers – would be wise not to downplay or ignore either psychological factors or environmental factors as primary causes and perpetuating factors in chronic complex illnesses like CFS and MCS. Treatment interventions should ideally be concurrent and multifactorial. A thorough comprehensive physical and psychological history and approach to treatment may yield the highest rates of success with patients.

About the author

Niki Gratrix, BA (Hons), Dip ION, mBANT, is one of the UK's leading nutritional therapists specialising in Chronic Fatigue Syndrome/ME and related illnesses. She is one of *CAM*'s contributing editors and a former CAM Award winner. See her website for practitioners at www.ExpertPractitioner.com.

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