Module 5 – The Neuroscience of High Energy – Summary Document

**BRAIN HEALTH IS CRITICAL FOR OPTIMAL ENERGY LEVELS**

The health of your brain and how you operate it is a major determinant of:

- Your quality of life
- Your mood
- Your tolerance to stress
- Your mental and physical performance
- Your energy levels
- Your ability to get back to normal after stress (resilience)

When your brain is not working properly—due to inflammation, or chronic stress, or another factor—it is extremely difficult to have great energy levels.

Stress in particular is a HUGE problem for a lot of people. (There are also many different hidden and surprising sources of stress for our brains that many people are unaware of).

Even if your diet, exercise, circadian rhythm, and other lifestyle habits are perfect, if your brain is not working well, you are not going to have good energy levels.

**A QUICK OVERVIEW OF STRESS**

**SOME KINDS OF STRESS ARE BAD WHILE OTHERS ARE not**

- Hormetic Stress vs. Pathological Stress
- Any stressor becomes pathological if it is not counterbalanced with equally intense cellular regeneration
- Chronic psychological/emotional stress is the most problematic stressor
- There are also many other types of lifestyle factors that act on the stress pathways in our brain besides the psychological stress that most of us think of when we hear the word “stress.”

Many people start having all of their health issues after a bout of chronic stress.

**For a lot of people, it all begins with STRESS.**

The Effects of Stress

1) **Lowers immune function.** This makes you more susceptible to infections.
2) **Increases inflammation.** This will negatively impact orexin levels, which is a huge player in energy.
3) **Disrupts your sleep.** Sleep is critical to cellular energy repletion, so this is a BIG problem.
4) **Disrupts your circadian rhythm.**
THE EFFECTS OF STRESS

- **LOWERS IMMUNE FUNCTION.**
  This makes you more susceptible to infections.

- **INCREASES INFLAMMATION.**
  This will negatively impact orexin levels, which is a huge player in energy.

- **DISRUPTS YOUR SLEEP.**
  Sleep is critical to cellular energy repletion, so this is a BIG problem.

- **DISRUPTS YOUR CIRCADIAN RHYTHM.**

- **CAUSES LIMBIC SYSTEM DYSFUNCTION.**

- **ENDOCANNABINOID DEFICIENCY.**

- **FAT GAIN.**
  Increases appetite and food cravings while negatively affecting metabolism, energy levels, and nutrient partitioning

- **DEPRESSION.**

- **HEART DAMAGE.**
  By increased adrenaline, oxygen demand on the body, spasm of the heart blood vessels, and electrical instability in the heart. It also lowers heart rate variability and resting heart rate and increasing blood pressure.

- **CAUSES GUT PROBLEMS.**
  Cortisol can cause gut leakiness, which will cause food sensitivities and inflammation from food.

- **DECREASES LEVELS OF BENEFICIAL HORMONES AND INCREASES SOME HARMFUL HORMONES.**
  Lower GnRH, LH, FSH, Pregnenolone, DHEA, Testosterone, Growth Hormone, Thyroid Hormones (T3, T4, TSH) and higher Prolactin, Cortisol, and Estragen

- **CAUSES LESS BLOOD FLOW IN CERTAIN REGIONS LIKE YOUR GUT AND LIVER.**
  This leads to poor oxygen delivery to the cells and poor GI function.

- **CAUSES NEUROTRANSMITTER DEFICIENCIES, RESISTANCE, AND IMBALANCES.**
  Stress will cause neurotransmitter resistance (Glutamate, Serotonin, GABA), and lower dopamine and acetylcholine.
5) Causes limbic system dysfunction.

6) Endocannabinoid Deficiency.

7) Fat gain. Increases appetite and food cravings while negatively affecting metabolism, energy levels, and nutrient partitioning

8) Depression.

9) Heart damage. By increased adrenaline, oxygen demand on the body, spasm of the heart blood vessels, and electrical instability in the heart. It also lowers heart rate variability and resting heart rate and increasing blood pressure

10) Causes gut problems. Cortisol can cause gut leakiness, which will cause food sensitivities and inflammation from food.

11) Decreases levels of beneficial hormones and increases some harmful hormones. Lower GnRH, LH, FSH, Pregnenolone, DHEA, Testosterone, Growth Hormone, Thyroid Hormones (T3, T4, TSH) and higher Prolactin, Cortisol, and Estrogen

12) Causes less blood flow in certain regions like your gut and liver. This leads to poor oxygen delivery to the cells and poor GI function.

13) Causes neurotransmitter deficiencies, resistance, and imbalances. Stress will cause neurotransmitter resistance (Glutamate, Serotonin, GABA), and lower dopamine and acetylcholine.
THE STRESS-FATIGUE LINK - MYTHS VS. FACTS

THE OLD MODEL – ADRENAL FATIGUE

Traditional thinking around “Adrenal Fatigue” is flawed and outdated.

That model relies on the notion that the adrenal glands are overworked and are not able to produce enough stress hormones to keep with the stress demands, so they wear down and weaken.

THE MORE RECENT MODEL – HPA AXIS DYSFUNCTION

These three parts work together to regulate numerous aspects of our physiology—from our alertness and mood, to our digestion, to our stress response and immune function, to our appetite and metabolism, to our energy levels.

The idea has been an extension of the original adrenal fatigue theory – but it’s not just the adrenals by themselves, it’s the parts of the brain that control adrenal function. Still very much adrenal and cortisol-centric.
MY JOURNEY THROUGH THE SCIENCE ON ADRENAL FATIGUE AND HPA AXIS DYSFUNCTION…

I wanted to create the most comprehensive science-based book to understanding adrenal fatigue in existence… "The Science-Based Guide to Adrenal Fatigue"

As I got into it, I found something totally and utterly bizarre

I went to Pubmed.com, which is basically a repository of all the world’s scientific research…

I was set to begin what I thought was going to be a 3-6 month long process of reading all the scientific research on adrenal fatigue that’s been conducted over the last several decades.

And then…

I discovered that literally almost no research on adrenal fatigue has ever been conducted.

Which was totally and completely baffling…

Because somehow there are thousands of people writing articles about adrenal fatigue and presenting scientific looking illustrations about the different phases of adrenal fatigue…

And MILLIONS of people who are being diagnosed with adrenal fatigue all the time.

So how could there be no scientific research on a condition that many naturopaths and other health practitioners all over the world are diagnosing people with every day?

If the craziness of this situation is not hitting you, let me explain this in a different way…

Think of a medical condition

- Diabetes
- Stroke
- Alzheimer’s
- Obesity
- Hypothyroidism
- Celiac disease
- Lung cancer
- Depression
- Schizophrenia
- Psoriasis
- Dementia
- Even obscure ones like Sjögren’s syndrome or Addison’s disease.

Any condition you can think of – just choose one….
Then go to Pubmed.com (it is a database of virtually all studies in existence – like Google for scientific studies) and do a search for that condition...

What did you find?

You will notice that between **HUNDREDS or THOUSANDS** of studies will quickly appear for each and every one of those conditions.

Now, if you do the same thing for “adrenal fatigue”

...guess how many studies you will find?

**VIRTUALLY NONE**

In fact, now (as of 2017), it’s even **WORSE** than a mere case of there being no scientific research.

Why?

Because if you do that search, you will, actually, find **negative scientific data**.

You will find research examining adrenal fatigue that has concluded that adrenal fatigue is a **myth** that has no basis in science.

That systematic review of the scientific literature all relevant studies on the topic is even titled “Adrenal Fatigue Does Not Exist”
"This systematic review proves that there is no substantiation that ‘adrenal fatigue’ is an actual medical condition. Therefore, adrenal fatigue is still a myth."
Unstimulated cortisol secretory activity in everyday life and its relationship with fatigue and chronic fatigue syndrome: a systematic review and subset meta-analysis.

Powell DJ, Locci C, Moos-Morris R, Scholz W.

Abstract

The hypothalamic-pituitary-adrenal (HPA) axis is a psychoneuroendocrine regulator of the stress response and immune system, and dysfunctions have been associated with outcomes in several physical health conditions. Its end product, cortisol, is relevant to fatigue due to its role in energy metabolism. The systematic review examined the relationship between different markers of unstimulated salivary cortisol activity in everyday life in chronic fatigue syndrome (CFS) and fatigue assessed in other clinical and general populations. Search terms for the review related to salivary cortisol assessments, everyday life contexts, and fatigue. All eligible studies (n=19) were reviewed narratively in terms of associations between fatigue and assessed cortisol markers, including the cortisol awakening response (CAR), circadian profile (CP) output, and diurnal cortisol slope (DCS). Subset meta-analyses were conducted of case-control CFS studies examining group differences in three cortisol outcomes: CAR output; CAR increase; and CP output. Meta-analyses revealed an attenuation of the CAR increase within CFS compared to controls (d=-.34) but no statistically significant differences between groups for other markers. In the narrative review, total cortisol output (CAR or CP) was rarely associated with fatigue in any population; CAR increase and DCS were most relevant. Outcomes

"Total cortisol output (or CAR) was rarely associated with fatigue in any population"


Lennartsson AK, Sjörs A, Wåhlin Borg P, Jonsson T, Jonassdottr H.

Abstract

BACKGROUND: Common consequences of long-term psychosocial stress are fatigue and burnout. It has been suggested that burnout could be associated with hypocortisolism, thus, inability to produce sufficient amounts of cortisol. This study aimed to investigate whether patients with clinical burnout exhibit aberrant ACTH and cortisol responses under acute psychosocial stress compared with healthy individuals.

METHODS: Nineteen patients (9 men and 10 women) and 37 healthy subjects (20 men and 17 women), underwent the Trier Social Stress Test. Blood samples and saliva samples were collected before, after, and during the stress test for measurements of plasma ACTH, serum cortisol, and salivary cortisol. Several statistical analyses were conducted to compare the responses between patients and controls. In addition, in order to investigate the possibility that burnout patients with more severe symptoms would respond differently, sub-groups of patients reporting higher and lower burnout scores were compared.

RESULTS: In both patients and healthy controls, we observed elevated levels of ACTH and cortisol after exposure to the stressor. There were no differences in responses of ACTH, serum cortisol, or salivary cortisol between patients and controls. Patients reporting higher burnout scores had lower salivary cortisol responses than controls, indicating that patients with more severe burnout symptoms may be suffering from hypocortisolism. In addition, patients with more severe burnout symptoms tended to have smaller ACTH responses than the other patients. However, there was no corresponding difference in serum cortisol.

CONCLUSION: This study indicates that hypocortisolism is not present in a clinical burnout patient group as a whole but may be present in the patients with more severe burnout symptoms.

"hypocortisolism is not present in a clinical burnout patient group"
Long-term follow-up of cortisol awakening response in patients treated for stress-related exhaustion

Anna Sjörs, Thomas Ljung, and Ingibjörg H Jonsdottrí

Abstract

Objectives

Studies on hypothalamus–pituitary–adrenal (HPA) axis activity in stress-related exhaustion and burnout have revealed incongruent results, and few longitudinal studies on clinical populations have been performed. This study was designed to investigate differences in HPA axis activity between patients with stress-related exhaustion and healthy controls and to investigate longitudinal changes in HPA axis activity in the patient group as they entered a multimodal treatment programme.

Design

HPA axis activity was assessed through the cortisol awakening response (CAR). Salivary cortisol was sampled at awakening and after 15 min. Follow-up measurements were performed in the patient group after 3, 6, 12 and 18 months.

Setting

An outpatient clinic specialising in stress-related illness.

Participants

Patients with clinically diagnosed stress-related exhaustion (n=162) and healthy controls (n=79).

Primary and secondary outcome measures

The primary measure was CAR measured as the difference between the two salivary cortisol samples. Changes in CAR during follow-up were related to changes in symptoms of burnout, depression and anxiety.

Results

Patients showed similar CAR as the controls and their CAR did not change significantly during treatment. No association was found between CAR and symptom development during treatment.

Conclusions

The authors conclude that CAR does not seem to discriminate clinically defined patients with exhaustion from healthy controls and it appears NOT to change during treatment. CAR, measured as salivary cortisol, at awakening and after 15 min, is thus NOT a valid marker for stress-related exhaustion.

“(Morning cortisol) does not seem to discriminate clinically defined patients with exhaustion from healthy controls, and it appears NOT to change during treatment.

(Morning cortisol) measured as salivary cortisol, at awakening and after 15 minutes, is thus NOT a valid marker for stress-related exhaustion.”
Clinical burnout is not reflected in the cortisol awakening response, the day-curve or the response to a low-dose dexamethasone suppression test.

Mommersroeg PM1, Heijnen CJ, Verbraak MJ, van Doornen LJ.

Author information

Abstract
Burnout is presumed to be the result of chronic stress, and chronic stress is known to affect the HPA-axis. To date, studies on HPA-axis functioning in burnout have showed inconsistent results. In the present study, a large sample (n=74) of clinically diagnosed burnout individuals, mostly on sick-leave, were included and compared with 36 healthy controls. Salivary cortisol was sampled on 2 days to determine the cortisol awakening response (CAR) and the day-curve. In addition, the dexamethasone suppression test (DST) was applied to assess the feedback efficacy of the HPA-axis. There were no differences observed in the CAR, day-curve or CAR after DST in the burnout group as compared to a healthy control group. Burnout shows overlap in symptoms with chronic fatigue syndrome (CFS) and depression. Therefore, differential changes in HPA-axis functioning that resemble the hypo-functioning of the HPA-axis in CFS, or rather the hyper-functioning of the HPA-axis in depression, might have obscured the findings. However, no effect of fatigue or depressive mood on HPA-axis functioning was found in the burnout group. We concluded that HPA-axis functioning in clinically diagnosed burnout participants as tested in the present study, seems to be normal.

“We concluded that HPA-axis functioning in clinically diagnosed burnout participants...seems to be NORMAL”

The neurobiology of burnout: the hypothalamus-pituitary-adrenal gland axis and other findings.

Author information

Abstract
OBJECTIVE: This review aimed to present an overview of neurobiological research on the etiology of burnout and to evaluate the proposed arguments.

METHOD: A retrospective literature review of the relevant studies conducted within the last 17 years. For this purpose a literature search was conducted via internet-based search engines, including PubMed, Science-Direct, Medline, GoogleScholar, ULAXBIM Turkish Medicine Index, and Turkish Psychiatry Index, using the key words, burnout, cortisol, the hypothalamus-pituitary-adrenal gland (HPA)-axis, stress, neurobiology, neurogenesis, BDNF, immunology, and etiology, in different combinations.

RESULTS: The pioneering studies that focused on the relationship between burnout and dysregulation of the HPA-axis have yielded inconsistent results. Data from subsequent studies with improved designs suggest there is no HPA-axis dysregulation in burnout, but the results do not lead to more concrete interpretations. There is some evidence of impaired immunity function in burnout as compared with

“There is no HPA axis dysregulation in burnout”
Diurnal salivary cortisol...give a rather poor reflection of the prolonged stress exposure experienced by patients with Exhaustion Disorder. Such basal salivary cortisol measurement do NOT seem suitable as biomarkers for stress-related conditions such as Exhaustion Disorder or burnout.

The HPA axis and the genesis of chronic fatigue syndrome

Many studies of patients with long-standing chronic fatigue syndrome (CFS) have found alterations to the hypothalamic-pituitary-adrenal (HPA) axis, including mild hypocortisolism, heightened negative feedback and blunted responses to challenge. However, recent prospective studies of high-risk cohorts suggest that there are no HPA axis changes present during the early stages of the genesis of fatigueing illnesses. Moreover, HPA axis changes can be reversed by modifying behavioural features of the illness, as such inactivity, deconditioning and sleep disturbance. Nevertheless, raising levels of cortisol pharmacologically can temporarily alleviate symptoms of fatigue. This article presents the case that there is no specific change to the HPA axis in CFS and that the observed changes are of multifactorial aetiology, with some factors occurring as a consequence of the illness. Nevertheless, the HPA axis might play a role in exacerbating or perpetuating symptoms late on in the course of the illness.
A systematic literature review - the highest level of scientific evidence - showed *no difference for cortisol awakening response or cortisol in blood* between people with BURNOUT vs. normal healthy people

Speaking on the studies, the researchers said:

“When taken together, among all the studies that investigated HPA-axis function and burnout,

- 3 support an increase in HPA-axis functions in burnout;
- 5 support a decrease in HPA-axis functions;
- 11 did not support a significant relationship.”

They concluded: “The pioneering studies that focused on the relationship between burnout and dysregulation of the HPA axis have yielded inconsistent results.

**Data from subsequent studies with improved designs suggest there is no HPA-axis dysregulation in burnout**

Overall I went through over 150 studies -- literally every relevant study in existence.

Here’s what I found:

- 23% of them showed HIGH cortisol levels associated with fatigue or burnout
- 22% of them showed LOW cortisol levels associated with fatigue or burnout
- 55% of them showed NO abnormalities whatsoever in either cortisol levels or the HPA Axis

And the systematic literature reviews all mesh with that, and conclude that cortisol and HPA axis abnormalities are not the cause of fatigue.

**BOTTOM LINE:** Adrenal dysfunction and HPA axis dysfunction are not the “cause” of fatigue. But HPA axis dysfunction can potentially occur deep in fatiguing illness.
Let me be clear that CHRONIC STRESS IS OBVIOUSLY VERY HARMFUL.

- I am simply saying the harmful effects of chronic stress are likely not due to the “fatiguing” of the adrenal glands and the inability to pump out more cortisol or even the HPA axis (for the most part).
- They are actually due to disruptions in key areas of the brain along with the mitochondria.

So, let’s talk about the neuroscience around the brain areas that are clearly implicated as causal factors in fatigue...

**THREE FACTORS THAT IMPAIR OUR BRAIN**

Unfortunately, most of us have inflamed, poorly functioning and poorly trained brains.

There are several different ways that our brain can break, and in this module, we’re going to cover exactly what those factors are, and how to fix them.

There are 3 primary reasons why our brains break down:

1. *Endocannabinoid system and limbic system dysfunction*
2. *HPA Axis Dysfunction*
3. *Lack of conscious brain training*

**ENDOCANNABINOID SYSTEM AND LIMBIC SYSTEM DYSFUNCTION**

Think of camping for a moment. Remember how you get the camp fire started? You first have to get the kindling to light.

Once that tinder has nurtured the spark into a small flame, it can be turned into a raging fire.
The limbic system is our brain’s threat-interpretation system. It decides what is dangerous and what is not. **Its job is to know when are we in danger and when are we safe.**

The limbic system is upstream of the HPA Axis, which is the system more commonly regarded as the “stress response” system of the brain.

That is important, because the HPA Axis dysfunction and altered cortisol patterns sometimes seen in people with fatigue are not the primary cause – they are often symptoms of dysfunction at the limbic system.
Limbic kindling is when small sparks of stressors create a raging fire in the limbic system of the brain.
Limbic Kindling is the primary mechanism in the brain that contributes to fatigue. This is the place in the brain where it all starts. While some practitioners have focused on cortisol and the HPA Axis, it is critical to understand that the HPA Axis is downstream from the limbic system – meaning that the HPA Axis only dysfunctions when there is first dysfunction in the limbic system.

Basically, the way limbic kindling happens is that the external stressor programs the brain to respond with a stress response to progressively smaller stressors. The threshold for creating a stress response has been lowered and the limbic system becomes hypersensitive.

Ultimately, it gets to the point where you do not even need the original stressor anymore – the brain will be in stress mode chronically because even the smallest provocation will put the brain into that mode.

The big problem here is limbic kindling can lead to chronic sympathetic nervous system activation.

That chronic over-activation of the sympathetic nervous system basically sends a nonstop "stress mode" signal to the body.

Having your brain and nervous system in chronic "stress mode" then leads to all sorts of nasty effects seen in people with fatigue.

**LEAKY GUT AND GUT DYSBIOSIS**

Chronic stress is now known to induce both leaky gut and gut permeability. It is also known that the majority of people with chronic fatigue have these gut issues.

Leaky gut and gut dysbiosis both cause their own set of problems – inflammation, immune system dysregulation, autoimmunity, and toxins leaking into the bloodstream.
IMPAIRED OXYGEN DELIVERY AND DETOXIFICATION

Chronic stress is now known to cause something known as pyrroluria, which is impaired hemoglobin synthesis.

Hemoglobin is the oxygen-carrying molecule that allows our red blood cells to carry oxygen from our lungs to our tissues.

So naturally, if you have low hemoglobin levels, you’re not going to be delivering oxygen to your cells very effectively.

Pyrroluria also results in depletion of vitamin B6 and zinc, which slows down one of our most important pathways of detoxification – the methylation cycle. So you’re not only getting less oxygen to the tissues, but it’s simultaneously causing toxins to build up in the body.

IMPAIRED LYMPH FLOW

It turns out that with chronic over-activation of this stress-response nervous system, it impairs lymph flow in the body.

As you might imagine, that impaired lymph flow leads to poor immune function, building up of junk in and around the cells, and susceptibility to infections.

Dr. Raymond Perrin, an osteopath specializing in fatigue has developed a form of deep lymphatic massage called the “Perrin Technique” and has studies on the effectiveness of his method.
IMMUNE SYSTEM DYSREGULATION
This naturally leads to increased susceptibility to infections and reactivation of latent viruses in the body.

HPA AXIS DYSFUNCTION
The limbic system is upstream of the HPA Axis and the dysfunction first starts in the limbic system.
Initially, it’s an increase in HPA Axis activity, which over time leads to reduced cortisol output and glandular depletion: In other words, the HPA Axis dysfunction and adrenal dysfunction – low cortisol – are not causes themselves, but symptoms of Limbic Kindling.
REDUCED GREY MATTER IN THE BRAIN, REDUCED GABA PRODUCTION, AND DEPLETED ACETYLCHOLINE
This can contribute to mood, sleep, and energy problems, as well as brain fog

DISRUPTED ION CHANNEL TRANSPORT
This makes it so cells can’t maintain the proper concentrations of minerals in and around the cells

DEPLETED ANTIOXIDANT LEVELS
When the body’s internal antioxidant defense system is depleted, it leads to chronic uncontrolled oxidative damage and the body’s antioxidants simply can’t keep up with the damage that’s happening
Ultimately, the end result of all this is:

- Uncontrolled oxidative stress damaging the mitochondria
- Increased opportunistic infections and reactivated latent infections
- Poor mitochondrial function
- Poor heart function
- Poor HPA axis and adrenal function
- Poor oxygen and fuel delivery to the muscles (thus poor stamina and being easily fatigued)
- Mood problems, buildup of toxins in the body, sleep problems
- Leaky gut and other gut problems – all of which tend to create vicious cycles of more dysfunction and symptoms.
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Unconscious amygdalar fear conditioning in a subset of chronic fatigue syndrome patients

Ashok Gupta

Abstract

Here, a novel hypothesis for chronic fatigue syndrome (CFS) is proposed. CFS may be a neurophysiological disorder focussing on the amygdala. During a ‘traumatic’ neurological event often involving acute psychological stress combined with a viral infection or other chemical or physiological stressor, a conditioned network or ‘cell assembly’ may be created in the amygdala. The unconscious amygdala may become conditioned to be chronically sensitised to negative symptoms arising from the body. Negative signals from the viscera or physiological, chemical and dietary stressors, become conditioned stimuli and the conditioned response is a chronic sympathetic outpouring from the amygdala via various brain pathways including the hypothalamus.

This cell assembly then produces the CFS vicious circle, where an unconscious negative reaction to symptoms causes immune reactivation/dysfunction, chronic sympathetic stimulation, leading to sympathetic dysfunction, mental and physical exhaustion, and a host of other distressing symptoms and secondary complications. And these are exactly the symptoms that the amygdala and associated limbic structures are trained to monitor and respond to, perpetuating a vicious circle. Recovery from CFS may involve projections from the medial prefrontal cortex to the amygdala, to control the amygdala’s expressions.
Can amygdala retraining techniques improve the wellbeing of patients with chronic fatigue syndrome

A clinical audit of subjective outcomes in a small sample

Ashok Gupta
Director, Harley Street Solutions

I suffered from ME (chronic fatigue syndrome) for three years. I spent years researching this mysterious illness to understand the causes, focusing on the brain neurology of conditioned traumas in the amygdala. I cured myself of the condition and wrote a medical hypothesis as to the cause of ME which was published in 2002. Subsequently I opened my clinic to help treat people with CFS and fibromyalgia, using amygdala retraining therapies combining a variety of approaches. I am a clinical hypnotherapist, a practitioner of NLP and a meditation teacher.

Summary
This paper is an initial clinical audit on Amygdala Retraining Techniques (ART), a novel set of holistic treatments for Chronic Fatigue Syndrome (CFS). ART is based on the hypothesis that CFS is caused by ongoing trauma in the amygdala. The clinical audit revealed higher rates of improvement in comparison to the natural remission rate in other intervention studies. Further randomised controlled studies are recommended to investigate the efficacy of the treatments.

Introduction
The clinical audit to assess the effects of amygdala retraining techniques (ART) on patients with chronic fatigue syndrome (CFS) studied 63 patients (average age 37.6, male:female ratio of 1:2) with a confirmed diagnosis of CFS based on international criteria. They were recruited for one-year. Participants consented to take part in the audit, and the techniques were taught in detail to them. Initial self-assessments of functional abilities were taken at the start and one year after treatment. Results 93% of participants reported improvement. Two-thirds of participants (67%) made considerable recoveries reaching “full functioning” (80–100% of pre-illness levels). Six participants dropped out of the survey.

Conclusions: The clinical audit revealed higher rates of improvement in comparison to the natural remission rate in other intervention studies. Further randomised controlled studies are recommended to test the efficacy of ART.

Background
Chronic fatigue syndrome is estimated to affect around 250,000 people in the UK. The clinical audit describes a pilot programme of a previously unpublished set of therapies known as amygdala retraining techniques (ART). This holistic set of treatments is underpinned by a medical hypothesis published in 2002, which implicates neurological trauma in the amygdala as the primary cause of CFS. This clinical audit was designed as a preliminary assessment of the effects of ART, and to prompt further research into its methods.

Amygdala retraining therapy is based on my novel hypothesis for the causes of CFS. I have suggested that following a traumatic event involving acute psychological stress (possibly combined with other dysregulating factors such as a viral infection or other chemical or physiological stresses), the amygdala may — through a conditioning process — become chronically sensitised to signals arising from the body. These signals from the viscera (perhaps triggered by physiological, chemical or dietary stresses) become conditioning stimuli. The visceral cortex may be involved in the process, as it interprets the emotional meaning of the symptoms, and passes that representation on to the

RESULTS:

- 93% of participants reported improvement.
- 67% of participants made considerable recoveries reaching “full functioning”: (80–100% of pre-illness levels).
Cannabinoid? Interesting word, right? Sounds sort of like cannabis (a.k.a. marijuana).

Most people are unaware of it, but we actually have an internal system (called the endocannabinoid system) that manufactures its own supplies of cannabis-like molecules.

And despite the fact that very few people (including health practitioners!) are aware of this system of the body...

The endocannabinoid system is one of the most important players in fatigue, brain health, mood, and getting your energy back!

The endocannabinoid system is a group of specialized fats, along with a set of receptors that respond to those fats, and the enzymes that produce and degrade them.

The endocannabinoids are known to modulate and influence a variety of physiological systems, including the stress-response system, hunger, pain, inflammation, muscle control, energy balance, metabolism, sleep, and motivation circuits in the brain.

But most importantly for our purposes here, the endocannabinoid system plays an enormous role in regulating our response to stress, alertness, and helping us re-establish homeostasis after stress.
New research is showing that the endocannabinoid system is a bigger player in our health and energy than any of us would’ve imagined just a few years ago. University of Washington neurologist Ethan Russo has shown that “clinical endocannabinoid deficiency” plays a big role “in migraines, fibromyalgia, irritable bowel disease, and a cluster of other degenerative conditions.”
Clinical endocannabinoid deficiency (CECD): can this concept explain therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions?

Russo EB.

Abstract

OBJECTIVES: This study examines the concept of clinical endocannabinoid deficiency (CECD), and the prospect that it could underlie the pathophysiology of migraine, fibromyalgia, irritable bowel syndrome, and other functional conditions alleviated by clinical cannabis.

METHODS: Available literature was reviewed, and literature searches pursued via the National Library of Medicine database and other resources.

RESULTS: Migraine has numerous relationships to endocannabinoid function. Anandamide (AEA) potentiates 5-HT1A and inhibits 5-HT2A receptors supporting therapeutic efficacy in acute and preventive migraine treatment. Cannabinoids also demonstrate dopamine-blocking and anti-inflammatory effects. AEA is tonically active in the periaqueductal gray matter, a migraine generator. THC modulates glutamatergic neurotransmission via NMDA receptors. Fibromyalgia is now conceived as a central sensitization state with secondary hyperalgesia. Cannabinoids have similarly demonstrated the ability to block spinal, peripheral and gastrointestinal mechanisms that promote pain in headache, fibromyalgia, IBS and related disorders. The past and potential clinical utility of cannabis-based medicines in their treatment is discussed, as are further suggestions for experimental investigation of CECD via CSF examination and neuro-imaging.

CONCLUSION: Migraine, fibromyalgia, IBS and related conditions display common clinical, biochemical and pathophysiological patterns that suggest an underlying clinical endocannabinoid deficiency that may be suitably treated with cannabinoid medicines.

Clinical endocannabinoid deficiency (CECD) revisited: can this concept explain the therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions?

Smith SC, Wagner MS.

Abstract

OBJECTIVES: Ethan B. Russo's paper of December 1, 2003 explored the concept of a clinical endocannabinoid deficiency (CECD) underlying the pathophysiology of migraine, fibromyalgia, irritable bowel syndrome and other functional conditions alleviated by clinical cannabis.

METHODS: Available literature was reviewed, including searches via the National Library of medicine database and other sources.

RESULTS: A review of the literature indicates that significant progress has been made since Dr. Ethan B. Russo's landmark paper, just ten years ago (February 2, 2004). Investigation at that time suggested that cannabinoids can block spinal, peripheral and gastrointestinal mechanisms that promote pain in headache, fibromyalgia, irritable bowel syndrome and muscle spasm.

CONCLUSION: Subsequent research has confirmed that underlying endocannabinoid deficiencies indeed play a role in migraine, fibromyalgia, irritable bowel syndrome and a growing list of other medical conditions. Clinical experience is bearing this out. Further research and especially, clinical trials will further demonstrate the usefulness of medical cannabis. As legal barriers fall and scientific bias fades this will become more apparent.
The role of the endocannabinoid system in the pathophysiology and treatment of irritable bowel syndrome

M. A. Storr, B. Yüce, C. N. Andrews, K. A. Sharkey

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Abstract

Irritable bowel syndrome (IBS) is a spectrum of disorders characterized by abdominal discomfort and pain, associated with altered bowel habits. Though gut motility, secretion and sensation may be altered in patients with IBS, the pathophysiology of this condition remains to be fully understood. The endocannabinoid system is involved in the regulation of numerous gastrointestinal functions including motility, sensation and secretion under both physiological and pathophysiological conditions. Activation of cannabinoid (CB1) and CB2 receptors under various circumstances reduces motility, limits secretion and decreases hypersensitivity in the gut. Drugs that alter the levels of endocannabinoids in the gut also reduce motility and attenuate inflammation. In this review, we discuss the role of the endocannabinoid system in gastrointestinal physiology. We go on to consider the involvement of the endocannabinoid system in the context of symptoms associated with IBS and a possible role of this system in the pathophysiology and treatment of IBS.
Here's the crux of the problem, and where the endocannabinoid system comes into play:

**Chronic stress progressively depletes our endocannabinoid supply.**
By doing that, we slowly lose the ability to properly ward off fear and anxiety. Most importantly, since this system is responsible for shutting down the stress response, when it’s depleted, we lose the ability to turn off stress!

Recall that Limbic Kindling is a progressive downward spiral of greater and greater stress response activation in the brain and body. The fear and danger processing centers of the brain are hypersensitized and extremely overactive. The brain and hormones are always in “stress mode.” A big part of what allows that to happen is depletion of the endocannabinoid system.

Thus, the endocannabinoid system is actually a gatekeeper of sorts—it’s only once the endocannabinoid system is depleted that all these other mechanisms of how stress wrecks our energy can take hold.

Having a depleted and imbalanced endocannabinoid system is thus one of the major (or perhaps the major) mechanism that causes stress to become chronic and prevents the body from getting out of “stress mode.”

**Limbic Kindling also lowers orexin levels**

We’ve already talked about orexin as a key regulator of our wakefulness and energy.

The endocannabinoid system is also intimately connected with orexin, and dysfunction in the Ec system can translate into lowered orexin levels, and by doing so, directly induce fatigue.

**Cannabinoid-hypocretin cross-talk in the central nervous system: what we know so far**

África Flores, Rafael Maldonado, and Fernando Barreiro*

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**Abstract**

Emerging findings suggest the existence of a cross-talk between hypocretinergic and endocannabinoid systems. Although few studies have examined this relationship, the apparent overlap observed in the neuroanatomical distribution of both systems as well as their putative functions strongly point to the existence of such cross-modulation. In agreement, biochemical and functional studies have revealed the existence of heterodimers between CB1 cannabinoid receptor and hypocretin receptor-1, which modulates the cellular localization and downstream signaling of both receptors. Moreover, the activation of hypocretin receptor-1 stimulates the synthesis of 2-arachidonoyl glycerol culminating in the retrograde inhibition of neighboring cells and suggesting that endocannabinoids could contribute to some hypocretin effects. Pharmacological data indicate that endocannabinoids and hypocretins might have common physiological functions in the regulation of appetite, reward and analgesia. In contrast, these neuromodulatory systems seem to play antagonistic roles in the regulation of sleep/wake cycle and anxiety-like responses. The present review attempts to piece together what is known about this interesting interaction and describes its potential therapeutic implications.
THE TWO MAIN SUBTYPES OF CANNABINOID RECEPTORS IN THE BODY – CB1 AND CB2

Research is accumulating that a great many people are suffering from CB1 dominance and CB2 underactivity, and that situation is associated with stress, anxiety, paranoia, increased appetite and food consumption, and an overactive immune system - which has been linked to cancer and other illnesses.

In contrast, CB2 dominance is associated with improved metabolic health, lower inflammation, and lower stress and anxiety.

If you want to overcome fatigue and reclaim your energy, you have to get your brain out of “chronic stress mode.”

To do that, you must reverse the downward spiral of Limbic Kindling and endocannabinoid deficiency.
Limbic kindling is when small sparks of stressors create a raging fire in the limbic system of the brain.
Rebuilding and balancing your endocannabinoid and limbic system is one of the most important steps for stopping the downward spiral of wiring your body into “stress mode.”

Remember, to get your body to be able to shut down “stress mode” and go into “safe mode” and “relaxation and regeneration mode,” your endocannabinoid system must be optimized. Without that, you’re going to stay stuck in stress mode no matter what you do.

So how do you correct limbic dysfunction and actually rebuild and rebalance your endocannabinoid system?

If you want to overcome fatigue and reclaim your energy, you have to get your brain out of “chronic stress mode.”

To do that, you must reverse the downward spiral of Limbic Kindling and endocannabinoid deficiency.

The first step in reversing an overactive limbic system is to simply de-stress as much possible. To do this, I recommend using the following 5 steps:
I2 STRATEGIES TO REBUILD THE LIMBIC AND ENDOCANNABINOID SYSTEMS

1. De-stress
Ultimately, the endocannabinoid system becomes strained through physical and mental stress, so it makes sense that avoiding stress like the plague will give your endocannabinoid system the opportunity to rebuild. There are several important strategies needed to de-stress:

**OPTIMIZE YOUR CIRCADIAN RHYTHM AND SLEEP**

- High alertness: 10:00
- Highest testosterone secretion: 09:00
- Bowel movement likely: 08:30
- Melatonin secretion stops: 07:30
- Sharpest rise in blood pressure: 06:45
- Lowest body temperature: 04:30
- Deepest sleep: 02:00
- Nocturnal repair: 00:00
- Midday coordination: 12:00
- Noon
- Best coordination: 14:30
- Fastest reaction time: 15:30
- Greatest cardiovascular efficiency and muscle strength: 17:00
- 18:30 Highest blood pressure
- 19:00 Highest body temperature
- 21:00 Melatonin secretion starts
- 22:30 Bowel movements suppressed

**MINIMIZE OR ELIMINATE STIMULANTS (AT LEAST TEMPORARILY)**
Caffeine is a chemical stimulant that increases activity in certain parts of the brain and central nervous system.

To understand caffeine, you first need to understand the neurotransmitter adenosine.
Adenosine have receptors in your brain that they latch on to, to control your energy levels.
Caffeine enters your system and has similar shape as adenosine, it then latches on to the adenosine receptors, preventing the adenosine to do so.

The caffeine makes you feel energized and alert.
The brain, thinking that there is not enough adenosine, starts producing more which makes you feel tired.

Now, you need more coffee to feel energetic and normal.

To illustrate, look at the image below.
By blocking the fatiguing effects of adenosine, it creates a stimulant effect that energizes you, for a little while. But caffeine wears off after a few hours, and then you will be feeling even worse.

Then you drink more of it. This is how you build up a tolerance for caffeine, and is why it eventually takes a second cup to fully wake you up in the morning.

**STRATEGIES TO WEEN OFF CAFFEINE CONSUMPTION**

- If you currently are a coffee addict, your goal is to slowly and progressively ween yourself off of it over the coming 4-8 weeks. Decaf is your friend!

- Then get yourself clean for at least 2-3 weeks.

- From there, if you really must drink coffee, you should limit yourself to just 1-2 per day and then you should use it in a pattern where you take off as many days as you use it.
LOWER YOUR SENSORY LOAD

Most of us living in the modern world are now constantly bombarded by flickering lights, rapidly changing sights and sounds, social media, text, phone, email, TVs, phones, music, games, movies.

All of that is on top of the hectic lives we live.

To cope, the brain is constantly TRYING to find a way to calm itself down. It does this through the inhibitory NTs, serotonin and GABA.

But when these systems are constantly taxed in this way, it’s a losing battle and you eventually wear out the system and start to create NT imbalance and issues with NT receptors.

DO RE-CHARGE RITUALS DAILY

This is probably the single most important part of taking the stress off the limbic system. Actively taking time to destress is a critical part of optimal health and energy. Take stress seriously and commit to making time for de-stressing. Your brain will thank you.

Intense stress should always be counterbalanced by INTENSE commitment to destressing. We’re going to talk about this later in this module when we discuss consciously operating your brain for optimal brain health.

Installing de-stressing rituals into your daily routines is VITAL to optimal HPA Axis function.

2. GET YOUR OMEGA 3S

Omega-3 fats are vital to the health of your endocannabinoid system.

Omega 3 fats help balance the endocannabinoid system by decreasing CB1 activity and increasing CB2 activity. Research has now linked the interaction of omega-3s with the

<table>
<thead>
<tr>
<th>Think about the following activities you may be doing:</th>
<th>Always being on the go doing things without taking breaks to recharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Listening to loud music while driving or exercising</td>
<td></td>
</tr>
<tr>
<td>Getting involved in exciting, fast-moving or violent movies or games before going to bed</td>
<td></td>
</tr>
<tr>
<td>Staring at a computer monitor for most of your workday</td>
<td></td>
</tr>
<tr>
<td>Staring at the TV for hours</td>
<td></td>
</tr>
<tr>
<td>Listening to overly stimulating background music</td>
<td></td>
</tr>
<tr>
<td>Being indoors under artificial light for most of the day</td>
<td></td>
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</table>
endocannabinoid receptors in the brain with protecting the brain cells from damage and inflammation.

3. Eat Greens
Greens are a wonderful source of beta-carophyllene, which is a phytocannabinoid that has powerful balancing effects on the endocannabinoid system by stimulating CB2 activity.

4. Use Essential Oils Rich in Beta-Carophyllene
Beta-carophyllene is found in significant quantities in most essential oils. But it is especially rich in Copaiba essential oils (roughly 50% of the oil is beta-carophyllene!). This makes it a powerful way to stimulate your CB2 activity.
5. **Eat foods rich in pterostilbene**

Pterostilbene is a powerful phytochemical similar to resveratrol that inhibits the enzyme that breaks down endocannabinoids in our bodies. In other words, it helps boost the amount of endocannabinoids we have floating around in our body.

**The best foods for this purpose are blueberries and mulberries.** In addition, pterostilbene can also be found in almonds and red grapes.

6. **Cut alcohol**

Alcohol is a must-avoid compound when trying to rebuild your endocannabinoid system, because it counteracts all the things we’re trying to do with balancing out our endocannabinoid activity.

7. **Do exercise**

Exercise is a powerful force for stimulating production of anandamide (known as the “bliss molecule”), which is one of endocannabinoids. The nitric oxide produced from exercise works to stimulate endocannabinoid production.

**Caveat:** You MUST tailor this to YOUR needs as an individual.

8. **Herbs and Spices**

There are a number of herbs and spices that research has shown to benefit the endocannabinoid system:

- Echinacea (stimulates the CB2 receptors)
- Saffron (general stimulation of the whole endocannabinoid system)
- Black pepper (rich in beta-carophyllene, which stimulates CB2 activity)
- Nutmeg (inhibits the enzymes that break down endocannabinoids)
- Cacao (inhibits the enzymes that break down endocannabinoids)
- Turmeric (inhibits CB1 activity and boosts endocannabinoid levels, likely by inhibiting the enzymes that break down endocannabinoids)

9. **Sunbathing**

This stimulates nitric oxide production, which can serve to boost endocannabinoids, without the intense stress of exercise.

10. **Heal emotional traumas**

There is research showing that emotional traumas and ACEs can cause long-lasting impairments in brain function and can contribute to limbic hypersensitization.

More on this from Niki Gratrix in the bonus...

11. **Get a massage, acupressure mats (or acupuncture) and self-myofascial release**

This is another tool that studies have found promote a balanced endocannabinoid system.
12. **Use cannabidiol (CBD)**

CBD, is a powerful endocannabinoid signaler found in marijuana and hemp plants.

CBD is a powerful anti-anxiety and anti-stress cannabinoid signaling compound that basically balances and helps rebuild the entire endocannabinoid system.

Hundreds of studies have now been done to show that CBD can benefit all sorts of illnesses and conditions.

The fastest acting way to get it in your system to crush anxiety and stress fast is through vaporizing it, [which you can do with this system](#). I don’t necessarily recommend vaporizing every day, multiple times a day, however. That’s best used in moments of anxiety and stress. For the rest of the time, I suggest using oral CBD, and [here is the one I suggest getting](#). Also note that Bluebird Botanicals has been rated as the #1 CBD on the market, so that’s why I recommend getting your CBD from them.
12 STRATEGIES TO REBUILD THE LIMBIC AND ENDOCANNABINOID SYSTEMS

1. DE-STRESS
2. OMEGA 3S
3. GREENS
4. ESSENTIAL OILS WITH BETA-CAROPHYLLENE
5. FOODS RICH IN PTEROSTILBENE
6. CUT ALCOHOL
7. EXERCISE
8. SUNBATHING
9. HEAL EMOTIONAL TRAUMA
10. HERBS (Echinacea, saffron, black pepper, nutmeg, cacao, and turmeric)
11. MASSAGE... (acupressure mats or acupuncture) and self-myofascial
12. CBD

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