

HORMESIS

Vitagenes & Adaptive Cellular Stress Response

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Foreword

In this series of eBooks delivered to you weekly, I present you with the most effective, evidence-based cognitive interventions within a brain cross training paradigm. Adopting a brain cross training framework is unique in a brain training industry that focuses exclusively on computer based applications and biometrics. It is my hope that [IQ Mindware apps and resources](#) can help set out an easily accessible set of strategies enabling you to draw from evidence-based interventions for improving your cognitive resilience, health and performance.

In the next few eBooks I look at exciting discoveries in biochemistry and the cellular and molecular neurosciences that have now provided us with a deeper understanding of how exercise, intermittent fasting, nootropics, mental challenges and other ‘good stressors’ can work synergistically to improve *not only brain health, performance and resilience, but overall health, immunity and longevity.*

There is a deep unifying principle underlying these interventions called **hormesis**. Hormesis is a *resilience-building principle* that can be widely and easily applied for better brain functioning and this eBook is a general introduction to hormesis.

Enjoy your training!



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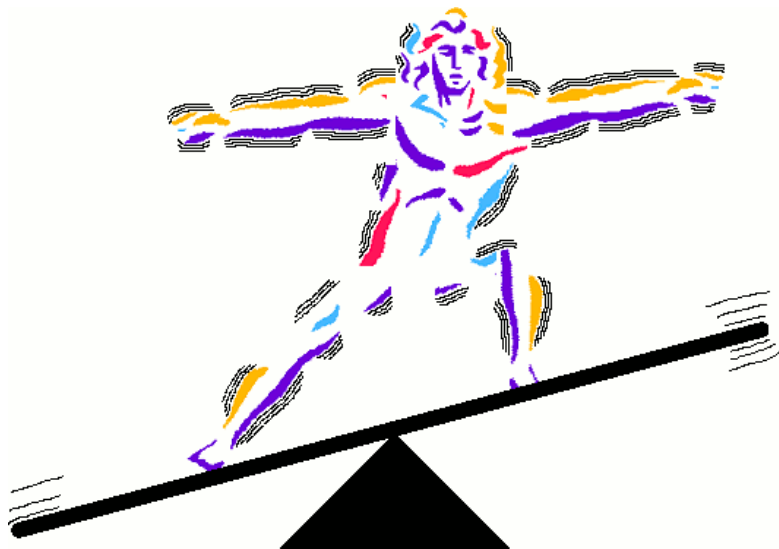
'Good Stress' & the Evolution of Vitagenes

This eBook is an introduction to a very powerful brain training principle: that *stress* – physical and psychological – is a 'magic bullet' for improving the brain's resilience, health and performance.

Before explaining why, we need some key definitions.

What is *stress*? Stress can be understood in terms of biological homeostasis.

Homeostasis is a biologically evolved self-regulation mechanism that works to keep internal conditions (such as body temperature) stable in the face of internal or external effects ('stressors') that tip the system off balance (such as a fever or severe cold). The more 'dynamic homeostasis' a system has the more it can 'bounce back' and the more *resilient* it is.



Stress – which can be physical or emotional – is a state in which homeostasis is threatened, when our internal systems that keep us in good health and able to perform are made more unstable.

In the drier environments of our distant ancestors, food was often scarce, and energy expenditure high. Life was often stressful, and this stress shaped the evolution of our brains. Three stressors in particular - relating to energy demands (called 'energetic stressors') - put strong pressures on the evolution of human brains and biochemistry:

- **Caloric restriction** (CR) in times of food scarcity. This is when energy sources for powering our bodies and brains was lacking.
- **Physical work** in times of intense or prolonged physical challenges such as hunting or long-distance travel. This was when we had to burn up a precious metabolic energy.
- **Mental challenges** when we were faced with complex situations needing learning or problem solving, or when we needed to plan and strategize to accomplish complex goals. The brain has evolved to be highly energy-consuming due to the work it does.

In addition to these energy-related stressors, there have been three other types of stressors that have recurred throughout the ages, shaping the evolution of our brain biochemistry:

- **Plant food chemicals** called phytochemicals that evolved to protect plant health and deter plant consumption. This kind of chemical defense mechanism is behind the intense taste of many spices, garlic and onions.
- **Temperature extremes** - whether severe heat during the day or severe cold during the night or during the long ice-age climates that punctuated our species' evolutionary history.
- **Sleep deprivation** - as a result of unpredictable interruptions in the sleeping phase of our circadian rhythms.

As our species evolved, those individuals who could cope with and thrive on these common stressors had an *adaptive advantage* in the struggle for survival and reproduction and their genes flourished. Over long periods of time, the human body and brain has become biochemically adapted to these stressors, and has developed biochemical mechanisms (types of cellular signaling pathways) to actually benefit from them in profound ways.

Vitagenes & Adaptive Cellular Stress Responses

Over time we have evolved genes controlling a biochemical package of **adaptive cellular stress responses** to the stressors our ancestors faced. These amazing biochemical mechanisms repair and build resilience, promoting our physical and mental performance. These genes are known as **vitagenes** – genes for cellular protection, repair and successful adaptation in the face of stress.

The specific biochemical pathways switched on by the vitagenes in response to calorie restriction, exercise and mental challenges – are shown in scientific detail in Appendix 1. Adaptive cellular responses are also triggered by phytochemicals, temperature stress and sleep deprivation.

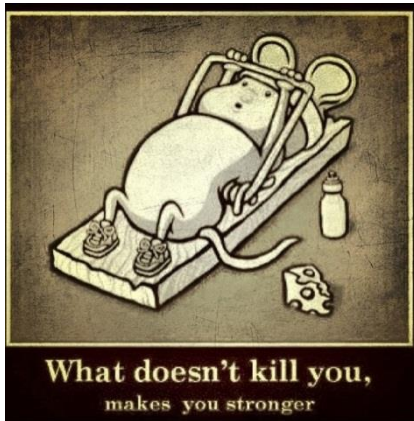
As meta-reviewed [here](#) and [here](#), the health benefits of stress-triggered cellular stress responses include:

- **Increased brain cell growth (neurogenesis) and neuroplasticity for learning and memory by producing nerve growth factors such as Brain Derived Neurotrophic Factor (BDNF) and insulin-like growth factor (IGF-1)**
- **Reduced cancer causing anabolic hormones**
- **Improved insulin sensitivity & reduced diabetes risk**
- **Improved mitochondrial function and energy metabolism**
- **Reduced inflammation**
- **Removal of damaged organelles and cells**
- **Activation of DNA repair systems for DNA stability**
- **Production of fatty acids/ketone bodies. [Ketones protect brain cells \(neurons\) against exposure to toxins associated with Alzheimer's or Parkinson's](#). They also provide a more efficient fuel source for the brain.**
- **[Possible increased life-expectancy due to the protective stress response gene SIRT3](#).**

By switching on our vitagenes, not only is brain health and neuroplasticity improved, but energy metabolism may be improved and the risk of diabetes, cancer, and inflammation related malignancies reduced.

How To Switch On The Vitagenes: The Hormesis Response

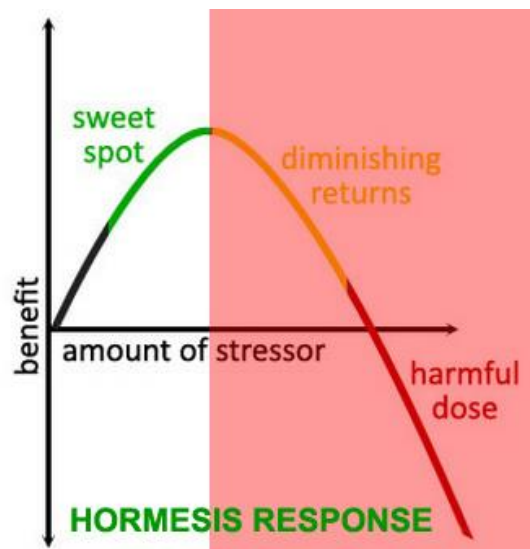
So how do we switch on (upregulate) our vitagenes that control the cellular stress responses, to unlock the remarkable benefits to health and brain function? The answer is we systematically harness a well-studied biological process called the **hormesis response**. We do some ‘biohacking’!



Hormesis can be defined as a biphasic response to a stressor - where a low dose of the stressor results in a beneficial effect and a high dose results in a toxic effect. For example, while a large ‘dose’ of the stress of caloric restriction (lack of food) results eventually in starvation and a collapse of our major biological systems such as metabolism and immunity, a smaller dose (i.e. fasting) activates biological repair mechanisms, builds resilience, and regenerates the brain and

body by upregulating the vitagenes. Hormesis underlies Nietzsche’s maxim: ‘What doesn’t kill you makes you stronger’!

What does ‘biphasic response’ mean in scientific terms? The general *biphasic response curve* for hormesis is shown in this diagram.



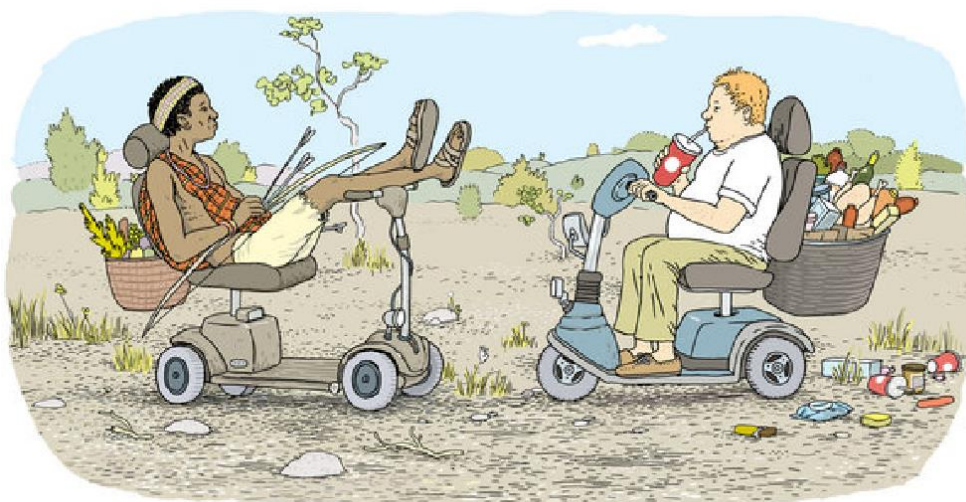
As the dose of the hermetic stressor (e.g. lack of food, exercise, mental effort, phytochemicals in plants) is increased, beneficial vitagenes are upregulated within a certain range – the ‘sweet spot’ of the hormesis responses. If the stressor exceeds this optimal range it increasingly results in harmful biological outcomes. These are the two phases of the response.

The doses are absolutely critical. It is easy to overshoot, and damage our biological systems and brain health with inappropriate doses of the stressors. And individuals all differ in these dynamics. While one person might be able to fast for 24 hours and reap a lot of biological benefits, someone else might be over-stressed by this, with adverse effects on the immune function and metabolism.

And by regularly activating the hormesis response *at the right dose*, the ability to take on increasing intensities of stressors increases. The response is *adaptive*. The biphasic curve shifts to the right as we become adapted to higher levels of stress, increasing the depth of our resilience and broadening the range of conditions over which we can remain healthy and perform at an optimal level.

So stress – in the right doses and applied at the right times – is highly beneficial for the brain and body. We can harness it in brain cross-training programs. Without stress, the vitagenes and adaptive cellular stress responses don't kick into action to build resilience, health and better brain functioning.

And while the (stressful) practices of fasting, exercise and taking on mental challenges are all known to promote our health and brain function, we see the opposite effect too: deteriorating health, immune function and neuroplasticity resulting from overeating, a sedentary lifestyle and cognitive inactivity.

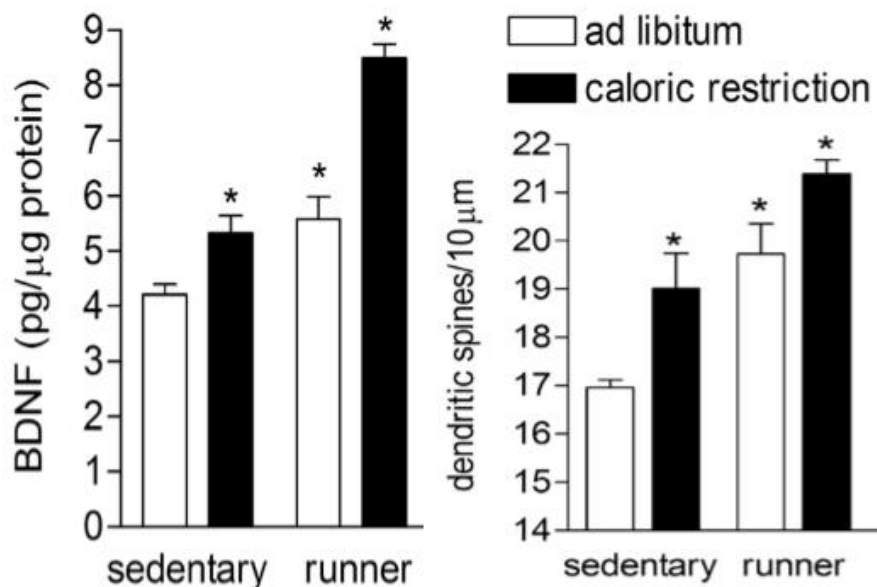


NY Times / Anders Nilsen

Hormetic Synergies

Combinations of hormetic stressors, such as running and fasting or phytochemical and fasting, may have biochemical interactions that are *synergistic*.

This study on the effects of hormetic stressors on the brain's *neuroplasticity* (ability to grow) in rats illustrates this synergy principle. Neuroplasticity was measured by amount of nerve growth factor (BDNF) and the amount of nerve cell connections (dendritic spines), shown in the graph below. It is clear that rats who were BOTH exercising (running) and calorie restricted gained the most neuroplasticity. ('Ad Libitum' means feeding was unrestricted.) These two energy stressors *in combination* gave the rats the best brain benefits. Due to a similar underlying brain biology, we can expect the same synergy effect for our own brains.



Synergisms for brain cross training in my own program include the following:

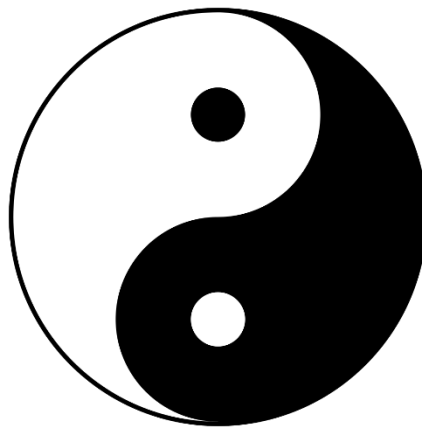
- High Intensity Interval Training (HIIT) combined with fasting.
- Phytochemical drinks combined with fasting.
- HIIT combined with phytochemical drinks.
- Exercise in extreme cold (e.g. sea swimming) or heat (e.g. Bikram yoga).
- Sleep deprivation combined with phytochemical drinks or exercise.

Of course, the doses are absolutely critical when you are experimenting with combinations. It is that much easier to overstress our systems and compromise

brain health and performance by overdoing the training. It is important to feel your way, starting at lower doses, and ensuring that you feel the health-enhancing effects as you go along.

The ‘Yin and Yang’ of Hormetic Stress & Active Relaxation

The evidence also suggests that combining *hermetic stressors* with *active relaxation* (a ‘Yin and Yang’ principle) is the optimal way of getting the best out of your vitagenes and the hormesis response.



There are many biologically programmed cycles of stress-followed-by-relaxation, where relaxation occurs naturally following periods of stress. These ‘rebound’ effects can be thought of as homeostatic – recovering balance by ‘overshooting’ in the other (relaxing) direction. This can be seen clearly in the 24 hour circadian cycle of:

- Wakefulness during the day – when body temperature and cortisol (stress hormone) levels are at their highest, to meet life’s challenges and stresses.
- Sleep at night – when body temperature and cortisol are at their lowest, and the body undergoes recovery and repair (e.g. secreting growth hormone).

We know that sleep is deeper and more restorative when there is more physical and mental challenge during the day. This is a homeostatic ‘rebound effect’.

And when we overcome stressful challenges during which we are goal-focused and aroused, which with generally lead to periods of relief and satisfaction that are forms of relaxation. In a healthy 'dynamic homeostasis' there is an ongoing interplay between (a) mental work, goal-focus, arousal, and problem solving engagement and (b) goal satisfaction, letting go, mind-wandering (e.g. day dreaming) and relaxation. Here mental relaxation is the 'rebound effect' of mental effort (a hormetic stressor).

When we are chronically stressed, high strung or burned out, and don't have a fluid, balanced interplay of stress and relaxation in our lives, and adaptive cellular stress responses will not result in optimal health and performance outcomes.

So how can we achieve the best overall balance?

The evidence tells us that deliberate experience of hormetic stressors, by exercising, fasting or eating spicy foods such as Turmeric for example, *promotes* better relaxation. Exercise reduces stress as we know. Fasting has been shown to decrease our nervous system's stress response, with decreased tone of our 'fight or flight' sympathetic nervous system, and increased tone of our 'rest and relax' parasympathetic nervous system. The same is true for pungent compounds (phytochemicals) in spices and vegetables. There has been repeated demonstration that these can decrease the stress response.

And the evidence indicates that *active* relaxation in combination with hormetic stressors such as exercise can be of synergistic benefit. For example, sports massage following intense exercise can improve the immune response.

In the cross brain training program I adopt I combine hormetic stressors with active relaxation in the following ways:

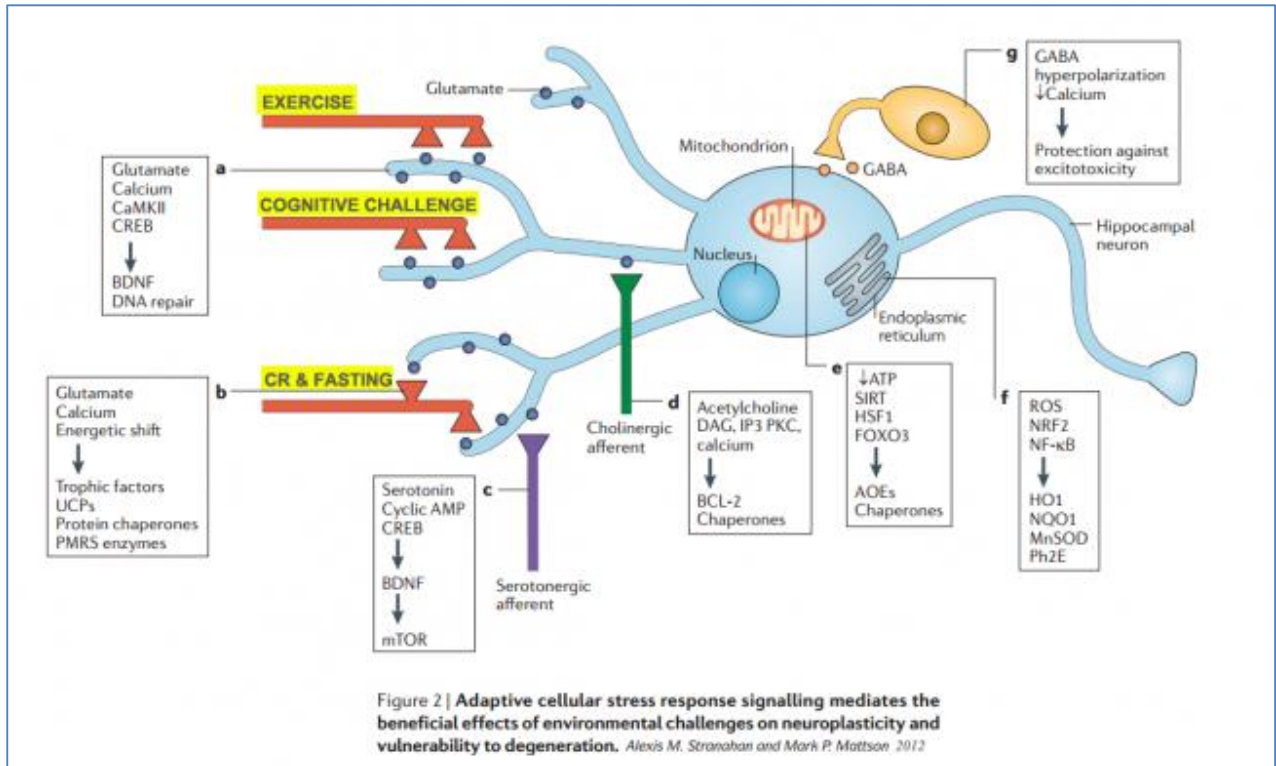
- High intensity interval training (HIIT) followed by meditation, breathing exercises, massage or a relaxing bath.
- Brain training followed by mindfulness meditation. Or vice versa.
- Intermittent fasting in combination with mindfulness meditation.
- Phytochemical-rich hot drinks followed by sleep.

Any number of combinations can be experimented with, using the same basic yin-yang principle.

We will look at specific programs to implement in the following eBooks that focus specifically on hormesis and active relaxation.

Appendix

The Adaptive Cellular Stress Response



Specific pathways of the adaptive cellular stress response include the following:

- Activation of **neuroprotective proteins** such as brain-derived neurotrophic factor (BDNF) (a).
- Increased **brain tissue growth and neuroplasticity** by the activation of BDNF (c).
- Activation of proteins (e.g. UCP) that **help regulate blood glucose energy** and prevent **diabetes** (b).
- Activation of anti-apoptotic proteins (e.g. BCL2) that **prevent the destruction of immune (white blood) cells** (d).
- Activation of protein chaperones and other proteins that **protect cell structures against stress** (b, d, e, f).
- Activation of **DNA repair and stabilization proteins** (a, f).

- Release of GABA during exercise and brain training **reduces excitotoxicity** (g) – the toxic effects of over-active neurons.
- Lower cell energy (ATP) levels during fasting **activate antioxidant enzymes** (PMRS, AOE) (b, e, f). These enzymes protect against **oxidative stress** which is damage to cell structure and cell function by overly reactive (**free radical producing**) oxygen-containing molecules and chronic **inflammation**.
- Activation of ATP involving enzymes (kinases) and other proteins that increase **removal of damaged cells and cell parts** (a, d, e).
- Activation of **anti-inflammatory enzymes** (e.g. HO1) (f).

