



Brain Cross Training

Non-invasive, non-synthetic brain training strategies for brain health, resilience & performance

Mark Ashton Smith, Ph.D. 2016.

www.iqmindware.com

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Foreword

We live in an increasingly *cognitive* world.

‘Cognition’ comes from the Latin *cognosco* – **con** ‘with’ + **gnōscō** ‘know’ – and the Ancient Greek verb **gi(g)nósko** meaning ‘I know, perceive’. Cognition concerns getting, storing, processing and using *knowledge*. It concerns perception, memory, learning, problem-solving, strategy, skill-sets, expertise and decision-making. At a meta-level it involves goal focus, mental flexibility, multi-tasking, prioritization and self-control.

- Cognitive health and ability enables us to better use the technologies, learn the skills, and process the information that enriches our culture and social lives.
- Maintaining brain health and cognitive functioning into a ripe old age is now a major health-care goal.
- Cognitive resilience, health and performance is valuable ‘cognitive capital’ in our complex, evolving, high tech, data-driven economy – in education, training and employment.
- Performance in our skills, knowledge and expertise can be improved substantially by applying the right strategies and interventions, allowing us to push our limits, unlocking our potential to excel.

In this eBook, I review 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 biofeedback. It’s my hope that IQ Mindware apps and resources can help you to access a wide variety of practical strategies to realize your potential for improving your cognitive resilience, health and performance.

Enjoy your training!

Mark Ashton Smith, Ph.D.



Chapter 1.

Brain Health, Resilience & Performance

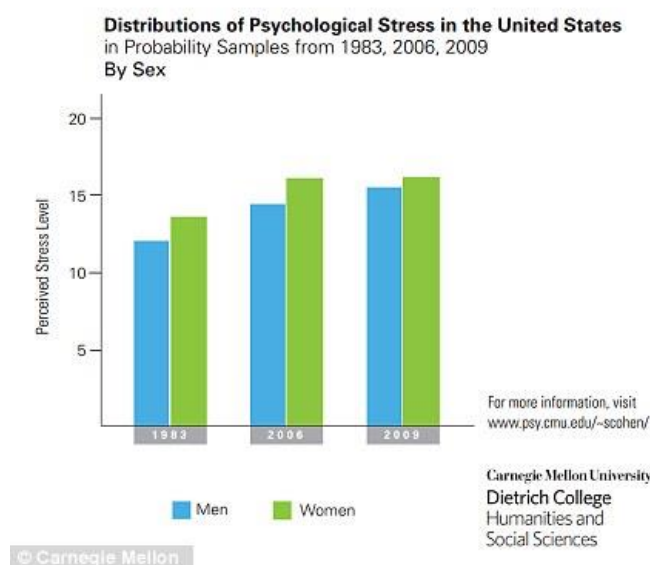
IQ Mindware products and services are dedicated to improving cognitive resilience, health and performance. These are all interdependent. Let's take a closer look at each of them.

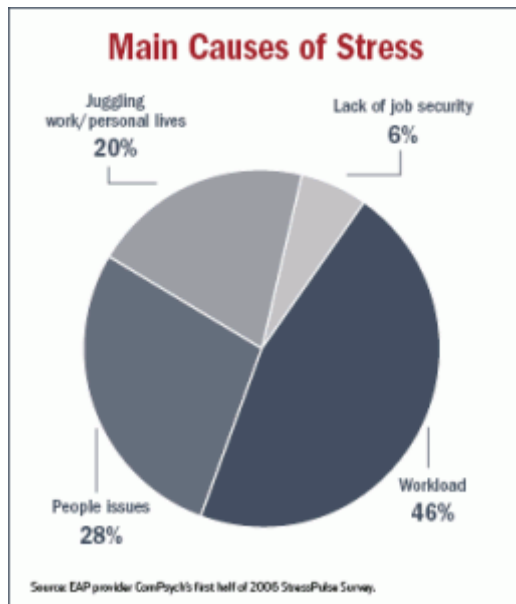
Cognitive Resilience

Cognitive resilience is ***the capacity to both overcome the negative effects of stressors on cognitive function or performance and harness stress for greater cognitive performance.***

People differ widely in cognitive resilience. Some individuals are able to take in their stride negative stressors such as intense work demands, interpersonal conflict, financial pressures or even loss of employment and poor health – stressors that can be devastating to other individuals. And very often these same individuals seek out stressors ('challenges') to motivate better cognitive functioning and performance. Others try to stay in their comfort zone, and in the face of unavoidable stressors, concentration, memory, problem solving and decision-making are all impaired.

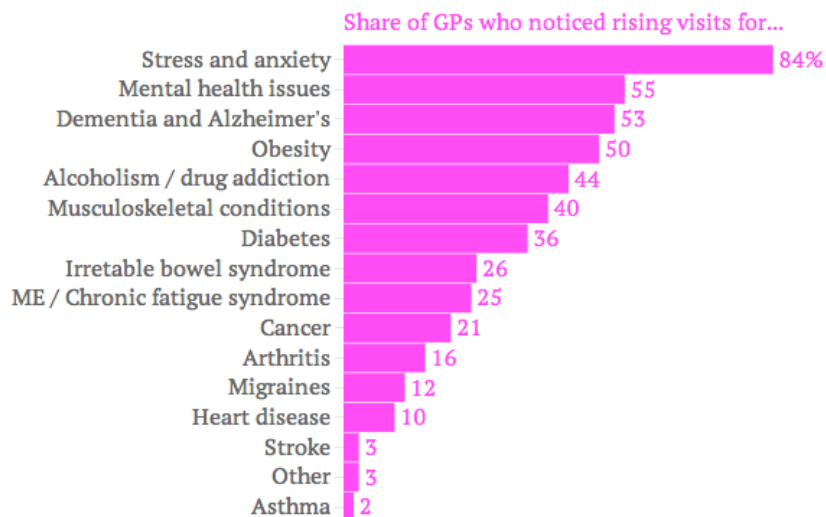
Finding effective interventions to improve cognitive resilience is more important than ever because (a) there has been a steady rise in stress levels over the past generation, and (c) much of this stress is due to workload that is typically the demand for high output cognitive performance.





And cognitive resilience reduces susceptibility to serious cognitive health issues – insomnia, anxiety, depression and burnout, as well as cognitive decline (dementia, Alzheimer’s) with aging. In recent years, UK doctors have been noticing a sharp uptick in visits from patients reporting stress, anxiety and dementia issues, and this trend is not confined to the UK.

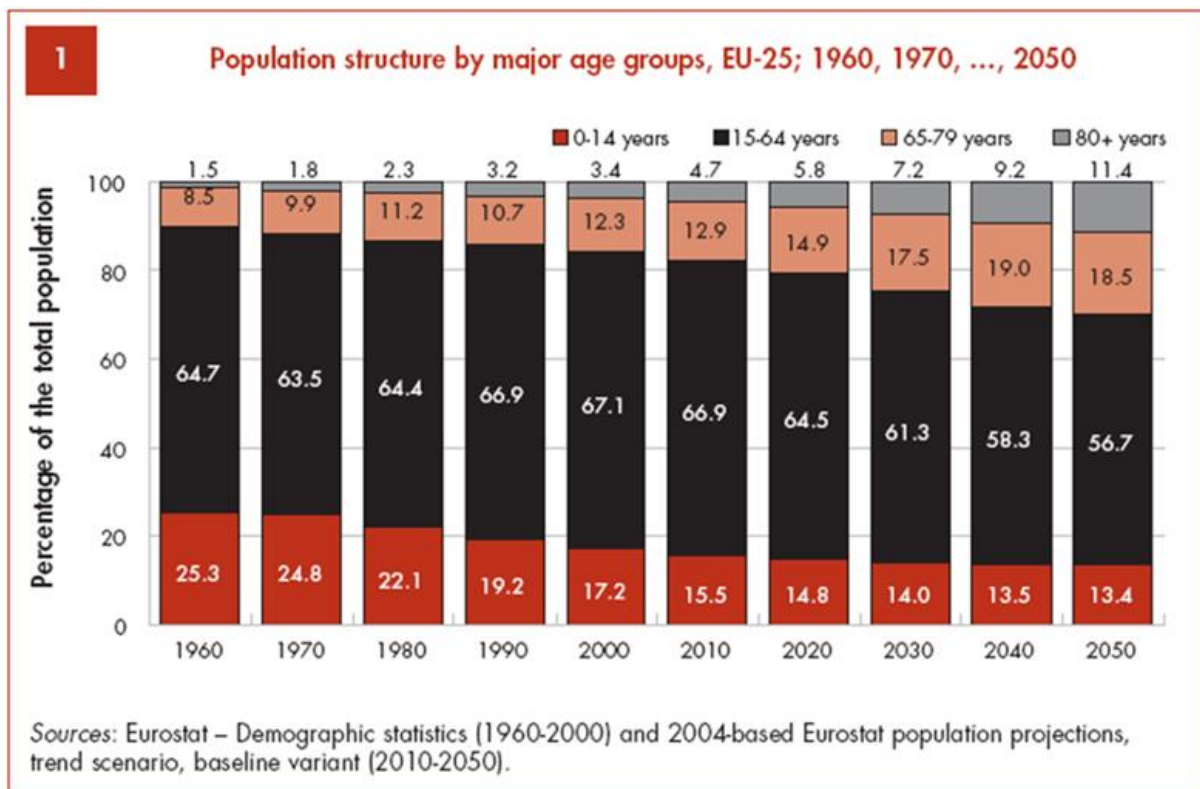
British GPs noticed an increase in visits for certain conditions



Brain Health

Cognitive resilience is one aspect of brain health. Brain health interventions focus on building resilience and preventing stress-related disorders, brain disease and cognitive decline with aging as well as retraining the brain to regain cognitive function. The most effective brain health interventions capitalize on the brain's dynamic capacity to be strengthened in health and repaired after brain injury or brain disease.

The world's demographics of the world are changing fast, with steadily increasing proportions of older people.



As we age, particularly beyond our 50s there is a general drop in cognitive performance in processing speed, problem solving and reasoning ability, spatial ability, as well as working memory.

Among adults over 50, 'staying mentally sharp' out ranks Social Security and physical health as the top priority and concern ([Sharpbrains market research](#)).

An increasing proportion of the population suffers from age-related dementia. The most common type of dementia is Alzheimer's. In 2006, there were 26.6

million sufferers worldwide. Alzheimer's is predicted to affect 1 in 85 people globally by 2050.

Given these data, tackling different forms of aging-related cognitive decline through active 'brain training' interventions has become a major focal point. The two major healthcare providers Bayer and Merck have both already integrated brain training into their health care strategies and this trend will only strengthen.

Cognitive Performance

We live in an age of self-improvement and personal growth more than at any other time in history. The envelope of human potential in our skills, endurance, health and performance is being pushed out everywhere. With this drive to tap potential and push limits, comes the understanding that we need use strategies to do so. We need to adopt practices, develop new habits, train, and access useful resources – technologies, tutorials, coaching, and other helpful interventions – to reach our goals and develop our abilities.

Cognitive performance is defined relative to some demand or challenge, and can be defined as competence and effectiveness in meeting that challenge. Examples include doing well in an entrance exam or job test, solving a problem at work, making a sound decision that has wide impact, devising an effective career strategy, learning a new skill efficiently or retaining self-control under pressure.

General Intelligence (G)

The most general idea of cognitive performance is that of **general intelligence**, sometimes simply called 'G'. General intelligence has been defined in different ways by different scientists. [An excellent compilation of definitions of general intelligence can be found here](#). Here are some of the better definitions:

“Intelligence is a very general mental capability that, among other things, involves the ability to reason, plan, solve problems, think abstractly, comprehend complex ideas, learn quickly and learn from experience.” L. S. Gottfredson

“...the capacity to reorganize one’s behaviour patterns so as to act more effectively and more appropriately in novel situations ...the ability to learn ...the extent to which a person is educable ...the ability to carry on abstract thinking ...the effective use of concepts and symbols in dealing with a problem to be solved ...” W. Freeman

“Intelligence is the ability to solve problems, or to create products, that are valued within one or more cultural settings.” H. Gardner

IQ Tests

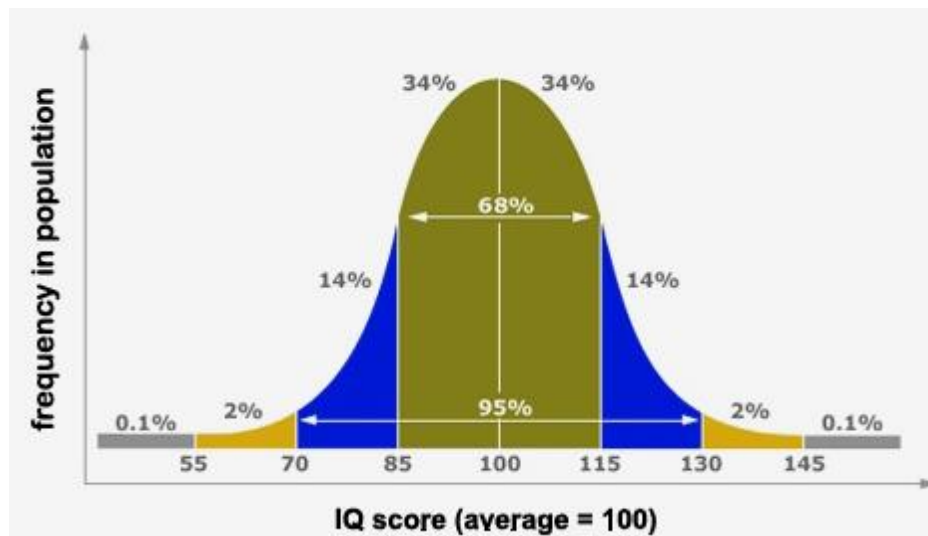
The most well-known measure of general intelligence is a standardized **IQ test**. ‘IQ’ stands for ‘intelligence quotient’. Standardized means that scores can be compared in the general population and you know what score is needed to be in a certain percentile – for instance above average, or in the top 2% (Mensa standard). Examples of IQ tests include the Wechsler Adult Intelligence Scale, the Stanford-Binet, and the Cattell Culture Fair test, and Raven’s Progressive Matrices.

There are many bogus IQ tests on the web that either don’t accurately or reliably measure your general intelligence, or which give you an inflated score. Valid, reliable, standardized tests are difficult to locate and are usually professionally administered.

IQ tests certainly aren’t designed to measure everything important about cognitive performance. They do not measure decision-making ability, attention control or self-control for instance. But IQ tests are the best tests for cognitive performance that scientists have devised. IQ test scores can be used to predict achievements in a wide range of abilities, including creativity, educational attainment, health, leadership, lifespan, professional achievement and income. IQ tests are widely used in our institutions and organisations because of their consistency and validity. Schools and universities use IQ tests (or ‘aptitude tests’) to select and stream students, companies use IQ tests to screen applicants, with estimates of 80% of Fortune 500 companies’ HR departments using these kinds of tests for recruitment.

IQ tests are designed so that the **average IQ score for test takers is 100**. IQ test scores have a distribution in the general population that looks like a

symmetrical bell – which is why the IQ distribution is often called a ‘bell curve’. You can see this ‘bell’ in the figure below:



By looking at areas of this curve, you can see that the majority of people (68%) have an IQ score between 85 and 115. Only around 2% have an IQ greater than 130 which is often called ‘gifted’ intelligence. This is the IQ score needed to join [Mensa](#).

Here is a table that helps us interpret what IQ scores within certain ranges mean:

Classification	IQ Range	%
highly gifted	140+	0.4%
Mensa membership	130+	2%
gifted	130+	2%
International High IQ Society membership	124	5%
high	115-129	15%
high average	110-115	25%
average	90-109	50%
low average	80-89	23%
borderline	70-79	8%

For a rough guide, an IQ of 115 or higher can be considered a ‘high IQ’. This equips someone to take on a university degree. An IQ of 130 or higher puts a

person into the 'IQ elite' – the sphere of Harvard undergraduates and grad students.

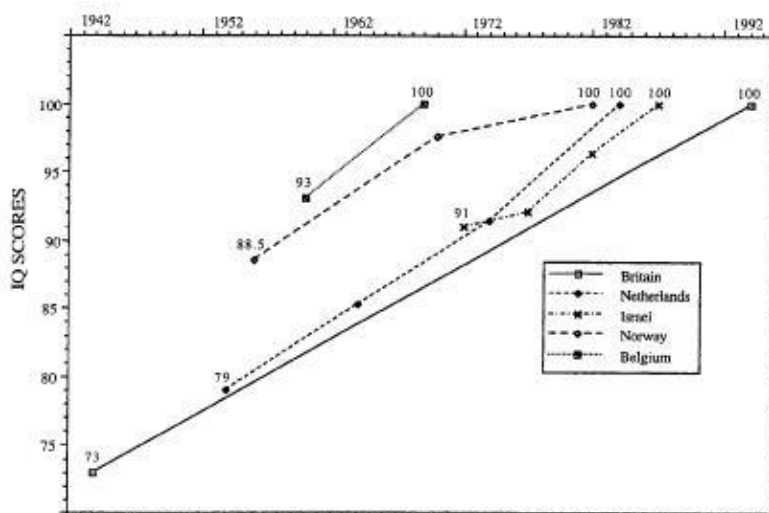
Is Intelligence 'Fixed In Stone'?

What determines our intelligence level and can it be improved? Individual differences in intelligence – as measured by IQ tests – are determined by a combination of *environmental* factors and *genetics*. Environmental factors include a mother's health during pregnancy, stressors from the physical environment, nutrition, general health and hygiene, education, cultural and social stimulation, and some types of brain training. Genetics is our *genome* – the genetic material we are born with encoded in our DNA. Environmental inputs in the [environment + genetics > IQ] equation are clearly not fixed in stone. And while our DNA cannot be modified to improve our IQ, how our DNA is *expressed* at a cellular level can be modified by the right interventions – including nutrition, fasting and exercise as we shall see.

Identical twins separated at birth and raised in different family, educational and cultural environments will have correlated IQ test scores due to the shared genetics. Taking into account a range of cultural environments, the genetic contribution to IQ differences has been estimated to be [close to 50%](#).

The 'Flynn Effect' is one demonstration of the impact of environmental factors on IQ. Throughout the last decades of the 20th Century, IQ test performance has risen substantially – typically about 3–5 IQ points per decade.

The Flynn Effect



This data suggests that if you gave a modern IQ test to your grandparent's generation their average score would have been around 80, not 100. This steady rise in IQ – called the 'Flynn Effect' – may have peaked in the late 1990s, with [a moderate decline since then](#). This is a well-known demonstration of why IQ levels are not 'fixed in stone'. In terms of the kind of intelligence that IQ tests measure, we have seen a period of several decades where environments were such that whole populations got smarter!

Self-Quantification



Improving cognition figures centrally in the **self-quantification movement**. This movement is interested in a) personal experimentation, and b) tracking and measuring outcomes to optimize outcomes. Using a variety of interventions, inventive self-experiments, and data-monitoring devices, biological and cognitive capacities such as sleep quality, cardiovascular health, strength, fitness, and cognitive performance are measured, tracked and improved– both physically and cognitively. This is a creative, dynamic movement, conducted the spirit of scientific inquiry and discovery. And looking at individuals in the self-quantification world like Peter Attia, it has led to some remarkable results. If you have some time, check out [this video on keto-adaptation](#).

“A thinker sees his own actions as experiments and questions—as attempts to find out something. Success and failure are for him answers above all.”

— Friedrich Nietzsche

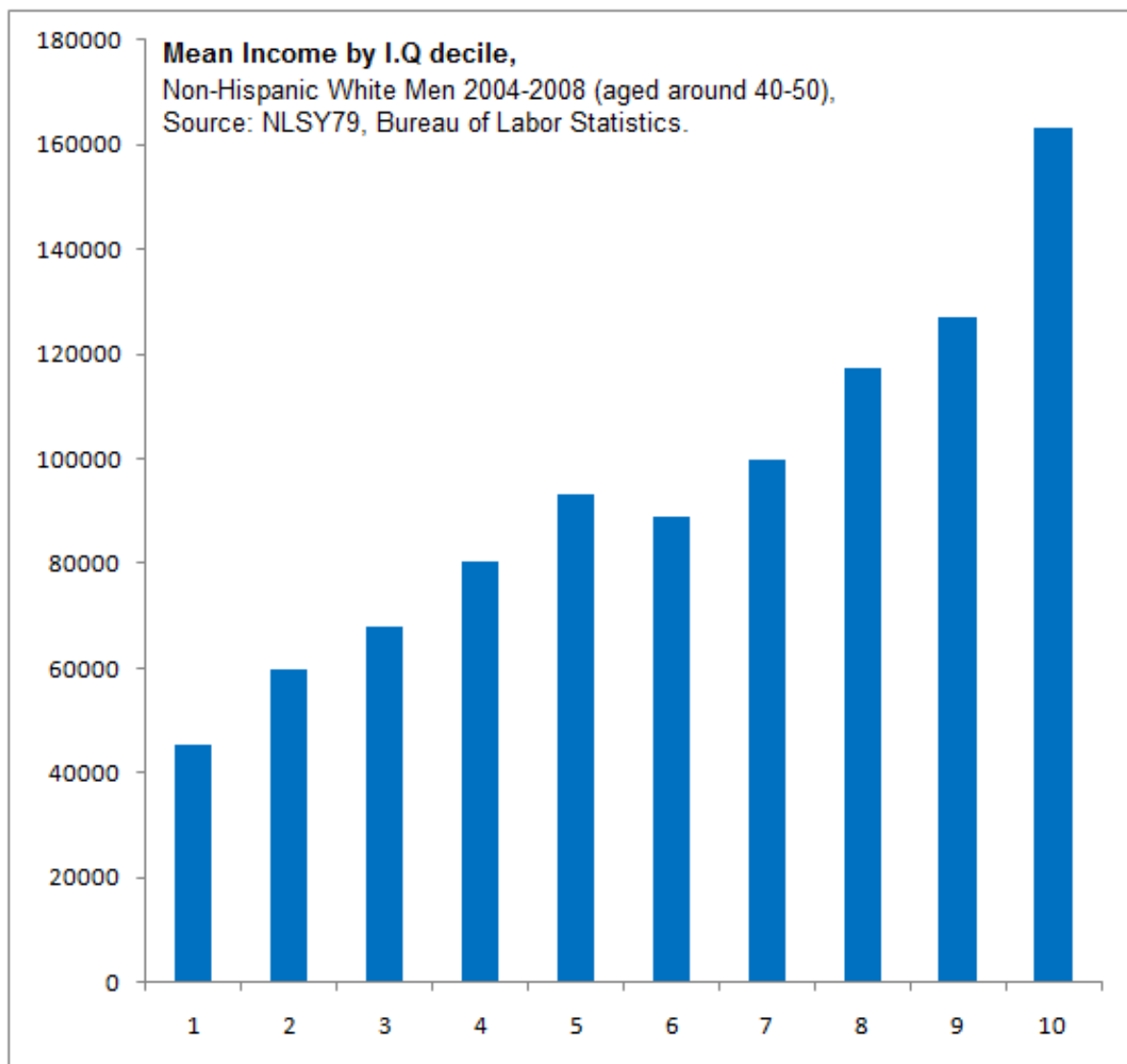
Cognitive Capital

The current economy is based in large part on cognitive performance – what has been called 'cognitive capital' or 'mental capital'.

“...One element of human capital is cognitive ability: quickness of mind, the ability to infer and apply patterns drawn from experience, and the

ability to deal with mental complexity. Another is character and social skills: self-discipline, persistence, responsibility. And a third is actual knowledge. All of these are becoming increasingly crucial for success in the post-industrial marketplace.” (Professor Jerry Muller, March 2013, Foreign Affairs)

Statistical research reveals a clear link between IQ level and income or wealth. Here is some data from the US Bureau of Labor Statistics back in 2008. Tested IQ scores range from 84 to 116.

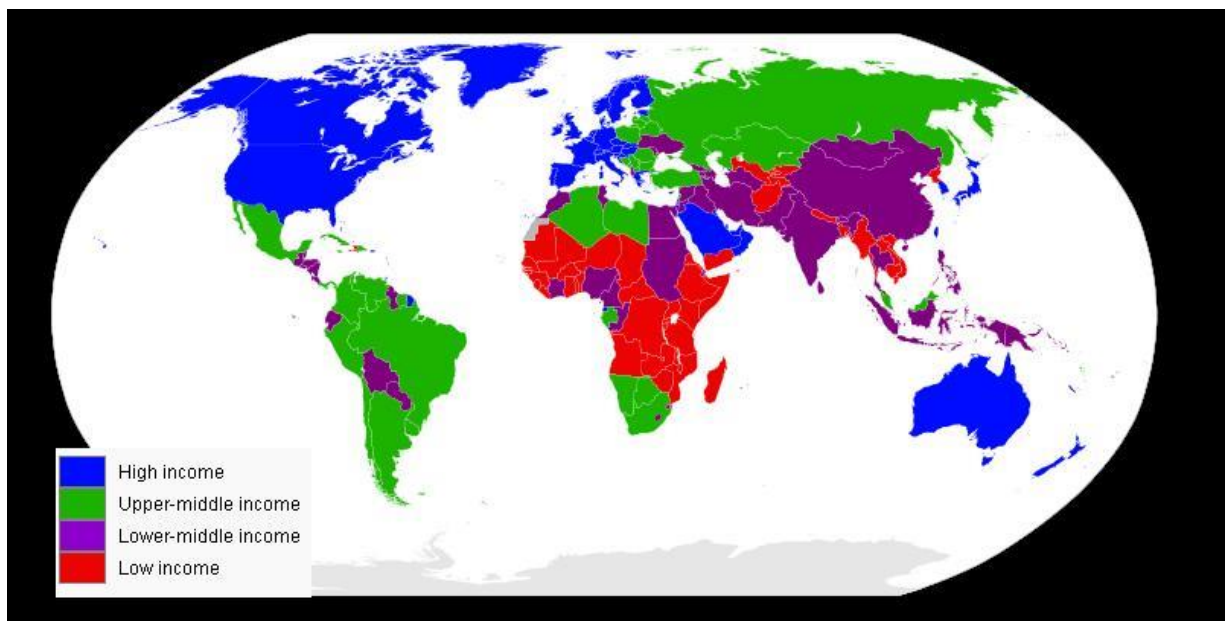


The current economy has...

“...increased the importance of human capital. One element of human capital is cognitive ability: quickness of mind, the ability to infer and apply patterns drawn from experience, and the ability to deal with mental

*complexity. Another is character and social skills: self-discipline, persistence, responsibility. And a third is actual knowledge. All of these are becoming increasingly crucial for success in the post-industrial marketplace.” (Professor Jerry Muller, March 2013, **Foreign Affairs**)*

Looking at cognitive performance more globally, in [2010 Rindermann & Thompson](#) analyzed IQ test scores from 90 countries and found that the intelligence of the people – especially the smartest 5 percent – made a big contribution to the strength of their economies.



For each one-point increase in a country’s average IQ, the per capita gross domestic product (GDP) was \$229 higher. For the smartest 5% of the population in each country it made an even greater difference: for every additional IQ point in that group, a country’s per capita GDP was \$468 higher.

Why is cognitive performance – IQ – so critical? Rindermann & Thompson offer some explanations, consistent with our definitions of intelligence:

“IQ is relevant for technological progress, for innovation, for leading a nation, for leading organizations, as entrepreneurs, and so on”

And:

“cognitive ability predicts the quality of economic and political institutions, which further determines the economic affluence of the nation”

And they conclude:

“in the modern economy, human capital and cognitive ability are more important than economic freedom.” (Dr. Rindermann)

Brain Cross Training Concept

Unlike other brain training providers that focus only on computerized cognitive training, IQ Mindware has adopted a ***brain cross training*** framework.

The mission of IQ Mindware to track the scientific literature on (1) effective computer-based brain training and translate the positive results of this research into useable apps with professional user interfaces. (2) *all other types of effective brain health and cognitive performance interventions* and to translate this research into practical strategies that you can readily incorporate into your schedule.

To keep up with the research reports and training tips, ensure that you follow us by subscribing to our Newsletter, YouTube Channel and Facebook page.



Chapter 2.

Computerized Cognitive Training (CCT)

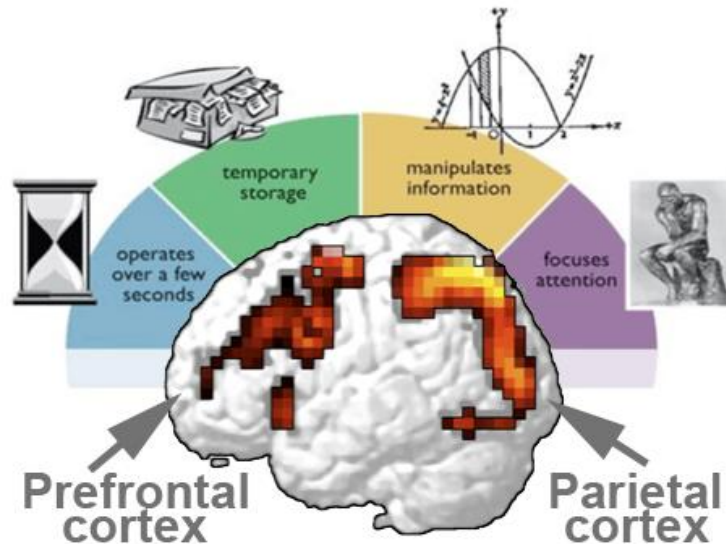
Generally what we understand by ‘brain training is **computerized cognitive training (CCT)** – apps usually designed to improve your attention, processing speed, memory, reasoning and so on. In this chapter I shall be reviewing what is known about the effectiveness of this kind of training for cognitive performance.

Increasing General Cognitive Ability with Computerized Cognitive Training: Working Memory Training

Over the past 10 years there has been a growing body of scientific evidence that a specific type of computerized cognitive training (CCT) has the potential to raise IQ significantly - namely **working memory training**. Commercial CCT comes in many forms. Many brain training companies divide training between different types of cognitive processing such as speed, memory, attention, and so on. In the light of all the studies done on these different types of training, it is only working memory training that has demonstrated real potential for increasing intelligence and executive functioning.

What Is Working Memory?

Working memory is a short-term memory and attention focus system – your ‘mental workspace’. It can be defined as a brain system that keeps information in mind temporarily while using it to think something through, make a decision, pursue a goal or comprehend something. It involves a pre-frontal – parietal brain circuit called the cognitive control network.



Working memory is necessary for staying focused on a task, blocking out distractions, keeping you updated and aware of what is going on in this process, and applying relevant thinking strategies to process the information.

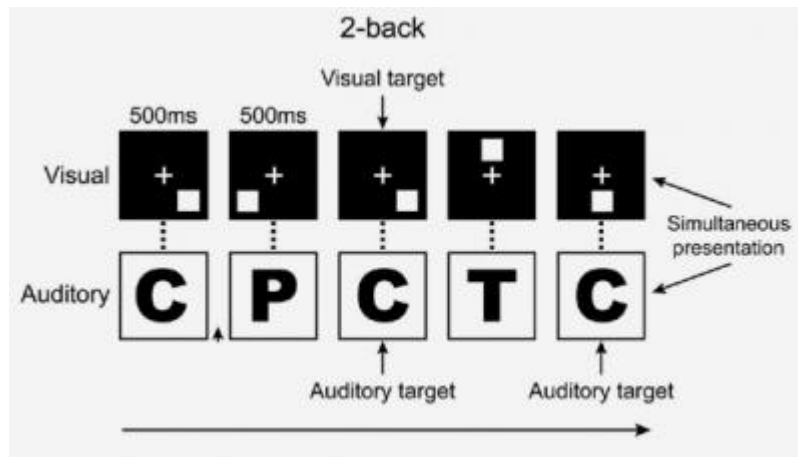
Working memory deficits result in loss of attentional focus (e.g. difficulty keeping track while reading a text), or memory problems such as forgetting what to do in the few seconds of walking from one room to the another, or being easily distracted while trying to focus on a task and not being able to finish an activity according to plan.

In general the larger your working memory capacity (mental workspace) the better your focus and the greater your capacity for focus, self-control, problem solving and comprehension. There is a strong correlation between working memory and IQ as well as emotion regulation.

What is Working Memory Brain Training?

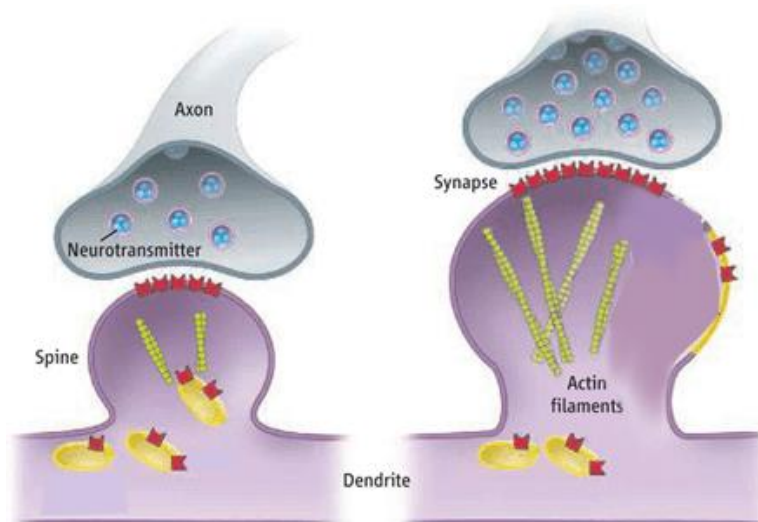
Working memory brain training is currently the most scientifically credible, effective brain training that is available. The aim of all working memory (WM) training programs is to expand working memory capacity.

The most widely studied brain training exercise targeting WM capacity is the **dual n-back**. This game involves viewing a continuous stream of both visual and audio items and deciding whether each item matches the stimulus presented n stimuli back. In the example shown here, the 2-back matches (targets) are shown.



Known Benefits of Working Memory Training

Working memory training has clear long-term **neuroplasticity effects** in brain regions involved in attention, executive function and intelligence, such as changes in the density of cortical dopamine D1 receptors (1, 2, 3)



There are many scientific studies demonstrating that WM training results in improvements in a range of important cognitive skills as well as improved cognitive function in clinical populations with known WM deficiencies. (1)

“The results of individual studies encourage optimism regarding the value of WM training as a tool for general cognitive enhancement. ...Studies of core training show improvements in a variety of areas of cognition... Core

WM training thus represents a favourable approach to achieve broad cognitive enhancement.” ([Morrison & Chein, 2011, p. 34](#)).

Working memory training has been shown in replicated studies and meta-reviews to result in the following brain benefits. Such benefits are often found for both younger and older benefits, indicating that neuroplasticity effects from training are not restricted to younger brains.

- Fluid intelligence (IQ) – i.e. abstract reasoning and problem-solving abilities ([1](#))
- Improvements in both verbal and visuospatial working memory ([1](#))
- Improvements in executive attention control such as multi-tasking in both younger and older adults ([1](#), [2](#)).
- Memory for personal experiences ([1,2](#))
- Reduced symptoms of ADHD and learning disabilities, for children and adults ([1](#), [2](#))

Can Working Memory Training Increase IQ?

The potential effectiveness of the dual n-back for increasing IQ was brought into the spotlight by Dr. Susanne Jaeggi and her group at the University of Michigan in a seminal PNAS paper in 2008: *Improving Fluid Intelligence By Training On Working Memory*. Their results led prominent IQ researchers to the conclusion:

“Increasing intelligence is possible after all ...with more training leading to greater gains ...across the spectrum of abilities. ...Almost 40 years ago, Jensen claimed that, when all is said and done, there is not much one can do to raise people’s IQs. Jaeggi and her colleagues have made an important contribution... by showing that intelligence is trainable to a significant and meaningful degree.”

Robert Sternberg, Professor of Cognitive Psychology, Indiana University

Since the Jaeggi study, numerous studies investigating the effects of dual n-back training on cognitive performance have been published, and there has been a heated controversy among both cognitive scientists and the popular media surrounding the idea that cognitive training can increase IQ.

Some studies have failed to replicate the IQ-boosting training effect – such as [this study](#) by a team led by Todd Thompson in MIT’s Department of Brain and Cognitive Sciences which concluded:

“[our] findings fail to support the idea that adaptive working memory training in healthy young adults enhances ...fluid intelligence.” (2013)

But other studies have found a significant ‘wide transfer’ IQ increasing effect, such as [this one](#) by Sarah Rudebeck in Oxford University’s Department of Experimental Psychology:

“we found that the trainers, compared to non-trainers, exhibited a significant improvement in fluid intelligence after 20 days.... Our findings demonstrate that practice on a ...working memory task can potentially improve aspects of bothmemory and fluid intelligence.” (2012)

So how are we to evaluate the conflicting evidence? Does dual n-back training work or not?

Meta-Analysis Studies

In answering this question, we need to look at the **meta-analysis** literature – which looks at multiple, peer-reviewed journal articles on the same topic, not just one or two studies that make the headlines.

We find that the latest meta-analyses for dual n-back / working memory training conclude dual n-back training is effective in improving general cognitive performance and IQ test scores on average. For reviews of this visit the website hrplab.org.

[For example, this 2014 meta-review](#) by Jacky Au and colleagues at the University of California, concludes:

“Our work demonstrates the efficacy of several weeks of n-back training in improving performance on measures of Gf [fluid intelligence]. We urge that future studies move beyond attempts to answer the simple question of whether or not there is transfer and, instead, seek to explore the nature and extent of how these improved test scores may reflect “true” improvements in Gf that can translate into practical, real-world settings.”

Training Optimization

Jacky Au and colleagues argue in their review of all published reports that the average increase in IQ from training they found is an **under-estimate** due to the samples and testing criteria. Moreover, they believe that the effect size they reported could be increased by **optimizing** certain game parameters including:

- Program completion
- Increasing intrinsic motivation for program completion

For these reasons the authors argue:

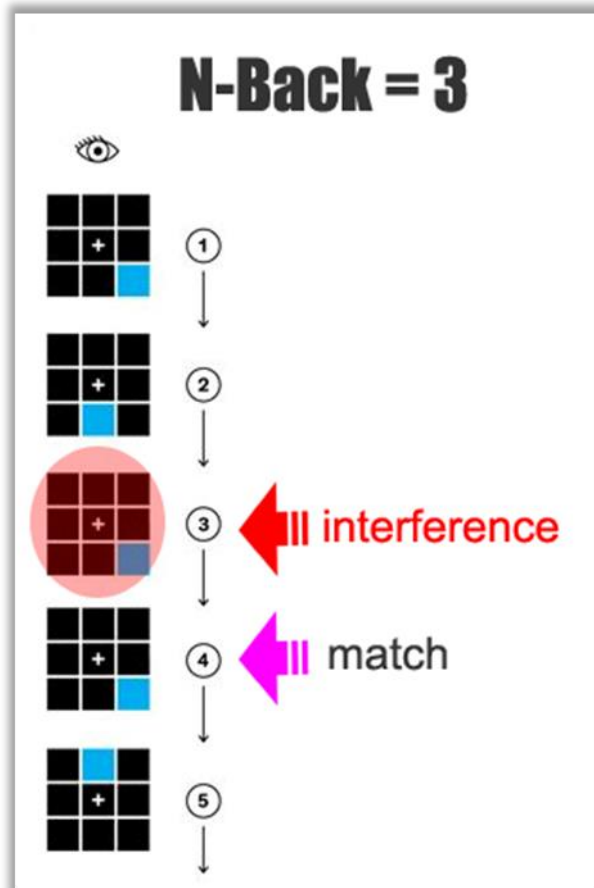
“the results reported in this meta-analysis represent a low-end estimate of the true extent of improvement that n-back training can have on measures of [intelligence]”.

The goal now is now is determining precisely what parameters of dual n-back training can optimize wide transfer to IQ and general cognitive performance. An analogy is growing tomatoes. If you know you can grow them, your next concern is to figure out how to make them bigger and better – by e.g. different watering schedules or adding fertilizer or varying the growing temperature!

Interference Control & ‘Second Generation’ N-Back Training

One strong candidate parameter for optimizing dual n-back training that I have been particularly interested in is **interference control**.

Interference is a technical term for **distracting information** that is similar to the information you need to perform well in a game or cognitive challenge. If you are playing the n-back game, and you are at a 3-back level, a matching stimulus for N=2 or N=4 would qualify as interference. This is shown in the diagram.



Another example of interference is found in the ‘Stroop task’. You can try the task for yourself now – going from left to right, as quickly as you can say aloud the *ink color* of the words here – ignoring the word meaning (the answer for the first one is ‘red’).

BLUE	GREEN	YELLOW
PINK	RED	ORANGE
GREY	BLACK	PURPLE
TAN	WHITE	BROWN

Because reading words is so well-practiced and automatic, there is a strong

interference effect in this task - as you'll have noticed! The meaning of the word captures your attention, and interferes with your ability to perform the task. It takes concentration to control this interference.

There is good scientific evidence that **interference control** – the ability to filter out distracting information of this sort – **underlies the link between working memory and intelligence**.

- First, brain imaging studies reveal that [neural mechanisms of interference control underlie the relationship between fluid intelligence and working memory span](#).
- Second, Claudia von Bastiana and Klaus Oberauer at the Department of Psychology, University of Zurich, have found that a game based on [‘supervision’ working memory training alone resulted in IQ gains](#). Supervision is terminology for **that aspect of working memory used for interference control** - defined as “selective activation of relevant and inhibition of irrelevant information”.

Based on the strong role of interference control in linking IQ with working memory capacity, interference training is now built into all the [IQ Mindware apps](#) as a default. Building interference control into the dual n-back game is something new, and for this reason we call it **second generation (2G) dual n-back training**.

The advanced working memory training app **i9** is also designed to selectively train different aspects of executive control such as updating, flexibility and interference control (focus). It is designed for optimizing improvements in IQ and attention-control.

Computerized Cognitive Training Summary

Based on meta-review evidence we can conclude that working memory training is worth investing your time and effort into if you want to achieve gains in general cognitive performance. No equivalent cognitive gains result from other types of computerized cognitive training, or learning musical instruments, playing video games.

We can consider an analogy with sports performance. Substantial gains in sports performance are now possible – and achieving those gains relies on scientifically guided training programs. Likewise it is becoming apparent that

cognitive performance gains are possible and these too rely on scientifically guided training programs. Evolved versions of the dual n-back and other forms of working memory training will be central over the next decade in achieving and maintaining the highest levels of cognitive health, resilience and performance.

More on Evidence-Based Apps

If you are interested in finding out more about effective working memory training apps, sign-up to [this invitation-only mailing list](#).



[Click for limited app promotions](#)



Chapter 3.

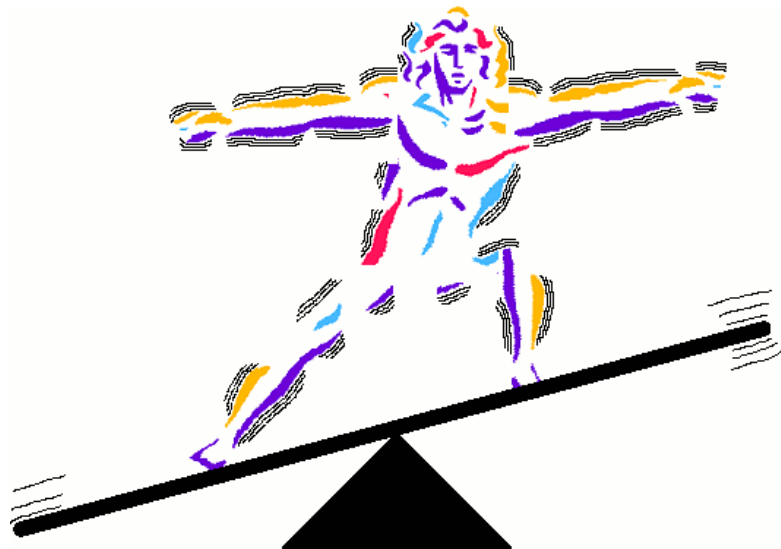
Hormesis: Good Stress & the Evolution of Vitagenes

This chapter 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.



"Daka Homo erectus" by Henry Gilbert and Kathy Schick - Own work. Licensed under CC BY-SA 3.0 via [Wikimedia Commons](#)

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:

- **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.
- **Caloric (energy) restriction** (CR) in times of food scarcity. This is when energy sources for powering our bodies and brains was lacking.
- **Cognitive 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 another type of stressor that have recurred for millions of years, 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 plant chemical defence mechanism is behind the intense taste of many spices, garlic and onions.

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 – called adaptive cellular stress responses – 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 cognitive 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:

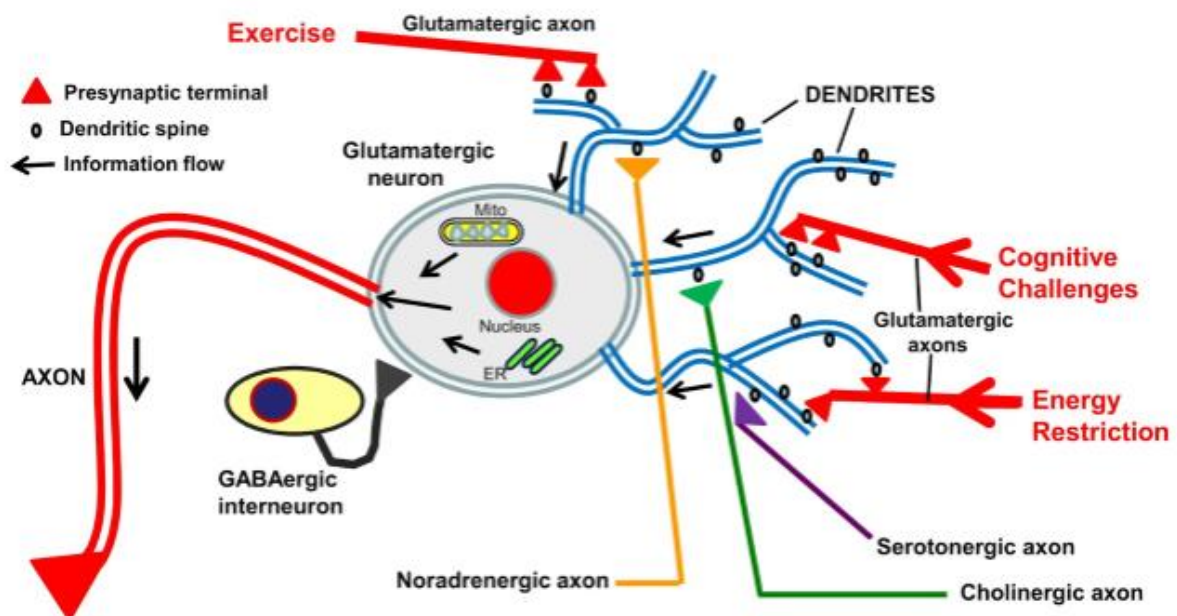
- Increased brain cell growth (neurogenesis) and neuroplasticity for learning and memory by producing nerve growth factors such as Brain Derived Neurotrophic Factor (BDNF) and insulin-like growth factor (IGF-1)
- Improved mitochondrial function and energy metabolism
- Removal of damaged organelles and 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.

- Reduced cancer causing anabolic hormones
- Improved insulin sensitivity & reduced diabetes risk
- Reduced inflammation
- [Possible increased life-expectancy due to the protective stress response gene SIRT3.](#)

Brain Benefits of Adaptive Cellular Stress Responses

Via the same adaptive cellular stress response that improves immune function, health and longevity reviewed above, **caloric restriction, exercise, cognitive effort can all promote optimal brain function and resistance to age-related brain diseases**, and does so via overlapping and complementary mechanisms.

The diagram from [this comprehensive review article](#) illustrates at a neuron (brain cell) circuit level the three types of intervention (in red) that induce brain health and performance benefits from the adaptive cellular stress response.

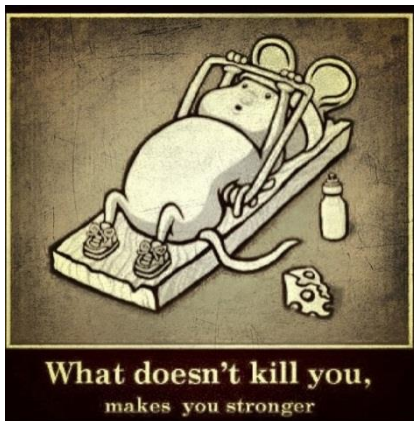


Three types of training regimes that help brain function in red. Triangles indicate synapses (communication points) between different brain cells (neurons).

In all three regimes – caloric restriction, aerobic exercise and cognitive (mental) effort – a **hormesis** response results in both **neuroplasticity** and **cell protection** – that is, both **the strengthening of synapses via protein enzymes and neuron stress resistance via DNA repair enzymes, and antioxidant enzymes.**

How to Switch On the Vitagenes: The Hormesis Response

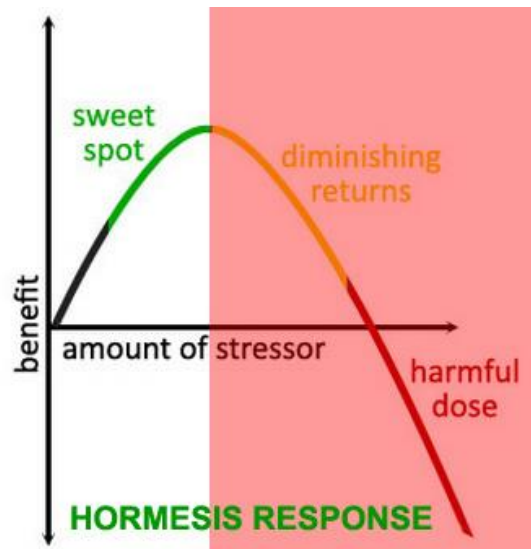
So how do we switch on (upregulate) our vitagenes that control the cellular stress responses, to unlock the remarkable benefits to health and brain function? The answer is we systematically harness a well-studied biological process called the **hormesis response**. We do some ‘biohacking’!



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, cognitive challenge) 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.



Chapter 4.

Exercise for Vitagenes

General Health Benefits from Exercise

Numerous studies have demonstrated that via adaptive cellular stress response mechanisms exercise can result in:

- Reduced fat mass
- Increased insulin sensitivity and improves glucose metabolism
- Decreases blood pressure
- Increased heart rate variability (HRV) – a good index of overall mental and physical health
- Less oxidative damage during cell metabolism (due to free radicals) to tissues and DNA
- Less inflammation
- Better autophagy – the detoxification process whereby your cells eliminate waste material and repair themselves)
- Protection against multiple age-related diseases including cancers, cardiovascular disease, diabetes, a (amount of blood glucose is too high) and sarcopenia (degenerative loss of skeletal muscle mass)

Anti-Cancer Effects of Exercise

Exercise is associated with low plasma growth factors and hormones that are linked to an increased risk of cancer. [A low animal protein diet has additional protective effects because it is associated with a greater decrease in circulating IGF-I than high levels of exercise alone.](#) Higher circulating IGF-1 levels are linked to a greater incidence of cancer. Lower IGF-1 levels are also associated with an extended lifespan.

Exercise for Brain Health & Performance

It has been known for a long time that exercise can promote brain health and performance.

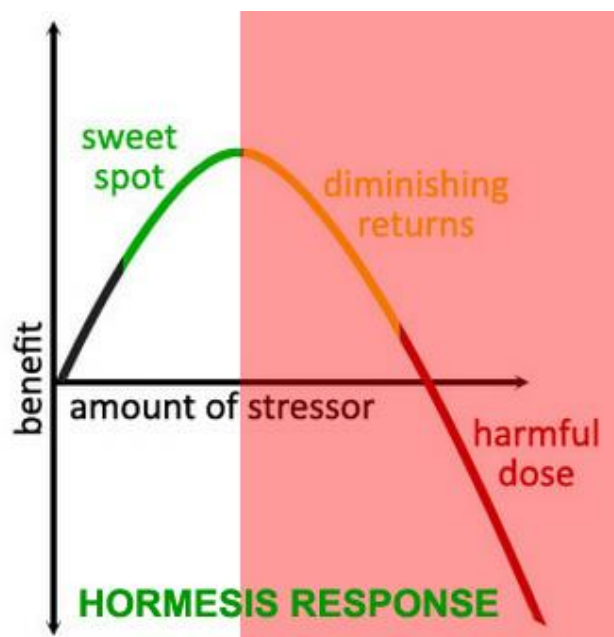
Human and other animal studies demonstrate that exercise targets many aspects of brain function and has broad effects on

overall brain health [including] learning and memory, protection from neurodegeneration and alleviation of depression. Exercise increases synaptic [neuro] plasticity. [Cotman, TRENDS in Neurosciences Vol.30 No.9](#)

Human and other animal studies demonstrate that exercise targets many aspects of brain function and has broad beneficial effects on overall brain health and performance including:

- Improved learning and memory
- Protection from neurodegeneration
- Increased BDNF and neuroplasticity
- Improved mood and reduction of depression

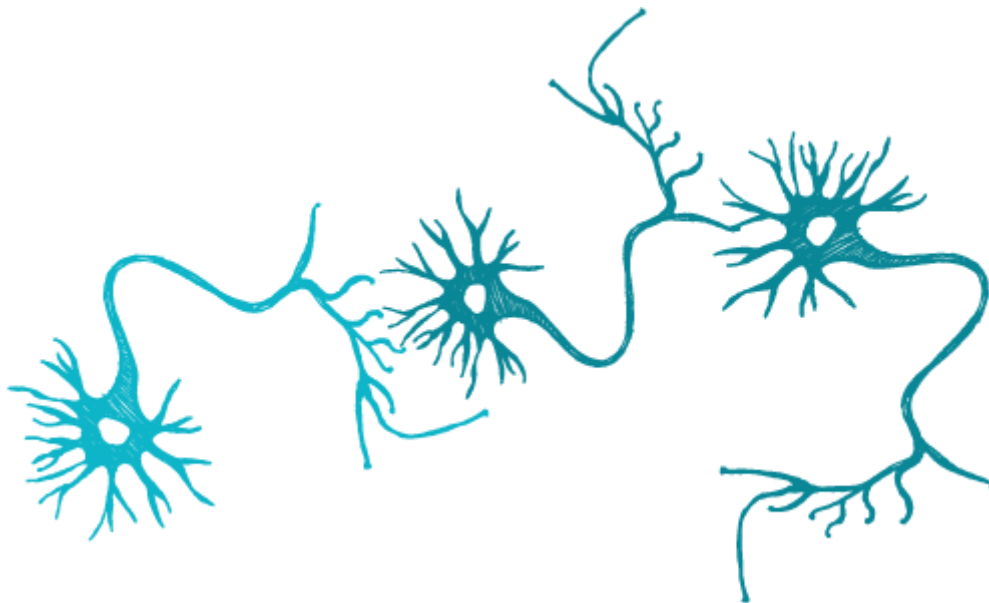
A key biological mechanism that explains the beneficial effects of exercise are [adaptive cellular stress responses](#) – discussed in the previous chapter. This set of responses to ‘good’ stressors trigger vitagenes responsible for widespread repair and regeneration processes in both the brain and body. Exercise stimulates this stress response at the cellular level throughout the brain and body – and engaging the **hormesis response** (below) can **promote a host of health benefits outlined above, as well as optimal brain function and resistance to age-related brain diseases.**



Adopting an exercise plan that puts you in the **hormesis ‘sweet spot’** improves **neuroplasticity** for adaptive learning and **cell protection** for healthy brain cells. Fasting can both strengthen the synapses (communication points between brain cells) via protein enzymes and improve neuron stress resistance via DNA repair enzymes, and antioxidant enzymes. We will now look at specific exercise for brain health benefits one by one. Much of this research can be found in [this Cell Metabolism review paper](#) and [this Nature Reviews Neuroscience paper](#).

Improved Neuroplasticity

Neuroplasticity is defined as the changes that occur in neural pathways and synapses (the communication points between brain cells) as **adaptive responses to environmental challenges**, including those that are voluntary (e.g., problem solving, learning skills, competing in sport) and those that are unwelcomed (e.g., a traumatic injury or disease). **Neuroplasticity is essential for learning and memory**, and as the brain ages it tends to become less neuroplastic.



Neurogenesis: The Growth of New Brain Cells

Neurogenesis is the creation of new brain cells (neurons) from neural stem cells. The new neurons can form synapses with existing neurons, thereby becoming part of a functional neural circuit.

- [Voluntary exercise such as running stimulates neurogenesis in the hippocampus of adult rodents](#). The hippocampus is critical for learning and memory.



Improved Gene Regulation

Exercise switches on a number of ‘repair genes’.

- [Both exercise and fasting can induce the expression of neurotrophic factors including the BDNF gene](#). This protein promotes the survival of nerve cells (neurons) by playing a role in the growth, and maintenance of these cells. It

also plays an important role in synapse plasticity which is important for learning and memory as described above.

Keeping the Aging Brain Young: Neuroplasticity And Brain Function

Numerous studies show that exercise [helps maintain brain volume and buffer against loss of memory and other cognitive functions that is associated with loss of neuroplasticity with aging.](#)

- [Aerobic exercise has been shown to aid in maintaining cognitive health by reducing age-related loss and adding to volume of grey and white matter in frontal and temporal cortices.](#)
- [Elderly subjects who exercised for 4 months showed better blood flow and functional connectivity in brain areas need for memory and higher cognitive functioning.](#)
- [Aerobic training for a year improved the aging brain's resting functional efficiency in higher-level brain networks and associated cognitive control.](#)

What Workouts for Brain Health & Performance?

Aerobic or Resistance Exercise

Most of the benefits reviewed above are based on **aerobic exercise**, not strength training. Some studies show greater benefits of aerobic training compared to resistance (strength) training. For example

- [Endurance fitness training](#), but [not strength training](#), has been shown to result in increased BDNF concentrations, a neurotrophic factor that plays an important role in neuronal growth and plasticity.

However, [this excellent article on the brain benefits of exercise](#) reviews diverse evidence for the brain benefits of strength training among the elderly,

and suggests that while evidence is limited for the benefits of strength training, this may be due in part to lack of studies – not something intrinsic to the type of exercise. The 2008 [Physical Activity Guidelines for Americans and the Harvard School of Public Health](#) recommends that healthy adults get:

- [A minimum of 2-1/2 hours per week of moderate-intensity aerobic activity, or get a minimum of 1-1/4 hours per week of vigorous-intensity aerobic activity, or a combination of the two.](#)
- A minimum of 2 ½ hours per week of moderate-intensity aerobic activity (e.g. brisk walking, jogging, swimming, cycling) or a minimum of 1 ¼ h/w of intense aerobic activity (e.g. spin classes, circuit training, CrossFit) – or combinations of both.
- Adults of all ages should also do muscle-strengthening activities on at least two days for the week.
- Children should get at least 1 hour or more a day of physical activity in age-appropriate activities.

Intensity is Good

Within reasonable limits, intense exercise changes the body and muscles at a molecular level in ways that milder physical activity doesn't match as reviewed in [this New York Times feature](#).

- [Walkers whose usual pace is brisk tend to live longer than those who move at a more leisurely rate, even if their overall energy expenditure is similar.](#)
- When the body is stressed by intense exercise, stress hormones (catecholamines) are released which trigger the production of an energy regulating protein (CRTC2) that improves glucose metabolism and fat release for burning fuel. [This has been shown to result in greater endurance and stronger muscles.](#) A similar effect results from fasting.

High Intensity Circuit Training (HIIT)

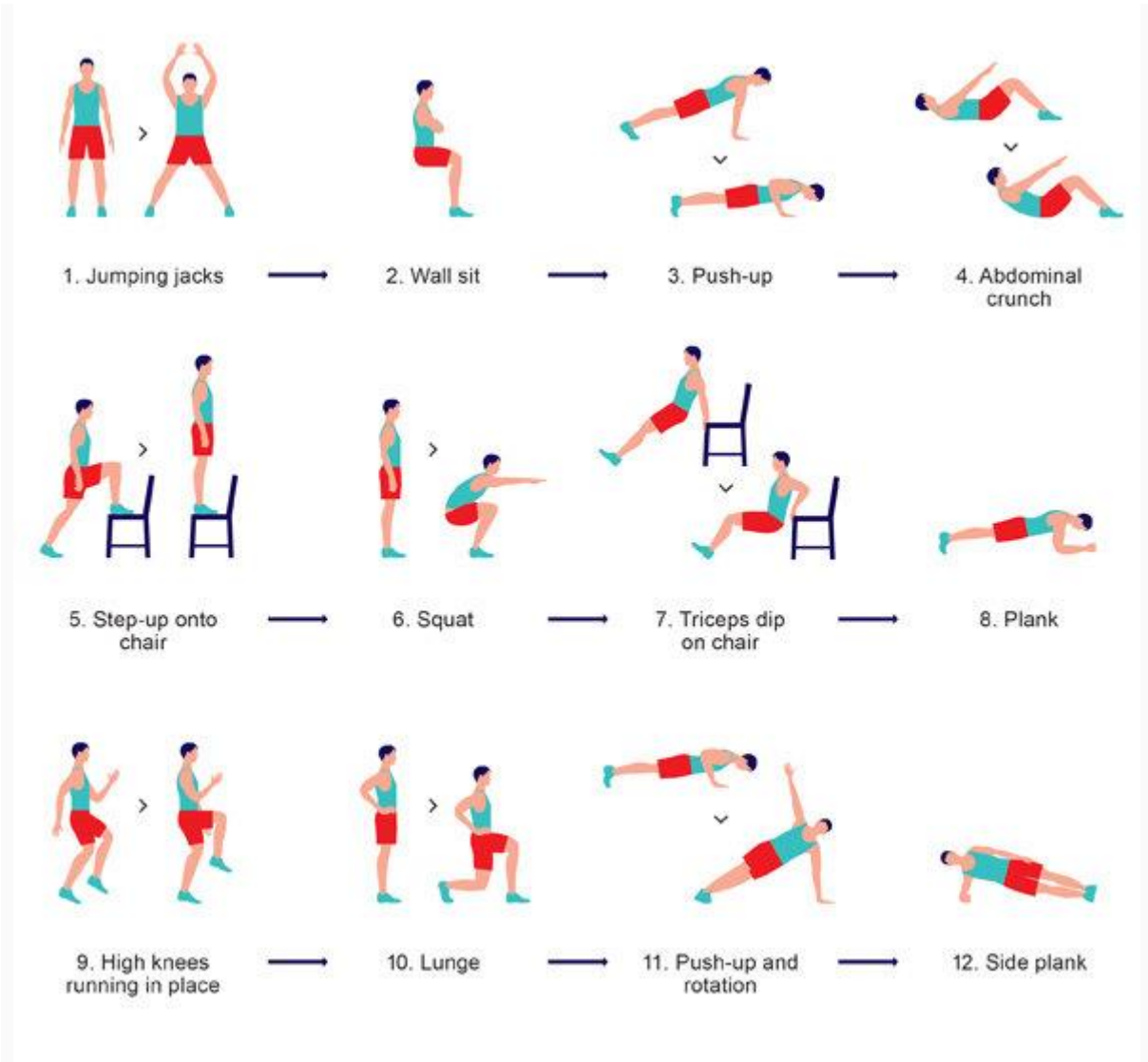
Scientific evidence indicates that **high intensity interval training** (HIIT pronounced 'hit') – combining aerobic and strength training – is an efficient means of exercise to help decrease body fat, improve insulin sensitivity, and improve VO₂max and muscular fitness. Interval training requires extremely

intense activity intermingled with brief periods of recovery. This intermittently triggers adaptive cellular stress responses in a very efficient way.

“There’s very good evidence” that high-intensity interval training provides “many of the fitness benefits of prolonged endurance training but in much less time.” **Chris Jordan, the director of exercise physiology at the Human Performance Institute in Orlando, Fla.**

Work by scientists at McMaster University in Hamilton, Ontario, and other institutions shows, for instance, that even a few minutes of training at an intensity approaching your maximum capacity produces molecular changes within muscles comparable to those of several hours of running or bike riding. **Based on the hormesis response, HIIT should be an effective type of brain training.**

[The ‘7 minute workout’ has been reviewed in the New York Times](#), and is a popular HIIT option. There are 12 exercises. Exercises are performed for 30 seconds, with 10 seconds of transition time between bouts. Total time for the entire circuit workout is approximately 7 minutes. The circuit can also be repeated 2 times, depending on time and fitness level.



The side plank (no. 12) should be done on both sides. Modifications or extensions to this routine can easily be improvised – for instance, adding pull-ups or burpees.



Chapter 5.

**Fasting
for Vitagenes**

Fasting in a Cultural Context

“I fast for greater physical and mental efficiency.” Plato (428-348 B.C.)

“Instead of using medicine, rather, fast a day.” Plutarch (45-120 A.D.)

Fasting has a respected history. Plato and Socrates fasted for physical and mental efficiency. Pythagoras required his students to fast before entering his classes. The Greek physician Hippocrates recognized fasting as of primary importance in therapeutics. In the 16th century a famous Swiss physician Paracelsus said, "Fasting is the greatest remedy".

Indeed the utility of fasting in spiritual quests is an integral part of the human religious history. All major religions to this day retain fasting as far more than simply a traditional ceremonial act. It remains a fundamental part of the spiritual practice to gain enlightenment as in the Muslim feast of Ramadan and the Jewish fast of Yom Kippur. Fasting was an expected discipline in both the Old and New Testament eras. According to scripture Moses fasted at least two recorded forty-day periods. Jesus fasted forty days and reminded his followers to fast. Yogis practice austerity with their diets and shamans fast during their vision quests.

General Health Benefits of Fasting

[A hefty body of research shows that caloric restriction \(with a maintained balanced diet\) results in the following benefits \(click on this link for review\):](#)

- **Reduced fat mass (weight loss)**
- Increased **insulin sensitivity** and improved **glucose metabolism**
- **Decreases blood pressure**
- Increased **heart rate variability** (HRV) – which has been used as an index of physical and psychosocial health, with lower HRV levels being linked to stress and negative emotions such as anxiety and hostility.
- **Less oxidative damage** during cell metabolism (due to free radicals) to tissues and DNA
- **Less inflammation**
- **Better autophagy** – the detoxification process whereby your cells eliminate waste material and repair themselves)

- **Protection against multiple age-related diseases** including cancers, cardiovascular disease, diabetes, a (amount of blood glucose is too high) and sarcopenia (degenerative loss of skeletal muscle mass)

Extending Lifespan

The data indicates that fasting has a similar effect to caloric restriction – cutting down on the amount of calories consumed each day while maintaining good nutrition. Data from numerous animal studies conducted over decades show that restricted calories (by 25-55%) with adequate micronutrients compared to ‘free-for-all’ eating [can dramatically extend maximal life span and retard aging – in some studies by up to 65%](#). Mice and rats put on a low-calorie, nutrient-rich diet live far longer – and [the same is true of monkeys](#).

[Caloric restriction \(70% of normal intake\) with maintained nutrition in monkeys protects against multiple age-related disorders. In the Wisconsin study of lifelong caloric restriction in monkeys, over 20 years monkeys whose diets were not restricted were nearly three times more likely to have died than those whose calories were counted.](#) In the photos, the monkey on the two monkeys are the same age; the one on the left has not been calorie restricted, the one on the right is aging very well on a 30% restricted calorie diet.



“They don’t just live longer, they are healthier. They actually aged biologically slower. Their hair has gone grey less quickly. Their hormones have stayed at their youthful profile and their immune function has stayed good.” **Dr. Susan Roberts**

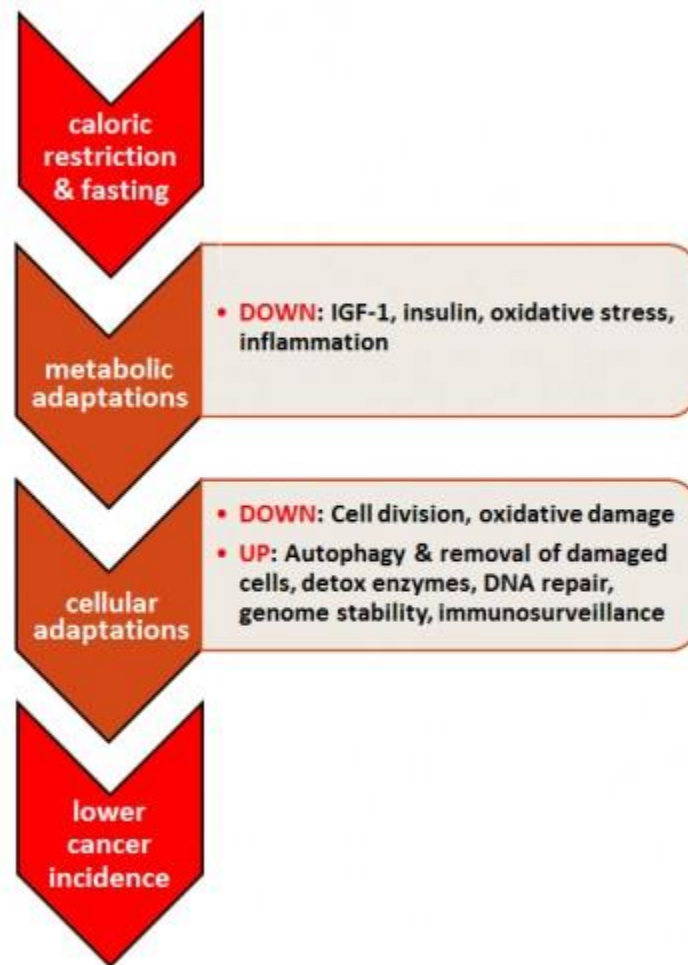
A similar study is currently being conducted with humans – the [Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy \(CALERIE\)](#) involving more than 130 people who have been cutting their calories by 25% for a number of years now. **Typically females consume 1500 Cal/day rather than 2000, and males consume 1875 Cal/day rather than 2500.** So far down the line, the biomarkers in this study have been consistent with the animal studies:

“I didn’t think calorie restriction worked in humans until I started working with people who’d been doing it for years. They are among the healthiest people I’ve ever known. Their heart function is similar to people 15 years younger, they have very low levels of inflammation and very few get cancer.” **Dr. John Holloszy, M.D., lead CALERIE investigator**

“... subjects have cholesterol around 160, blood pressure around 100 over 60, high HDL, low triglycerides and very low levels of inflammation. ... here we have such a powerful intervention that is basically cleaning out the arteries.” **Dr. Luigi Fontana & Dr. Susan Roberts, Washington University and Tufts University investigators for the NIH- funded CALERIE Study**

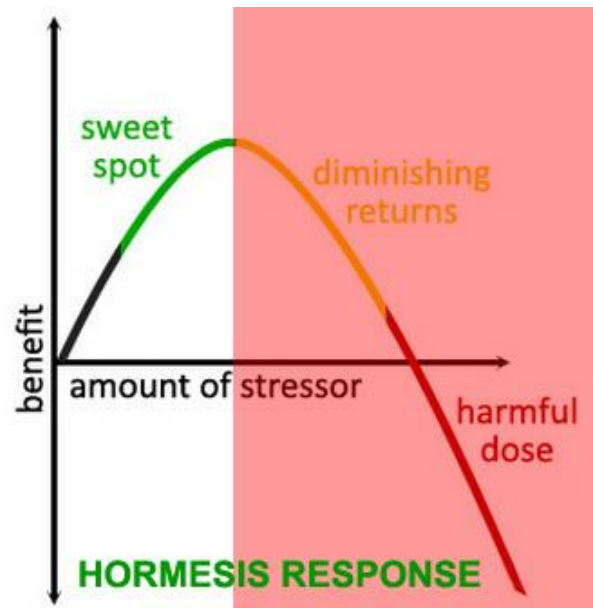
Anti-Cancer Effects of Caloric Restriction & Fasting

Long-term fasting is associated with low plasma growth factors and hormones that are linked to an increased risk of cancer. This diagram summarizes the adaptive response to caloric restriction or intermittent fasting that helps fight cancer (adapted from [this review article](#)).



CR & Intermittent Fasting for Brain Health & Performance

Via the same [adaptive cellular stress response](#) that improves immune function, health and longevity reviewed above, practicing caloric restriction or intermittent fasting in a way that hits the ‘sweet spot’ in the **hormesis response** can **promote optimal brain function and resistance to age-related brain diseases**.



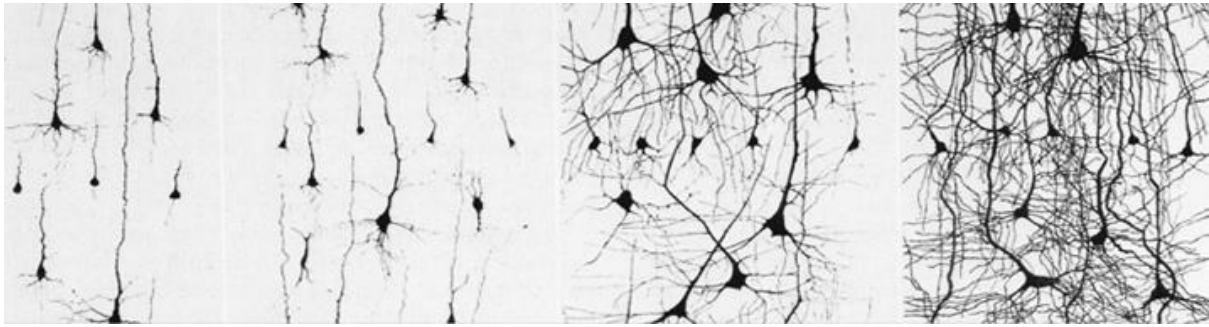
Adopting a diet plan that puts you in the **hormesis response ‘sweet spot’** improves **neuroplasticity** for adaptive learning and **cell protection** for healthy brain cells. Fasting can both strengthen the synapses (communication points between brain cells) via protein enzymes and improve neuron stress resistance via DNA repair enzymes, and antioxidant enzymes.

We will now look at specific evidence-based brain benefits of caloric restriction. Much of this research can be found in [this excellent Cell Metabolism review paper](#) and this [Nature Reviews Neuroscience paper](#).

Improved Neuroplasticity

Neuroplasticity can be defined as structural changes that occur in neural (brain cell) circuits as adaptive responses to environmental challenges. Neuroplasticity is essential for learning and memory, and as the brain ages it tends to become less neuroplastic.

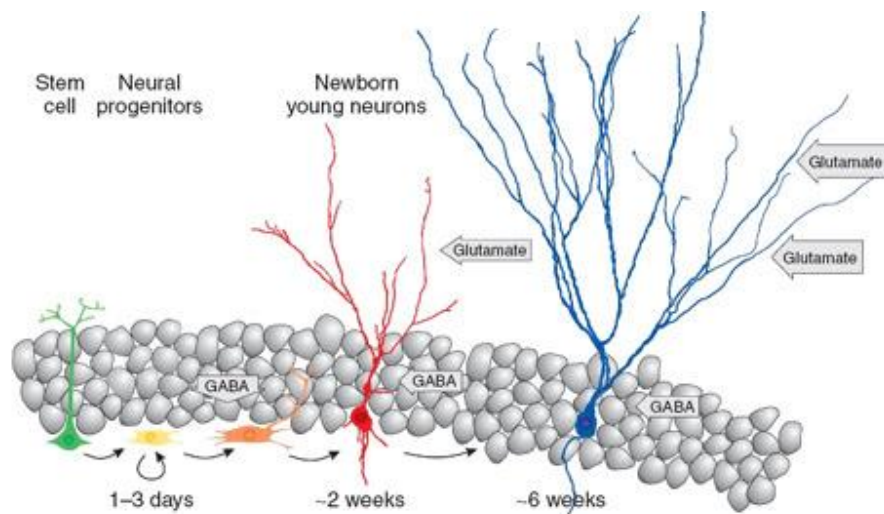
[Intermittent fasting promotes neuroplasticity in both synapses \(connections between individual neurons\) and neural stem cells.](#)



Neurogenesis: The Growth of New Brain Cells

Neurogenesis is the creation of new brain cells (neurons) from neural stem cells. The new neurons can form synapses with existing neurons, thereby becoming part of a functional neural circuit.

[Caloric restriction can increase neurogenesis in rodents by increasing the survival rate of newly created hippocampal cells, thereby improving learning and memory.](#)



Improved Gene Regulation

Going without food for even short periods of time switches on a number of 'repair genes' – the so-called 'vitagenes'.

[Fasting can induce the expression of neurotrophic factors including the BDNF gene](#). This protein promotes the survival of nerve cells (neurons) by playing a role in the growth, and maintenance of these cells. It also plays an important role in synapse plasticity which is important for learning and memory.

Ketones – Superfuel and Protection for the Brain

Our biology is adapted for times of food scarcity. During these periods, the main goal of our system is to provide enough glucose to the brain and other tissues. If you're not eating where does this glucose come from? Lack of food causes the brain to shift away from using glucose as a fuel to using **ketones**. Ketones are produced when the body burns fat for fuel. Ketones act as a stand in for sugar in the brain. By reducing the body's need for sugar, less protein is required, protecting muscle mass - the protein reservoir that might otherwise be used to power the brain.

- [The principal ketone \(beta-HBA\) is not just a fuel, but a “superfuel” more efficiently producing ATP energy for brain cells than glucose](#). Ketones are also the preferred fuel for the heart, making that organ operate at around 30% greater efficiency. **Thus fasting can increase your brain and body's energy production.**
- [Ketones also protected neuronal cells in tissue culture against exposure to toxins associated with Alzheimer's or Parkinson's.](#)

Both caloric restriction and exercise have been shown to increase the production of ketone bodies, which can enter the brain and protect neurons against injury and disease. For an interesting theory on the benefits of being 'keto-adapted', see **Appendix 2**.

Resilience to Stress and Emotion Control

Stress reactivity means being threat reactive. High stress reactivity means a low threshold for threat, and perceived threat triggers a stress response. This can result in stress response disorders, such as fatigue, anxiety and cognitive impairments. Some studies indicate that caloric restriction can help reduce stress reactivity – although experimenting with fasting regimes should be done with care if you are already highly stressed.

- [Caloric restriction results in reduced stress reactivity and preservation of volumes of brain structures involved in emotional control including the prefrontal cortex and amygdala.](#)

Heightened susceptibility to stress increases with aging. This is linked to atrophy of the hippocampus (a memory related region of the brain), and age-related cognitive deficits such as memory loss, as well as increased risk for Alzheimer's disease.

- [Long-term caloric restriction results in lower-stress reactivity and increased sizes of the brain regions \(e.g. hippocampus\) associated with lower stress reactivity.](#)

Keeping Your Brain Young: Neuroplasticity and Brain Function



Numerous studies show that caloric restriction [helps maintain brain volume and buffer against loss of memory and other cognitive functions that is associated with loss of neuroplasticity with aging.](#)

- [When the caloric intake of fifty normal elderly subjects was reduced by 30% for 3 months, the performance on memory tests improved significantly.](#)

What Fasting Diet?

25% Caloric Restriction (CR) Diet

Most of the animal studies on caloric restriction reviewed above have involved **cutting daily calorie intake by 25%**, while ensuring that the diet has the recommended micronutrients. (The evidence strongly suggests the same benefits accrue with intermittent fasting – although fewer studies have been done with this kind of diet). With CR diets, calories are reduced but essential nutrients are maintained. This is the diet adopted by individuals in the [CALERIE](#) study. And this is what [CRON](#) (Calorie Restriction with Optimal Nutrition) dieters are doing in their thousands.

A good starting point to get you underway with a CR diet if you find it appealing is this - the [Painless Calorie Restriction for People Who Love to Eat](#). The information on this site follows CALERIE guidelines, such as:

- Sticking to the most nutrient-dense foods like fruits, vegetables, whole grains, and legumes--although the CALERIE study is not vegan or vegetarian.
- Eating foods that are filling, appealing, low in calories, and nutrient-rich.
- Eating lots of fibre--at least 50 grams a day without counting grams or even trying. Fiber is key to keeping satisfied and full - and it likely activates the satiety receptors in the lower intestine.

In addition, it is important to reduce the amount of animal protein.

- Reducing animal proteins (meat, fish, yoghurt, eggs and milk) to 10% of calories eaten or less reduces risk factors for prostate, breast, and colon cancers, and neurodegenerative diseases.



A 1500 Calorie Day

Macros in Numbers

[To calculate your required calorie intake, you can use this online calculator.](#)

Simply multiply your recommended Calories (to maintain current weight) by 0.75.

[To get your macro breakdown, feed this diet-restricted number into this calculator](#), setting your protein intake to no more than 10% if you consume animal proteins. For instance, 55% carbohydrates, 10% proteins, and 35% fats. The exact carb-fat ratio is something you could experiment with. The research does not have a clear recommendation here. See Appendix 1 for a more radical low carb diet plan.

If you consume mainly vegetable proteins and want a higher protein diet a 55/15/30 or 50/20/30 ratio may be preferred. **Higher protein intake is recommended if you are over 65 or high a highly active lifestyle.**

Intermittent Fasting (IF)

Many would find a CR diet unrealistic to maintain over the long term – particularly for individuals pursuing active lifestyles with high energy demands.

Research shows that the same health giving and brain enhancing genetic pathways and biochemical responses activated by constant caloric restriction are similarly engaged by intermittent fasting, even for relatively short periods of time.

[This review](#) and [this review](#) (scroll down to paper) strongly indicate that “the reported beneficial health effects from caloric restriction... **can be mimicked by alternating periods of short term fasting with periods of refeeding, without deliberately altering the total caloric intake.**”

One of the most [comprehensive recent reviews of the benefits of caloric restriction](#) concludes:

“Incorporation of intermittent energetic challenges into our daily and weekly schedules should be a guiding principle for achieving optimal brain health. ...a prescription of CR and regular exercise will improve the health and longevity of the brain and body. Individuals who are overweight and sedentary must reduce their energy intake and engage in regular vigorous exercise in order to improve their brain health and reduce their risk for

neurodegenerative disorders. Those of normal weight can expect to optimize the performance of their brain by CR and exercise.”

Intermittent fasting is more similar to the availability-scarcity cycles of our evolutionary past. As with exercise and cognitive challenges, by periodically **triggering the adaptive cellular stress response we can benefit from the hormesis response** (see above).

There are three popular varieties of intermittent fasting:

Alternate Day Fasting (ADF)

This requires **eating what you want one day, then cutting down to a quarter of your normal calories the next**. This amounts to around 500 Cal / day for women and 600 Cal / day for men.

Intriguingly, the research indicates that it might not matter much what proportion of fat you eat on non-fast days – although studies are limited. Dr Krista Varady of the University of Illinois at Chicago carried out an eight-week trial comparing two groups of overweight patients on ADF. She observed:

“If you were sticking to your fast days, then in terms of cardiovascular disease risk, it didn’t seem to matter if you were eating a high-fat or low-fat diet on your feed (non-fast) days”

5:2 Diet

This is a less intensive and often more practical version of ADF. **Five days a week you eat normally and then for two days a week what you do is you cut down to a quarter of your normal calories as in ADF.**

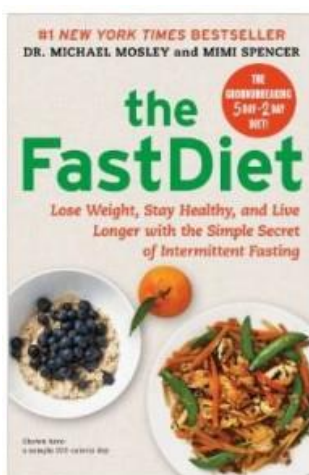
The 5:2 diet has been popularized by the Michael Mosley in the [BBC Horizon program Eat, Fast and Live Longer](#) (also given a BBC feature [here](#)). The feature is well worth a watch for an introduction to the science between restricted diet and intermittent fasting.



Michael Mosley having his health assessed before starting his 5:2 intermittent fasting diet. [Click for video.](#)

Recipes for 500-600 Calorie Intermittent Fasting

Michael Mosley's book [The Fast Diet](#) is recommended if you want a practical plan for adopting alternate day fasting or the 5:2 diet. You can download it in an instant to your Kindle. Examples of the fasting day diets are:



Breakfast: 1 boiled egg, half a grapefruit (125 calories)

Dinner: vegetarian chilli (378 calories)

Breakfast: Porridge with blueberries (197 calories)

Dinner: Chicken stir fry (306 calories)

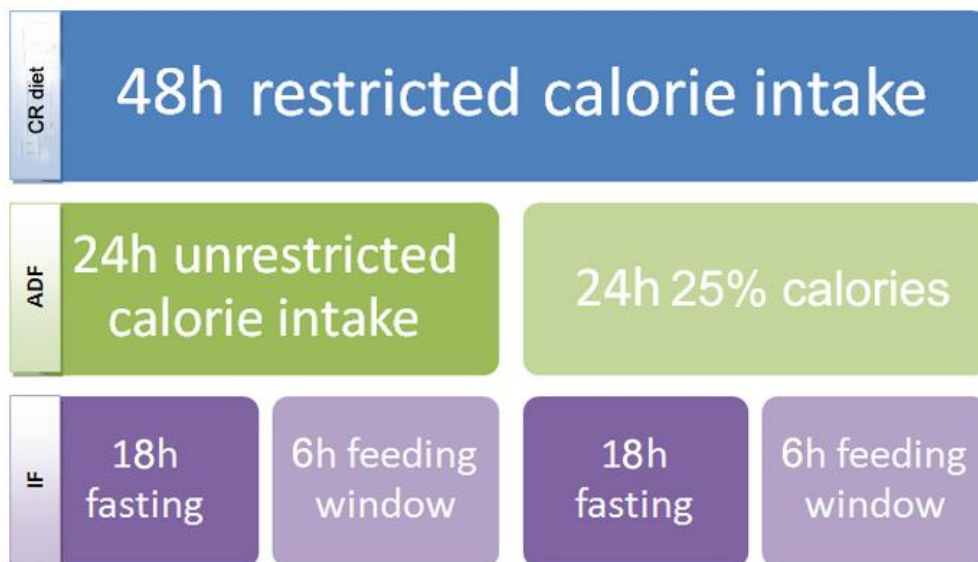
Breakfast: strawberry smoothie (171 calories)

Dinner: Oven-baked smoked haddock (325 calories)

Same Day Intermittent Fasting

This is another popular intermittent fasting variant - eating only during a short time window each day (e.g., not eating breakfast or lunch). One version of same day intermittent fasting has been adopted in [Bulletproof Intermittent Fasting](#). In this diet, you eat freely between 2pm and 8pm and fast for the remaining 18 hours in a day. Less research has been conducted looking directly at same-day intermittent fasting, but it triggers the same adaptive cellular stress response as CR and ADF.

Calorie Restricted dieting, alternate day fasting and same-day intermittent fasting schedules over a two day period are shown in the diagram.



Optimal Weight Range

Being underweight - just like being overweight - can result in negative health and cognitive outcomes. Excessive caloric restriction - putting you in the 'red zone' of the hormesis response - results in muscle wasting, bone mineral density reduction, libido lowering, general malaise. [And being underweight long-term in adulthood and weight loss late in life is associated with poorer cognitive outcomes.](#)

There seems to be a window for energy intake and expenditure that promotes optimal health and brain function. An energy balance that results in a BMI (body mass index) between 20 and 24 appears to be optimal for most people

eating Western diets. Ensure that you remain within this window while practicing caloric restriction or intermittent fasting.

[You can calculate your current BMI here](#)

Male-Female Differences with Caloric Restriction and Intermittent Fasting

There are a number of studies indicating that caloric restriction and IF **shouldn't be practiced during pregnancy** since it alters foetal [breathing patterns](#), [foetal heart rate](#), and may [increase gestational diabetes](#). This is not surprising since metabolic demands are going to be very different during pregnancy.

There may also be more general sex-differences in response to caloric restriction or IF, indicating that women should exercise more caution in their experimentation, being careful not to become overstressed due to fasting. In her ['Paleo for Women' blog](#), Stefani Ruper has observed:

“Many women find that with intermittent fasting comes sleeplessness, anxiety, and irregular periods.... I have also personally experienced metabolic distress as a result of fasting.”

Rat studies on 40% caloric restriction indicate that compared to males, females respond with a heightened stress response, greatly increased spontaneous activity, improved alertness, learning and memory with elevated levels of circulating brain-derived neurotrophic factor. Female rats also stop ovulating and menstruating. ***This suggests that females may have evolved a greater 'survival mode' response during times of energy scarcity.***

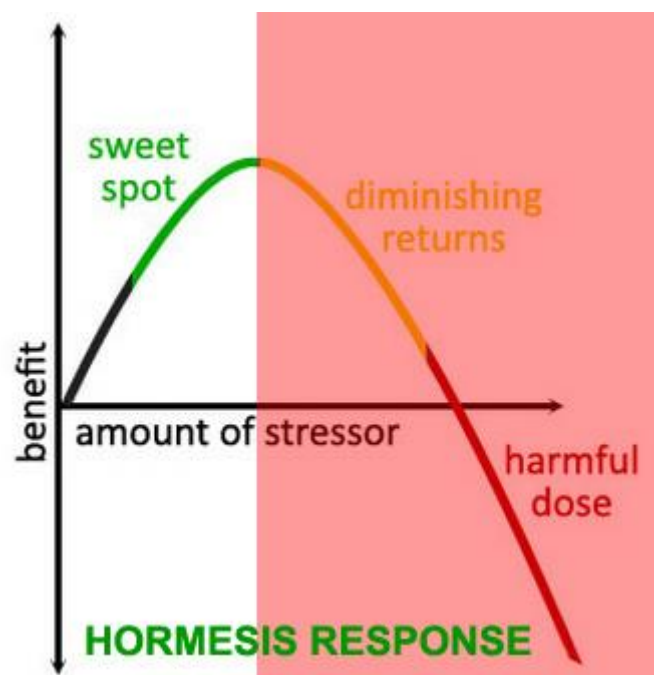
However, these are animal studies, looking at high levels of caloric restriction - not the kind of intermittent fasting that is widely practiced by women who report its benefits. There are only a handful of studies looking specifically at sex differences in the effects of intermittent fasting (IF).

- [Intermittent fasting improved insulin sensitivity in men, but not women, and glucose tolerance of fasting women slightly worsened.](#)

- [After a regime of intermittent \(whole day\) fasting women’s HDL \(‘good’ cholesterol\) improved and their triglycerides remained stable, while men’s HDL remained stable and their triglycerides decreased.](#)
- One study looked at fitness biomarkers as a result of a program of cycle training comparing training after an overnight fast with training after a morning meal. [Both men and women displayed greater increases in VO₂ max and resting muscle glycogen concentration in response to fasted cycling training, but only men showed greater skeletal muscle adaptations.](#) Women had better muscle adaptations when fed.

But these are non-replicated, isolated studies with small numbers of subjects and relatively small effect sizes. They also look at whole day (36 hour) fasting rather than 25% caloric restriction fasting.

It’s clear that many biomarkers of improved physical and cognitive health improve in (non-pregnant) women on intermittent fasting programs - as a result of the adaptive cellular stress response. The 5:2 fast, for example, is very popular with women. There may even be greater cognitive benefits for women. But the evidence suggests that there may be a more heightened stress response to calorie deprivation, suggesting that there needs to be more care about not crossing into the ‘red’ region of the hormesis response where there may be “sleeplessness, anxiety, and irregular periods”. Special care should be taken with respect to reproductive health.



Tips for successful fasting

- Experiment with different fasting programs to find out what you can **successfully make a part of your lifestyle**. These diets should be thought of as a long-term lifestyle change – not a temporary diet plan. It is for this reason that permanent **caloric restriction (e.g. 20-25%) diets are not recommended**, as they tend to be unsustainable in the long-term.
- The diet should, after a couple of weeks, be helping you feel **“more energy, more bounce, a greater zest for life”** in the words of Dr Michael Mosley. If you are feeling fatigued, over-stressed, or run down, or are experiencing disruptive swings in mood and energy levels, then the diet is not working and should be adjusted.
- You may need to develop a **tolerance for feelings of hunger** on fasting days – which in itself is not a negative.
- The idea of caloric restriction/fasting is to create **an energetic stressor to activate all the benefits of the hormesis response**. But if you overdo the fasting, or skimp on essential nutrients, you will cause the kind of system breakdown that you are trying to build resilience to – leading, for instance, to insulin resistance and poorer glucose metabolism. For women, the effects of being overstressed from fasting may be more dramatic.
- Related to the above, combining fasting with intense exercise may result in a **stress-reactivity response**, with sleeplessness and anxiety. I would recommend stocking up with a high carb meal the evening before endurance workouts, and ensuring that on the training day you are also well fuelled with carbs.
- **Ensure that you don’t become weaker through muscle loss**. Maintain at least 0.8 grams of (complete) protein per kilogram of body weight – e.g. 64 g for a 80 kg man (i.e. 256 calories) ; 45 g for a 56 kg woman (180 calories).

- **Drinking coffee may be beneficial for fat-burning**, especially during a fast. [One study found that an infusion of epinephrine \(a hormone that coffee increases\) during 48 hour fasting up-regulated fat-burning and metabolism.](#) Epinephrine also **lowers appetite**, which can be helpful for people trying to stave off hunger during a fast.
- **Avoid alcohol during fasting.** The inebriating effects of alcohol are more pronounced during fasting, and alcohol is itself relatively high in calories.
- **Meditation on fasting days is recommended.** Mindfulness meditation before sleep on fasting days helps counteract stress-reactivity, and helps with overall adaptation to prolonged intermittent fasting.
- **Phytochemical consumption on fasting days is recommended.** The health and cognitive benefits of phytochemical-rich nootropics such as green tea, blueberries, and Turmeric may be heightened when the adaptive cellular stress response is already ‘primed’ by fasting.
- **High Intensity Interval Training (HIIT) is recommended for fasting days.** Based on the same principle of brain cross training synergy, combining briefer periods of high intensity workouts with fasting may be a highly beneficial strategy. Experimentation is needed, to ensure that this doesn’t result in an unhealthy stress-reactivity outcome.
- **Intensive computerized brain training** (such as HighIQPro, i3, i9, EQ Pro or IQ-HIT) ay also act synergistically with fasting, with greater neuroplasticity and brain health benefits when the adaptive cellular stress response is already primed.



Chapter 6.

**Phytochemicals
for Vitagenes**

Considering diet in general terms, certain nutrients are known to be beneficial to brain health. For example, people with low folic acid levels (found in spinach, asparagus and Brussels sprouts), are at increased risk of Alzheimer's disease (AD). [Folic acid is critical in brain tissue DNA repair](#). Moreover, high fibre diets can [reduce the risk of strokes](#). Other foods such as saturated fats and refined sugars have a negative impact on not only general health but brain health and neuroplasticity. Regularly eating these foods, for example, [accelerates age-related deficits in learning](#).

This chapter looks a specifically at a specific type of dietary chemical that triggers the hormesis response; namely, **phytochemicals**.

Mounting research shows phytochemicals' effectiveness in preventing and treating a range of conditions including everything from cancer and heart disease, diabetes, high blood pressure, cognitive aging, and neurodegeneration.

Phytochemicals definition: Phytochemicals are non-nutritive plant chemicals, many of which have protective or disease preventive properties. They are nonessential nutrients, meaning that they are not required by the human body for sustaining life. Plants evolved many of these chemicals to protect themselves from disease and predation. Research reveals phytochemicals can also protect humans against diseases and promote neuroplasticity.

Phytochemicals Biology – Why They Evolved?

Phytochemicals are chemical compounds that occur naturally in plants ('phyto' is Greek for 'plant'). They are chemicals that have a biological function, such as plant pigmentation for pollination or plant defence, but are not essential nutrients - whether carbohydrates, protein, fat, vitamins, minerals or water. We notice phytochemicals in the vivid sensations that plants may give us - whether through vivid color (such as red peppers), intense aromas (such as essential oils) or strong tastes (such as spices or bitter vegetables).

Plant chemicals come in two major categories – **primary metabolites** directly involved in growth or reproduction (e.g. sugars, proteins, amino acids, nucleic acids) for the plant, and **secondary metabolites** which are organic compounds. Humans use secondary metabolites as medicines, flavorings, dyes, and recreational drugs. Phytochemicals are secondary metabolites.

Flowers, fruits and seeds are rich sources of many phytochemicals – especially in annual plants. In perennial species, phytochemicals may be present in high level in bulbs, roots, rhizomes, bark and stems.

Phytochemicals have a variety of biological functions. Some act as acting as volatile chemicals that attract birds and insects for pollination. Plant colouring for the purpose of either camouflage or attraction.



But [the primary use of phytochemicals is for defence](#). Plants can use muscles to run or fight, but they have evolved a stunning array of structural, chemical, and protein-based defences designed to detect invading organisms and stop them before they are able to cause life-threatening damage.



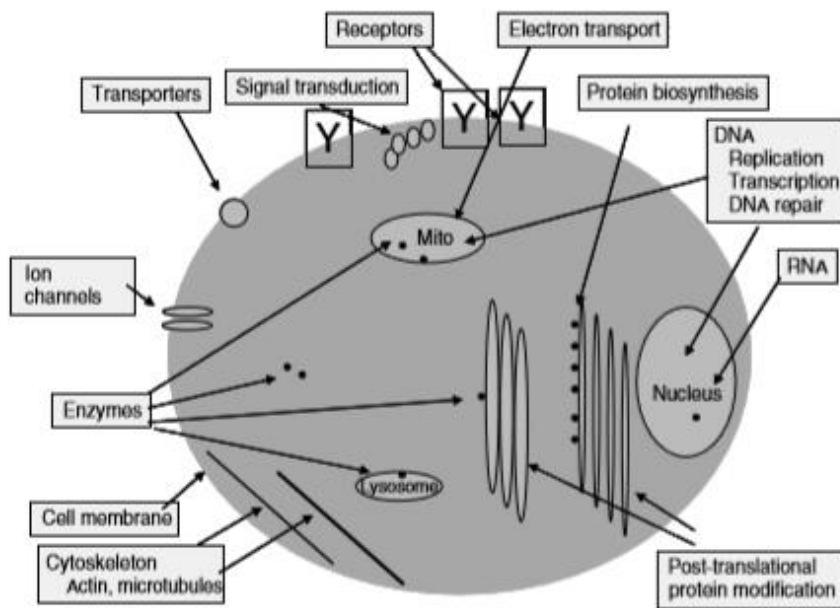
Plant defences can be structural or chemical. Structural defences include waxes, bark, sharp crystals that tear mouth parts during feeding, stinging cells (found in stinging nettles), leaf hairs and thorns. Phytochemicals are a type of **chemical defence**, and include toxic chemicals and pathogen-degrading enzymes for

- Defence against grazing herbivores and insects
- Defence against micro-organisms, including bacteria, fungi and viruses
- Defence against other plants competing for nutrients and light
- Protection against the damaging effect of UV light

Examples of a 'grazing' defences include the volatile nature of the essential oils (Trichomes) or the astringent and bitter taste of tannins (found in young red grapes) and alkaloids (morphine, caffeine). In nature, these are all deterrents to predators.

Phytochemicals Biology: Cell Targets

Phytochemicals have been designed to interact with many different molecular and cellular targets, including enzymes, hormone receptors, neurotransmitter receptors and transmembrane transporters. There is hardly any cellular target that some phytochemical cannot modulate (see figure below). Thousands of phytochemicals have been identified, many exert their effects in synergy.



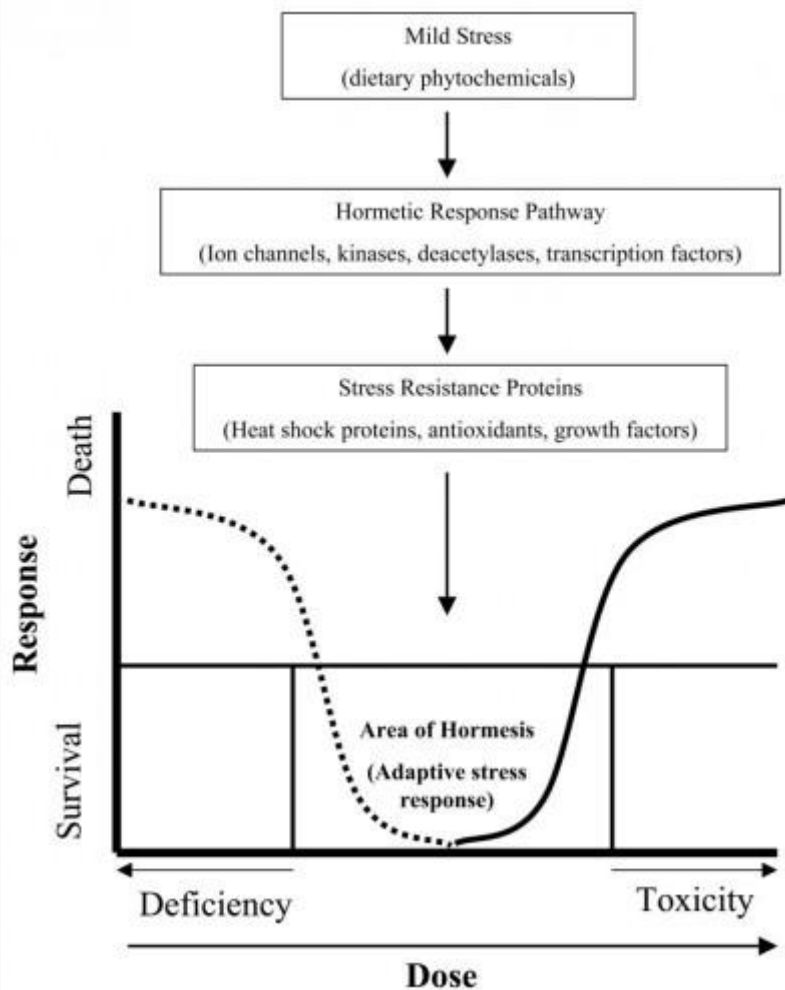
Possible cellular targets for plant phytochemicals (From Acamovic and Brooker, 2005)

Hormetic Phytochemicals & Adaptive Cellular Stress Responses

At the subtoxic doses ingested by humans that consume the plants, the phytochemicals induce mild **adaptive cellular stress responses** via the principle of **hormesis**.

When we consume phytochemicals, they trigger adaptive cellular stress responses- much like exercise, fasting and cognitive challenges can trigger them.

As reviewed previously, the adaptive **cellular stress response** (CSR) evolved at the biochemical level as a powerful mechanism to protect and regenerate the organism under conditions of stress - for instance calorie restriction, or high energy stress from intense physical or mental activity. When we consume phytochemicals, the CSR is triggered by **chemical** stress.



The Hormesis Response with Phytochemicals

Intermittent fasting, aerobic exercise, phytochemical-rich foods, and cognitive challenges are all cellular stressors. Through the hormesis response, they switch on stress-response genes called ‘vitagenes’ in adaptive cellular stress responses(CSR) that promote health, immunity and physical and mental performance.

[Evidence from both human and animal populations](#) shows that phytochemicals can be neuro-protective, stimulate neuron (brain cell) growth and support neuroplasticity essential for learning, memory and maintained brain health in old age.

Phytochemicals with Brain Benefits

[As reviewed here](#), extracts of various **fruits and vegetables have neuroprotective properties** that help with neurodegenerative conditions including stroke, and Alzheimer's and Parkinson's diseases.

Supplementation of the diet of rats with **strawberry, blueberry or spinach** extracts for 8 weeks resulted in [the reversal of age-related brain deficits, and improved motor performance and maze learning](#).

Blueberry supplementation [prevented learning and memory deficits in a mouse Alzheimer's disease](#).

In laboratory experiments, **blueberry extracts** have extended the **life span** in two different models of aging. These studies, as well as a summary of a wide range of other studies related to the health benefits of blueberries can be [found here](#).

Various studies have shown the **neuroprotective effects of green tea** – with [benefits for models of Parkinson's disease, eye disease, Huntington's disease models and Alzheimer's](#).

These effects are due to the food's phytochemicals with known brain benefits. For example, **Flavonoids** found in fruits such as red grapes and blueberries [promotes learning and memory](#).

Other phytochemicals with benefits to brain health, resilience and performance include the following:

- **Curcumin** (the yellow pigment in the spice turmeric), [stimulates neurogenesis and in animal models activates detoxification enzymes and helps prevent strokes, and Parkinson's disease](#). A host of other general health benefits such as treatment for depression are [reviewed in this blog article](#).
- **Sulphoraphane** (present in high amounts in broccoli) [activates antioxidant enzymes](#) that protect brain tissues against oxidative (free radical), toxins in mitochondria (the energy factories of brain cells), and degeneration of photoreceptors in the eye ([reviewed here](#)).

- **Resveratrol** (found in red grapes/red wine, blueberries and peanuts) has anti-inflammatory and anti-oxidant properties. [The neuroprotective effects of resveratrol have been reported by several different laboratories](#); it protects neurons (brain cells) in a number of brain regions against cell death, degeneration and toxicity stress.
- **Catechins and epicatechins** (found in green tea) [activate brain cell survival genes, and protect brain tissue](#).
- **Terpenes extracted as essential oils** from Sage ([1,2](#)), Lemon Balm ([1](#)) and Rosemary ([1](#)) have been found to improve cognitive performance (memory, attention and alertness).
- **Plumbagin** (found in [Limonium flowers](#)) and has [antioxidant, antiinflammatory, anticancer, antibacterial properties](#) that support brain tissue health.
- **Hericenones and erinacines**. [Numerous studies have shown that the phytochemicals hericenones and erinacines found in the Lion's Mane mushroom stimulate nerve regeneration](#). In one clinical trial, giving lion's mane to 30 Japanese patients with mild cognitive impairment resulted in significant benefits for as long as they consumed the mushrooms ([1](#)).

Combing phytochemicals with piperine can effectively increase their bio-availability. For example, [piperine \(found in black pepper\) can enhance the body's absorption of curcumin by 2000%](#).



Chapter 7.

**Cognitive Challenges and
Mental Effort for Vitagenes**

Mental effort is defined as energy mobilisation in the brain in the service of cognitive goals.



Mental effort facilitates performance in the presence of increased task demands (time pressure, multi-tasking, working memory load or the inhibition habitual responses) as well as psychological stressors such as fatigue, sleep deprivation, drugs, or noise.

The brain has substantial energy needs: 20–30% of all energy expenditure at rest. It is dependent on a constant supply of glucose and oxygen from the bloodstream. With more cognitive challenge, there is more glucose and oxygen consumption. This can lead to an **adaptive cellular stress response** in the brain, which can be tapped with the hormesis response.

Most of the rodent studies demonstrating beneficial biochemical and cognitive outcomes from ‘cognitive challenges’ involve inducing psychological stress in novel (‘enriched’) environments. Remembering that the brain is a huge energy consumer, this kind of energetic stressor taps exactly **the same adaptive cellular stress response that is found in caloric restriction / fasting and intense exercise.**

Any kind of cognitive challenge requiring mental effort should be beneficial to brain resilience, health and performance. The question here is: how can we maximize broad brain health and cognitive performance gains returns from this hormetic response to mental effort in a planned way? **How can we maximize gains from mental effort in the way the high intensity circuit training maximizes gains from physical effort?**

The answer involves identifying and training a type of mental process that is **stressful** (but not too stressful), **effortful and high in energy demand**, involves **novelty that requires adaptive learning** and is **core to the broad range of cognitive processes** underlying our **fluid intelligence** - the kind of intelligence that plans, problem solves and learns in novel situations. The

brain areas known to be important for fluid intelligence are part of an interconnected system associated with emotional arousal and the stress response.

The best candidate we have for this set of criteria is working memory training.

Working memory is the ‘executive’ brain system for short term storage and control of the information needed for higher level cognitive tasks such as language comprehension, learning, and reasoning. It is our ‘mental workspace’, and the more we load it with cognitive challenges, the more energy it consumes and the more we stimulate the adaptive cellular stress response.

Studies on working memory training have shown:

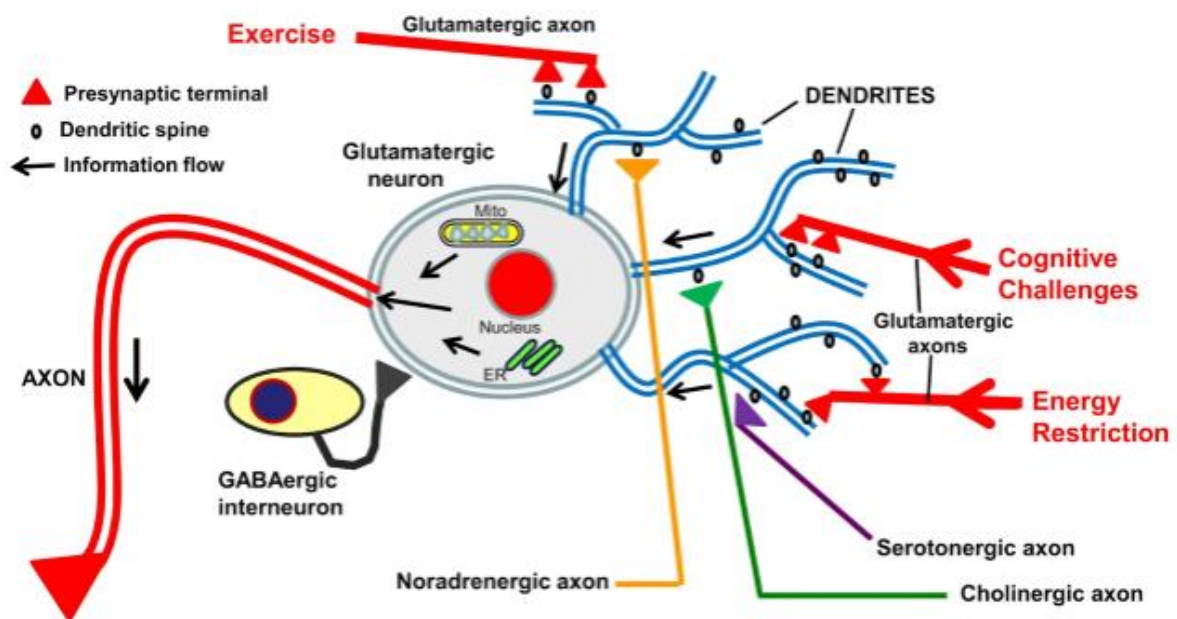
- [Gamma \(30–60 Hz\) oscillations increase linearly with working memory load](#) and gamma brainwaves are known to be [associated with high energy demand](#), requiring both rapid adaptation of oxidative energy metabolism and sufficient supply with oxygen and nutrients.
- The high metabolic demands of working memory activity explain the **vulnerability of working-memory related functions to circulatory disturbances, genetic mitochondrial diseases, and neurodegeneration** and why **training working memory can help stimulate the adaptive cellular stress response** to counter these vulnerabilities for better brain health, neuroplasticity and cognitive performance.
- Prolonged (1 month) working memory training fulfils all the [5 criteria identified as critical for effective brain training](#) by Dr Alvaro Fernandez and the consumer research group [SharpBrains](#).
- [This review of the benefits of working memory training](#) concludes:

“The results of individual studies encourage optimism regarding the value of working memory training as a tool for general cognitive enhancement. ...Studies of core training show improvements in a variety of areas of cognition (e.g. cognitive control, reading comprehension), persist even with the use of tightly matched controls, and are consistent with neuroimaging studies demonstrating activation changes in regions associated with domain-general cognitive performance. Core working memory training thus represents a favourable approach to achieve broad cognitive enhancement.”

- The most popular ‘brain training’ providers on the market – much like the most popular ‘workouts’ and diets – do not work as energetic stressors that induce strong adaptive cellular stress responses. They are too easy and not stressful enough over a long-enough training period. [Consequently the evidence for their benefits is lacking.](#)

Recommended working memory training providers include the following:

- [IQ Mindware](#) – my own brain training company, focusing on **core working memory training** apps for IQ, productivity, resilience, problem solving and skills learning. These products are designed around the principles reviewed in this article, and require systematic, focused training effort.
- [CogMed](#) – Clinical working memory training.
- [BrainWorkshop](#) – Home-coded variations of the n-back working memory task.



Three types of training regimes that help brain function in red. Triangles indicate synapses (communication points) between different brain cells (neurons).



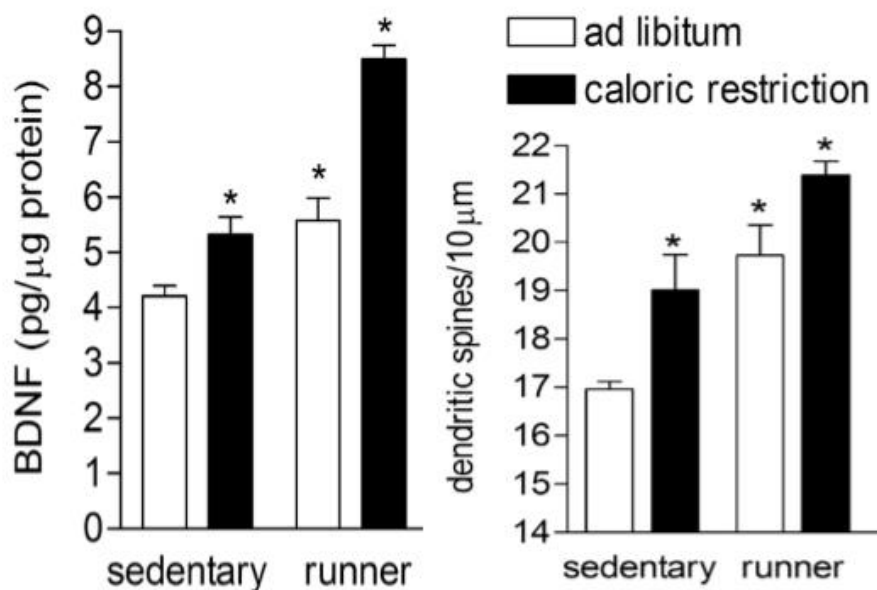
Chapter 8.

Hormetic Synergies for Brain Cross-Training

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.



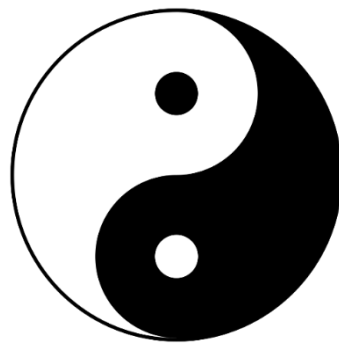
Synergisms for brain cross training could include the following in addition to working memory training, scheduled into two day cycles:

- High Intensity Interval Training (HIIT) combined with fasting.
- Phytochemical drinks combined with fasting.
- HIIT combined with phytochemical drinks.

Of course, the doses are critical when you are experimenting with combinations. We have to ‘listen to our physical and mental condition’ as we train to ensure that we don’t overstress our systems and compromise brain health and performance by over-training. Occasional spikes of high intensity stress can be beneficial, provided we give ourselves good recovery time. 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* (which we might call 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, actually *promotes* better relaxation. One effect of exercise is a reduction in stress as we know. Fasting has also been shown to **decrease** our nervous system’s stress response, with decreased activation of our ‘fight or flight’ sympathetic nervous system, and increased activation 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 stress and promote relaxation.

And the evidence indicates that **active relaxation** in combination with the de-stressing effects of hormesis can be of synergistic benefit. For example, sports massage following intense exercise can improve the immune response.

Active relaxation techniques can be combined with the hormesis response 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.

Experimentation is encouraged, using the ‘yin-yang’ stress-relaxation principle.

Chapter 9.

**Self Quantification for
Brain Cross-Training**

It is both informative and motivating to track certain variables to track potential gains from your brain cross-training. Useful measures that are freely available (some involving a trip to the doctor) include the following:

- weight
- BMI (body mass index)
- body fat percentage
- blood sugar
- cholesterol levels (e.g. HDL, LDL)
- blood pressure
- serum cortisol (measured at different times during the day)
- resting heart rate

Measures of physical performance can also be tracked such as weight lifted, reps completed, distance run/walked/cycled/rowed.

For **brain health & resilience**, you may use a short test battery such as the **Mindware Lab Test Battery** which you are given with any [IQ Mindware app](#) purchase. This battery includes standardized scales for:

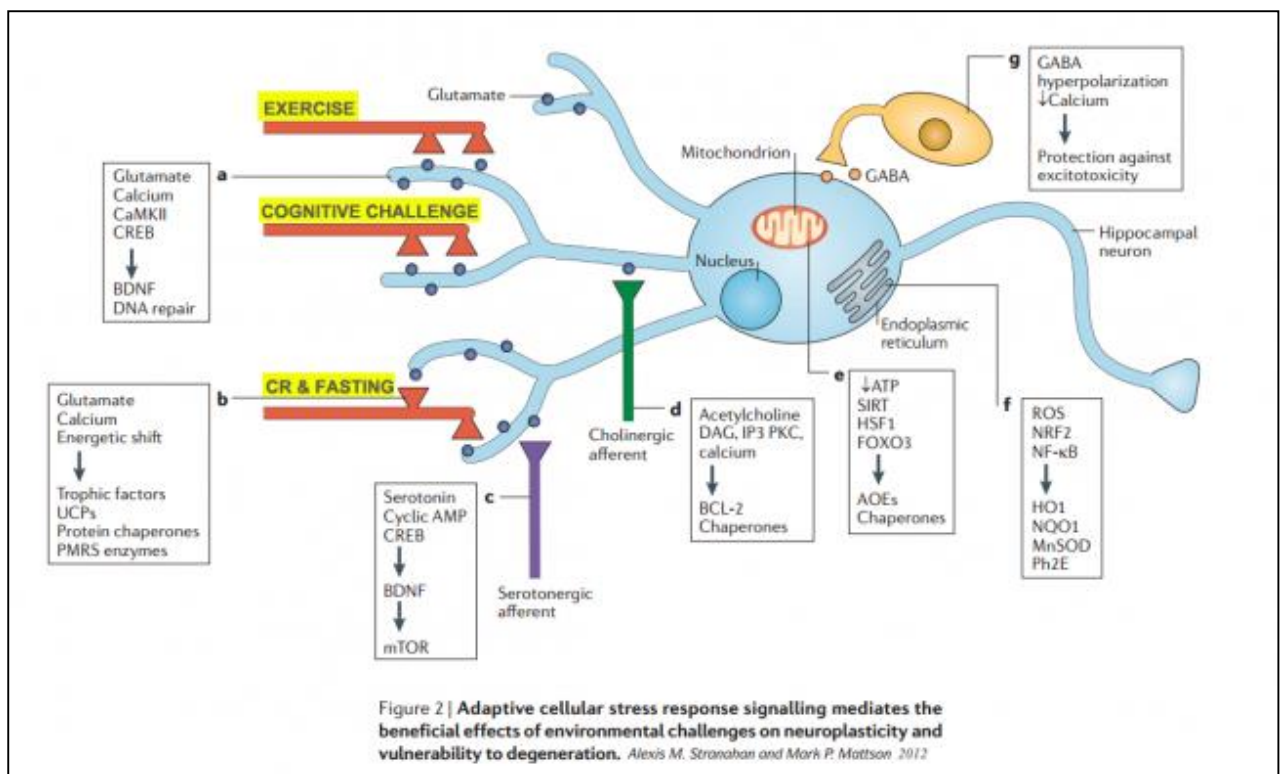
- Depression, anxiety and burnout
- Cognitive resilience
- Decision making competence
- EQ

These tests could be combined with independent measures of IQ and working memory, also provided with the [IQ Mindware app](#) licenses.

Such 'self-quantification' measures used before and after training can be used to give you a valid measure the effects of your training, and can motivate you to continue your training.

Appendix 1

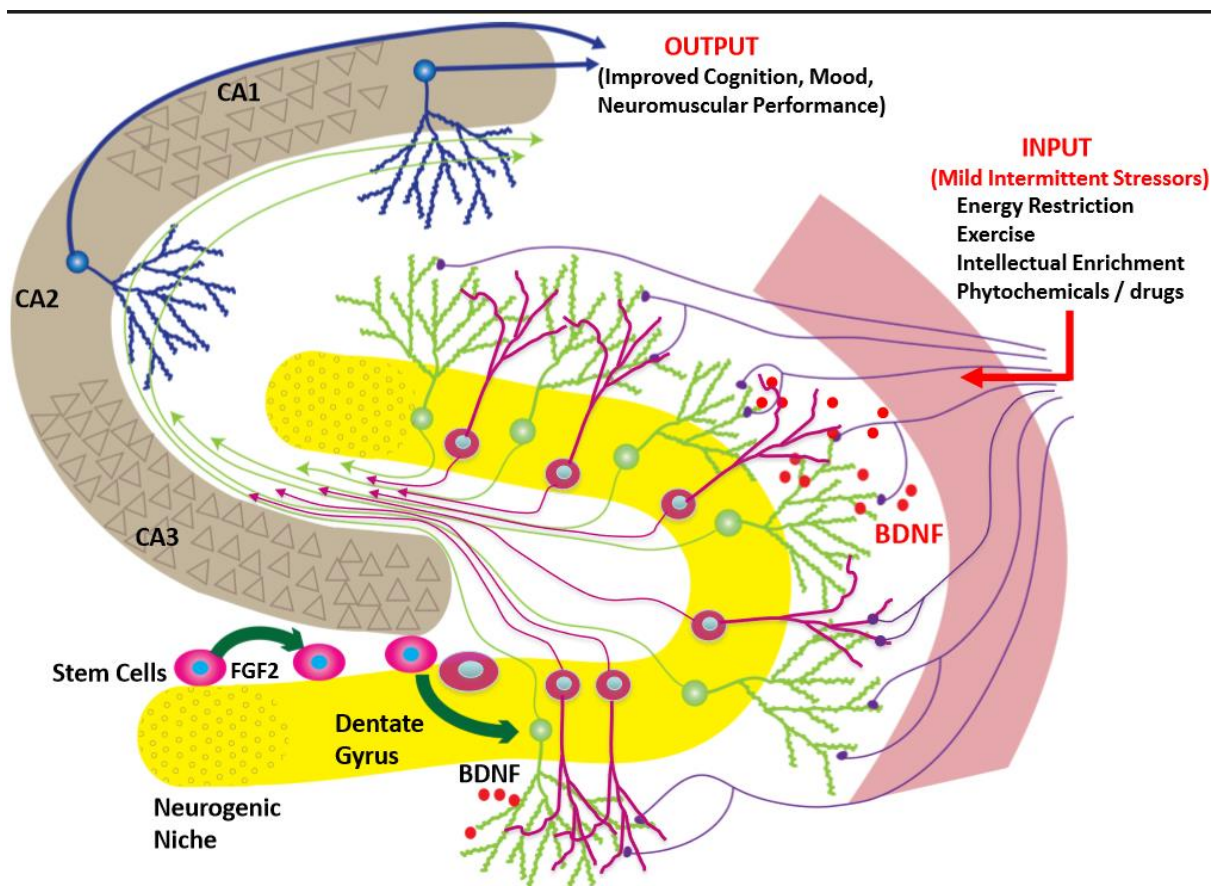
The Adaptive Cellular Stress Response



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).



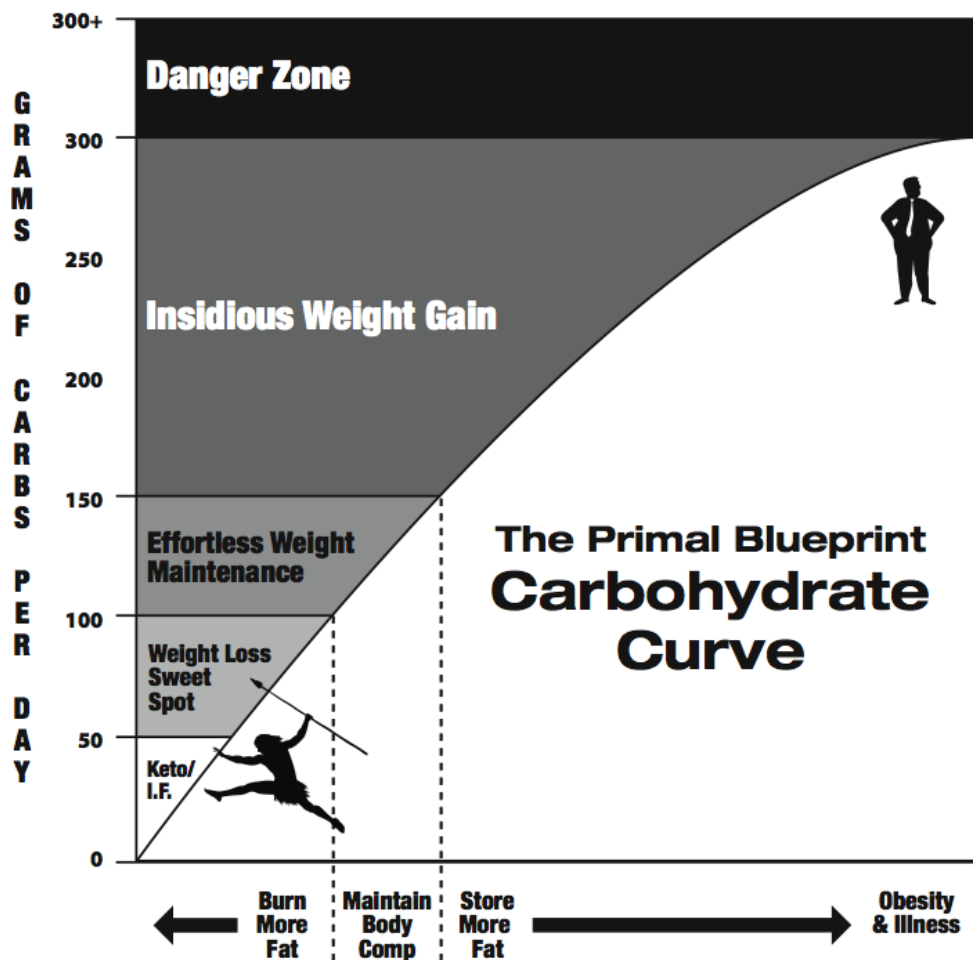
APPENDIX 2

Keto-Adaptation

According to Mark Sisson and other advocates of the ‘keto-diet’ we are stuck in a biologically maladaptive ‘carb’ paradigm that we need to break out, adopting a low carb-eating diet and reprogramming our genes to become ‘keto-adapted’.

Sisson argues that in our evolutionary history, the periodic lack of regular access to food and carbohydrates necessitated the adaptation of efficient metabolic processes to store and access body fat, and that **human metabolism is pre-programmed by evolution to be primarily fat-based, not glucose based.**

*“Our movement patterns were such that we never required large amounts of glucose or that we needed to store very much glycogen. **It was predominantly fats, ketones and the minimal infusion of glucose via gluconeogenesis that got us here. Dietary carbs were insignificant.** In fact, when you consider how ridiculously small the body’s glycogen reservoirs are, you understand that it would have been impossible for us to survive as a species if glucose were truly the “preferred” fuel. The liver, the main back-up glycogen/glucose storage facility for the brain and other glucose-burning organs, can only store about 100 grams of glycogen. Less than a day’s worth. Your muscles can only hold another 350-500 grams, barely enough to run for 90 minutes at a reasonable clip, and that glycogen isn’t even available to provide fuel for the brain. Meanwhile, we have a virtually unlimited storage capacity for fat (like 100,000 grams or close to a million calories on some people).” [Mark Sisson](#)*



Taken from Mark Sisson - [Mark's Daily Apple](#)

By adopting a low carb diet we can become keto-adapted and more efficient fat-burners – through [gluconeogenesis](#) and [ketosis](#) rather than the carbohydrate based use of glucose and glycogen stores.

“most typical human movement patterns can be fuelled almost entirely by fats and/or ketones if need be, but can draw on glycogen when energy bursts are required (and which can then be replaced over time). It acknowledges that fat (and cholesterol) are not the proximate cause of heart disease. It acknowledges that fat cells are designed to release stored fatty acids as required, especially during times of scarcity or fasting. It allows for intermittent fasting as a means of accelerating fat loss without sacrificing muscle tissue. It increases insulin sensitivity, modulates energy and mood swings, and allows for a normal and healthy drop in hunger and cravings.”

For more scientifically grounded information on the ‘ketogenic diet’, have a look at [this comprehensive introduction by Dr. Peter Attia](#).

Notice. *As a general warning, the ketogenic diet for the general population is scientifically controversial. There are no systematic clinical trials looking at the effect of the ketogenic diet on general health. Dr. Peter Attia represents just one point of view. The evolutionary arguments are also very controversial. Adopting the ketogenic diet is for most people a radical dietary intervention, and may result in unwanted side effects. Experiments with the ketogenic diet, motivated by the intention to burn more ketones, should only be attempted with a gradual, tapering transition from a higher to a lower carbohydrate diet.*

More on Evidence-Based Apps

If you are interested in finding out more about effective working memory training apps, sign-up to [this invitation-only mailing list](#).



[Click for limited app promotions](#)