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The Hormesis of Thinking: A Deeper Quantum Thermodynamic Perspective?

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Abstract

We are able to read this because of quantum and thermodynamic principles that via an inorganic proton gradient, possibly generated 4.2 billion years ago, gave rise to a system that has an awareness of time and space by using energy to integrate information. Life can be described as a *dissipative system* driven by an energy gradient that uses information to positively reinforce its self-sustaining structure, which in turn increases its non-linear decisional capacity. Key in the evolution of life has been stress coupled to natural selection, which usually meant an increased demand for energy. As hormesis describes the adaptive response to stress, we propose that hormesis embraces not only the evolution of life, but that of intelligence itself, as natural selection would favour systems that enhances its efficiency. A component of the hormetic response in eukaryotes is the mitochondrion, which itself relies on quantum effects such as *tunnelling*. This suggests that quantum effects control the stability of individual cells as well as long-lived cellular networks. Hormesis, which can be anti-inflammatory, is therefore key in maintaining the functional stability of complex systems, including the brain. In contrast, a lack of classical hormetic factors, such as physical activity, plant polyphenols, or calorie restriction, will lead to accelerated cognitive decline, which is associated with increased inflammation. However, there may be another previously unidentified factor that could also be considered hormetic, and that is thinking itself. Here we propose that the process of "thinking", and managing complex movement, induces "stress" in the neuronal system and is therefore in itself part of maintaining cognitive health and reserve throughout life. In effect, the right amount of thinking and information processing can beneficially induce adaptation, and this itself could be explainable by quantum thermodynamics.

Keywords: Quantum; Thinking; Mitochondria; Thermodynamics; Inflammation; Hormesis; Intelligence

Introduction to Cognitive Hormesis

Hormesis describes a biological epiphenomenon that is central to evolution: the ability to adapt to environmental stresses. The basic principle has been intrinsically understood throughout history by the phrase, "*what does not kill you makes you stronger*". This phrase should be extended to *what doesn't kill you not only makes you stronger, but longer lived and smarter*. Hormesis may not enable us to live for ever, but it might improve functional longevity and cognitive reserve. However, it might also suggest that too much "brain stress", especially if chronic, could be detrimental- a lack of sleep could be a prime example.

In a world where a larger proportion of individuals are longer lived thanks to reduced infection and enhanced nutritional availability, old age is often associated with a prolonged period of disability before death- a state of *morbidity expansion*. In particular, the ageing process is associated with increased frailty and declining cognitive abilities. One of the main reasons for this may be the removal of hormetic stresses (hormetins) from our environment. For instance, we have removed the need for significant physical activity, reduced our intake of bioactive plant compounds, largely removed exposure to extremes of temperature, and critically, taken away seasonal food availability. It might also be argued that under some circumstances we have also reduced our need to think [1]. In fact, a poor lifestyle can reduce cognition at quite a young age [2]. In contrast, a healthier lifestyle does lead to a relatively reduced period of disability later in life [3]. Hormesis may thus lead to *morbidity compression*.

There are at least six key factors that may shed light on how hormesis maintains cognitive function. The first is that inflammation can accelerate cognitive decline and is linked to the ageing process [4-6]. Secondly, the mitochondrion is implicated both in the inflammatory and ageing process [7-9]. Thirdly, there is a fundamental relationship between energy and information [10]. The fourth is that information is describable as a thermodynamic entity [11]. The fifth concept refers to the emergence of order in complex systems when subject to perturbation and life as a *dissipative system* [12,13]. This ties in with the idea that life exhibits *negative entropy* [14], which via quantum mechanics, leads to the emergence of a new field of "quantum biology" [15]. The sixth concept is the importance of integrating the fields of thermodynamics and quantum physics as "quantum thermodynamics" [16]; life must certainly obey principles of both thermodynamics and quantum physics [17]. Thus information is a key to life, as it enables time awareness by learning from the past to predict the future. In fact, it could be said that intelligence, in its broadest sense, is part of the definition of life. This suggests that hormesis was not only essential in the evolution of advanced intelligence, but also in maintaining it [18] with the mitochondrion playing a key role [19].

Is it therefore possible that things that make the brain "work", which have been shown to slow cognitive decline such as environmental enrichment, "brain training" and physical activity [20-23], can be considered hormetic? Does "thought" make the brain more robust? In engineering terms, *robustness* is a product of negative feedback, and when applied to biological systems, represents conditions (parameters) for which the system evolved for; if exposed to conditions outside of this, it tends to become more fragile [24]. It is thus interesting that

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network control theory is being used to described cognitive reserve, with connectivity being very important and the brain is viewed as a dynamic network [25]. In this paper we aim to bring together aspects of quantum thermodynamics, mitochondrial function and inflammation, to explain how they might be important in the maintenance of cognition. We argue that hormesis is fundamentally an informational process that enhances robustness and adaptive plasticity, and hence is pivotal to optimal cognitive health and is very likely to embrace quantum principles.

The Emergence of Quantum Biology

For a more general introduction to both quantum physics, and quantum biology, the reader is directed to these references [15,26-28]. Briefly, many scientists have toyed with the possibility that quantum physics can be used to explain biological phenomena. For example, Erwin Schrödinger in his 1944 book "What is life" predicted some of the basic characteristics of DNA before it had been discovered [14]. More recently, it has been suggested that quantum effects would have been selected for at the beginnings of life due to their ability to improve efficiency – in particular, quantum tunnelling and superposition [29,30]. Indeed, the concept of directed "quantum evolution" has been proposed, which could explain how the first "self-replicator" molecules arose using basic quantum principles and gets around the problem of how, given the enormous degrees of freedom even a relatively short 15-20 unit peptide or nucleic acid displays, could have arisen [31].

Although there is still much debate as to how the first steps of life evolved the ability to incorporate heritable information, there is perhaps a little more support for the role of quantum effects in metabolism. New data does suggest that the last universal common ancestor of all cells (LUCA) was an hydrogen-dependent autotroph using carbon dioxide as the ultimate electron acceptor, relying on iron-sulphur clusters for catalysis that may have originated in a hydrothermal setting [32]; gene ontology is suggesting that the earliest life was indeed metabolism-driven [33]. It is also thought that the earliest photosynthetic organisms were anoxygenic, but electron transport was fundamental to the process [34]. Thus efficient electron transport may well be a key component of life. In fact it has been long thought that electrons can move along enzymes in a manner similar to that observed in semi-conductors [35], which may be due to quantum tunnelling [36]. It also appears that enzymes also utilise proton tunnelling [37]. Life may use thermal vibrations to pump coherence, which results in a phenomenon known as *quantum beating*. There is thus an optimal zone where just the right amount of "noise" can result in enhanced coherence and tunnelling due to stimulating particular vibrational modes in proteins- so called *vibronic coupling* [38-41]. Moreover many biomolecules exhibit *quantum criticality*, displaying properties somewhere between an insulator and a conductor, so potentially acting as charge carriers [42]. For example tubulin, because of its high content of aromatic compounds containing delocalised pi electrons, may be important in coherent energy transfer within a cell [43,44].

It therefore seems that long-range electron tunnelling may occur in many proteins, in particular in oxidoreductases and key components of respiratory chains [46] and thus may be important in how mitochondria produce energy [46,47], ensuring a tight coupling between electron flow and protonation via *redox tuning* [48]. It is now also thought that photosynthesis utilises fundamental quantum principles, involving coherence and excitons to transfer energy efficiently [38,39,41] This is especially interesting as lysozyme appears to demonstrate a *Fröhlich condensate;* Fröhlich suggested that terahertz radiation could be absorbed by proteins leading to them behaving as a series of coupled oscillators generating a macroscopic quantum effect [49]. If combined with the concept that the electro-magnetic (EM) fields generated by mitochondria can lead to *water order*, this suggests an overall protection against decoherence within the cell [50]. Indeed, it has been suggested that quantum coherence can be maintained for significant periods of time in complex biological systems as they can hover in a *poised realm* between the pure quantum and incoherent classical worlds [51]. It has also been proposed that quantum effects may play a role in ion channel selectivity; these ideas have been used to account for differences between those predicted by the Hodgkin-Huxley equation, which is a mathematical model describing how action potentials are initiated and propagated in nerves, and what has actually been observed in neural circuits [52,53]. In fact, some authors are now proposing that non-trivial quantum effects are possibly essential to explain biological systems, for instance explaining Levinthal's paradox (in relation to macromolecule folding), information processing and quantum adaptive dynamics, as well as evolution and consciousness [54]. The take home message is that life seems to use basic quantum (thermodynamic) principles to function, which not only has optimised efficiency of energy transfer, but also to use it synchronise information transfer and potentially, storage.

The Quantum Mitochondria; Hormesis and the Evolution of Intelligence

It has long been thought that the mitochondrion is central to the ageing process. The most established theory was proposed by Harman in 1956 [55]. Although some aspects of Harman's original theory have been challenged, the basic concept still appears to hold up; reactive oxygen species (ROS) play a key role in determining lifespan. Mitochondrial ROS is tightly controlled, so rather than being some random destructive force, it is now thought to be a key cellular signal. In fact, lifespan does not appear to be determined by the rate of living, but by how well controlled the ROS production is [56]. This of course suggests the efficient electron transport is key, which may well be controlled by quantum effects.

Declining cognition- a gradual loss of quantum coherence hinting at adaptive senescence?

Hayflick suggested that ageing was either programmed or a stochastic process leading to a loss of molecular fidelity associated with an increase in entropy and molecular disorder [57]. Some do favour the theory that ageing is non-adaptive and not specifically programmed [58]. However, others suggest programmed death of an organism is favoured by natural selection, as it ensures long-term stability of resources for the species [59]. The concept of programmed death of an organism to benefit the species was first suggested by Weismann in 1889 and following the discovery of apoptosis, it was given the name "phenoptosis" [60]. The fact that many forms of programmed cell death (PCD) do involve the mitochondrion may be of relevance in determining lifespan of a multicellular organism. Certainly PCD is thought to have evolved in prokaryotes [61]. This suggests that for life to remain functional, natural selection has to operate to constantly select for efficient systems while removing failing ones- in particular, in the case of eukaryotes, matching of mitochondrial genes encoded in the nuclear and mitochondrial DNA [62]. Of course this raises the question of whether or not natural selection would have evolved mechanisms that accelerate the demise of a system as it starts to malfunction, as it could potentially reduce the chances of survival of other, fitter systems- for instance, by production of too much ROS.

The lifespan of multicellular organisms is controlled by

mitochondrial ROS, with long lived animals displaying greatly reduced production, which is coupled with both decreased fatty acid saturation index, and counter-intuitively, with reduced anti-oxidant defences and DNA repair mechanisms; the reason being that energetically, it is far more efficient to reduce ROS production rather than compensate for its effects [56]. In this light, it is interesting that mitochondria can act as net *sinks* of ROS in a respiration-dependent manner, involving the thioredoxin/peridoxin system [63]. The underlying principle here is that mitochondria can direct electrons both towards the ETC for energy, or towards anti-oxidant systems and are thus central in redox signalling [64]. All of this tends to suggest that improving electron transfer efficiency, while minimising ROS, has been an important natural selective pressure for longevity.

It has been proposed that iron generated magnetic fields can reduce *triplet* states, decreasing ROS in biological systems; a pure quantum effect [65]. Briefly, two electrons if existing in a single orbital, can be said to exist in a singlet state when they have opposite spins, so the spin=0. If one of them is excited with extra energy and "rises" to a higher orbital but its spin direction switches, so as it now has the same spin as its partner, it cannot fall back due to Pauli's exclusion principle – so it can potentially be more reactive; the triplet designation comes from the quantum description of the two electrons now having spin=1, as they can exist in three different values. This triplet state may be important in how many organisms detect the earth's magnetic field, as the electrons remain entangled [66]. Putting this together with the observations that quantum tunnelling is important in ETC [46,47] there is a clear precedent not only for ROS in controlling lifespan and signalling, but that it is ultimately controlled by quantum effects. In particular, the maintenance of localised coherence to optimise electron flux [19].

Understanding this relationship between mitochondria, electrons, ROS and energy may therefore be key to our understanding of the longevity of neurons in the brain. For instance, the role of the astrocyte-neuron shuttle and how neurons protect themselves against oxidative stress; neurons preferentially use glucose to generate reducing equivalents via the pentose phosphate pathway (PPP), rather than using it for energy – the source of electrons for ETC appears to be supplied via astrocytes in the form of lactate and pyruvate [67]. Furthermore, astrocytes can deliver mitochondria to neurons after injury, so aiding their recovery [68], while mitochondria can be transferred between cell via nanotubes and prevent apoptosis [69].

Given that neurons have to last a lifetime in many organisms, controlling free radical production must underlie their longevity and maintenance of optimal cognitive function. Indeed, it has been suggested that because mitochondria naturally produce ROS, a process which its free living ancestor used for defence, management of ROS shaped eukaryote evolution, in particular, how cells compensate for the increased production of ROS during beta oxidation (e.g. by evolving peroxisomes). It would certainly go some way in explaining why neurons do not use fatty acids for fuel [70,71]. If we accept that quantum processes are key in energy generation and signalling, in particular in the ETC, a reduction in the ability to modulate coherence at the quantum level could underlie the ageing process and the ability to process information. The ability to maintain coherence would be linked to protein structure, which degrades with age. This of course takes us back to the idea of entropy, which may ultimately underlie the ageing process. An individual is generally doomed because its "system" slowly degrades. Reproduction allows a reshuffling of the genes and natural selection of the fittest combinations, enabling a new organism to be born young.

Given the enormous range of lifespans exhibited by animals, with a general trend for increasing intelligence being linked with longevity, then it might be predicted that this process can continue as long as there is selective pressure; which is a big question for mankind to consider. So to answer the original question, is lifespan stochastic or programmed, the answer is probably both, as the requirement to fulfil an ecological niche is determined by what is required to compete. There has not been selective pressure for animals to live for ever, as they would never evolve, so the natural propensity for a gradual increase in disorder in biological systems is only counter-acted by improved feedback systems where they provide a survival advantage (in effect, storage of information). Equally, if a species is short-lived in a particular niche, there is no pressure for individual members to live longer; if conditions change, there might even be pressure for phenoptosis to ensure natural selection. So when we view the ageing brain, it only lasts as long as it needs to, and given the process of PCD, it is clear that removal of damaged members (nodes) of a community can benefit the whole; this could extend from molecules, to organelles, to an individual multicellular organism. In effect, life can be viewed as a series of nested networks starting from the atomic all the way up to whole communities of individuals, but it is based on the essentially random quantum nature of everything. Critically, life as a whole keeps going, although individuals and species come and go – so fulfilling entropy. And this is where perturbation and thus hormesis becomes pivotal.

What hormesis tells us; order from chaos

Most forms of life display some sort of biphasic response to stress – low stress inducing adaptation, but too much causing damage. The prime example of this is the effects of calcium on mitochondrial function: mitochondria can rapidly take up calcium, which stimulates their function, but too much induces mitochondrial permeability transition and death [72]. The stress can come in many forms, ranging from compounds that inhibit cellular function, to hypoxia, to starvation, radiation and critically, physical activity. This concept became known as "hormesis" [73]. Thus one of the key organelles in sensing stress is the mitochondrion, which has given rise to the concept of "mitohormesis" [74,75]. However, it is not just ROS that can initiate this response – so can energy stress. For example, increased levels of AMP and NAD^+ induce mitochondrial biogenesis and increase anti-oxidant capacity, as well as mitophagy [76]. Furthermore, small increases in ROS inside individual mitochondria can increase the localised production of ETC components; if this process was to solely rely on nuclear genes, it would be too slow [77,78]. Figure 1 depicts the hormetic curve, and how it could apply to calcium modulation of mitochondrial function.

The modern cell therefore has a series of adaptive strategies, depending on the stress level, to maintain energy production. These initially revolve around improving energy production within individual mitochondria. However, as the stress increases, mitochondrial turnover is enhanced, but if the damage is still too great, the cell is removed by PCD – unless it can be rescued by other cells with fresh mitochondria. They can also use glycolysis, which while it can quickly produce substantial levels of energy, is very inefficient and cannot be sustained indefinitely by larger organisms. This suggests a very tight integration between the mitochondrial membrane potential and the link between proton and electron flux. Not enough electrons, or electrons in the wrong place, or a lack of the ultimate electron acceptor, such as oxygen, are powerful adaptive signals, as are changes in pH and the proton motive force (PMF). In this way, the process of hormesis describes an adaptation to changes in electron flow and proton gradients, and in turn coherence. Hence hormesis can improve electron flux efficiency

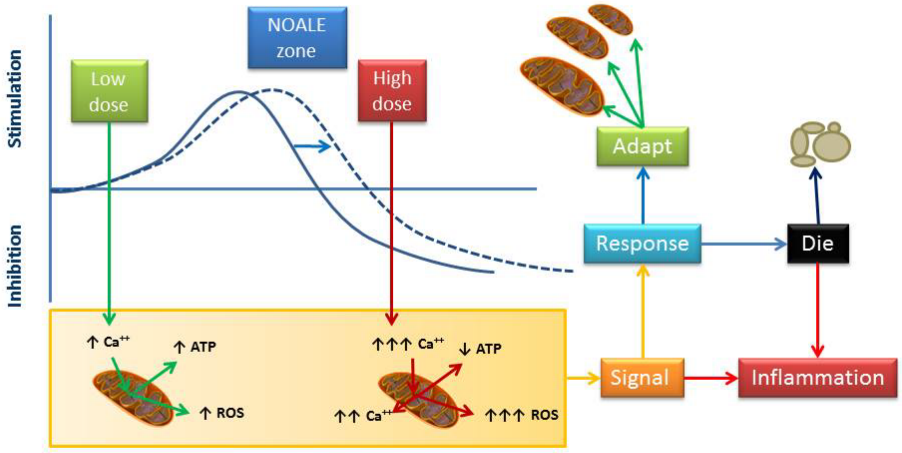

Figure 1: Hormesis – an integrated adaptive homodynamic epiphenomena to stress that increases robustness; mitochondrial example.
Solid curve: Immediate response; this is where a "low" dose of a potentially damaging factor, below its No Observed Adverse Effect Level (NOAEL) appears to directly and immediately stimulate an adaptive response, and is a composite of an inhibitory effect of the factor plus a generally counteracting and over-compensating response. For instance, calcium influx into the mitochondrion, generated by a potentially toxic compound opening a plasma membrane calcium channel stimulates production of ATP and buffers calcium. However, too much calcium (or the factor itself) can inhibit mitochondrial function, potentially inducing cell death, ranging from non-inflammatory apoptosis to inflammatory necrosis. Whether or not the stimulation or inhibition is beneficial will therefore depend on context, for instance, it could stimulate neurogenesis or cancer growth via generation of ROS or kill the cells.
Dashed curve: Adaptive response; inherent in the system is an overcompensation response. In the above example, increased calcium flux into the mitochondria could generate a ROS signal to enhance mitophagy, anti-oxidant defence and mitochondrial biogenesis, so improving overall calcium buffering and mitochondrial function within a cell. Along with activation of xenobiotic systems, this would make the cell more able to resist a potentially damaging factor if it were re-exposed to it, for instance, if it were a mitochondrial toxin. Hence the curve is shifted to the right and the NOALE and toxicity threshold is raised. The system could therefore be said to be more robust.

and potentially capacity; in electrical terms, it increases the current, reduces the resistance and removes any short-circuits, describing a classic feedback loop. Thermodynamically, it increases the capacity of the system to do work and consequently, extract information. Although the mitochondrion is not the only eukaryotic sensor system, it can rapidly detect environmental change and induce adaptation to enhance information capture. Its major role is perhaps inferred if life was initiated in a thermal vent [79] and then evolved the ability to use electron gradients to generate its own proton gradient; perturbation of these gradients would provide a selective pressure to capture information to improve efficiency.

One description of life is related to a fundamental mathematical principle outlining the appearance of order out of complex systems when exposed to some kind of stressor. In effect, life could be viewed as a localised area of order in a universe becoming increasingly disordered, as described by the concept of entropy. Life, as described by Schrödinger, displays negative entropy, as it can increase disorder around it by using energy to create structure and order in a localised form through the incorporation of information [14]. One definition of entropy is that it describes the flow of energy, in the form of heat, which is itself a measure of molecular vibration, from high to low, becoming increasingly disordered as it does so. Brillouin, in the late 1940s, realised that information itself can be viewed as a genuine thermodynamic entity that in relation to life leads to non-linearity in complex systems by feedback (transfer of information) and increases the systems organisation. Life can therefore be viewed as a self-organising machine; the principle being that although acquiring information is energy-consuming, information itself is actually capable of making the system more efficient. In effect through positive feedback it manages, retrieves and stores information, as described by the *information cycle of Brillouin*. The evolution of life therefore represents billions of these cycles, where information has been slowly accrued in reproducible and transmittable storage systems such as DNA, slowly raising its ability to interpret and adapt to the environment and learn as it became more complex. Thermodynamically no laws are broken, as although at a local level life displays negative entropy, the acquisition of information has a larger energy cost [11].

This has led to the concept that life is actually a localised *dissipative structure* driven by energy gradients [12]. In effect, life uses high energy photons to create order and accumulates negative entropy (information), and then emits them at a longer and thus lower energy wavelength. Of course due to natural selection and competition, only the most efficient form survives- which is to say, the best at using energy and information from its surrounding environment [80].

Hence living systems must operate far from thermodynamic equilibrium because they are driven by a constant flow of information; this information comes in the form of environmental perturbation that results in a loss of order, which in turn generates a correction. This information flows to the nucleus, for instance, via charged signalling proteins that initiates a corrective response. Systems that fail to do this are rapidly eliminated by natural selection. A key element to this is that a cell can be viewed, thermodynamically, as a semi-open system, allowing energy to enter and waste entropy to leave, but is obviously subject to the basic laws relating to size. In this light, as a cell grows, it becomes more and more difficult for it to maintain internal order due to a rapid increase in volume, but as soon as it undergoes mitosis, this internal order is restored in the smaller daughter cells. In contrast, if energy levels fall, it becomes increasingly difficult for the cell to survive as its internal order decays [13]; this would explain why cells can only grow to a certain size, and there is fundamental drive to divide. In other words life "eats order" [14] and information can be viewed as another physical characteristic of our universe. Mitochondria have enabled cells to get bigger by providing localised energy sources, which

in turn has enabled more genes and thus greater protein production and complexity [81]. In a way, mitochondria can be viewed as highly developed entropic engines that use quantum principles to release energy and capture information.

In summary, hormesis describes a positive adaptive process induced by perturbation. It therefore seems logical that as information can increase organisation, hormesis can be viewed as a situation where information is *injected* into the system, thus increasing its order. This suggests that biological systems are inherently non-linear and dynamically unstable, but show emergent self-organisational properties under perturbation. In other words they only exhibit the appearance of stability by negative regulation and this very instability has enabled evolution to occur [82,83]. In biological systems, this self-organising emergent property appears to arise in response to environmental perturbation resulting in robustness [84]. In simple terms, the emergence of life and intelligence, and thus adaptability, are products of constantly stressing a complex set of molecules in an energy gradient, and are definable through thermodynamics – with information being central.

Hormesis in action- Mitochondrial networks

Fused mitochondria can transmit energy [85] and calcium signals, enhancing sensitivity to apoptosis [86]. Mitochondrial fusion is also important in anti-viral signalling [7] and in protecting the cell during starvation by inhibiting mitophagy/autophagy [87]. However, this has to be balanced by fission to remove damaged mitochondria, transport of individual mitochondria, and partitioning during mitosis. Neurons are especially sensitive to imbalances in the axonal mitochondrial transport process as both energy supply and calcium handling are vital at the synapse [8]. At the other extreme, excessive stress generally results in mitochondrial fragmentation and formation of small, punctate mitochondria and ultimately, apoptosis if the cell is too damaged [89,90].

Mitochondrial morphology therefore shows a biphasic and dynamic, but adaptable response to stress, as predicted by hormesis. Interestingly, modern bacteria also demonstrate similar changes to stress both forming networks and committing mass PCD [61] supporting a possible ancient origin for this process. In fact bacteria also show stress-induced asymmetric damage segregation at the population level with the benefit rising with greater stress [91]; this is of course similar to what happens in mitophagy. In this way a small amount of stress seems to induce a co-operative mitochondrial network within the cell that can transmit information and energy. As the stress increases, mitophagy encourages natural selection of the fittest mitochondria and perhaps prevents propagation of damaging signals or dangerous molecular moieties. Ultimately, too much stress will kill the cell, but this can help the rest of the organism to survive.

Mitochondrial dynamics is therefore reminiscent of what happens to networks of cells. Stress induces adaptive rearrangements of cellular networks the so called "Le Chatelier Principle for Networks". In effect, when a network is stressed it weakens some connections, inducing competition between the different nodes and strengthening other connections. When the stress passes, the network re-establishes itself back to its original mode or a slightly modified but more robust state. Clearly, if the components of the system cannot recover from the stress, the system can suffer a catastrophic failure, and this could be what happens as the system ages and its robustness decreases [92]. For mitochondrial networks, the likelihood of this happening is dictated by mitochondrial efficiency, and therefore the ability to utilise quantum effects. The importance of this is reflected by the observation that components of the ETC exist as super-complexes and their assembly can determine electron flux [93]. Hence, any disruption of the structure would be expected to reduce tunnelling efficiency. As an organism ages, its ability to maintain these complexes diminishes as its systems degrade, suggesting that there is a gradual loss in tunnelling efficiency and rising electron leakage. However, if the right amount of stress is applied, these structures can be subjected to perturbation, helping to maintain optimal functioning for longer. This suggests that without hormesis the degradation would happen to a higher degree, so accelerating the aging process. With regards the cognitive process, perturbation of the mitochondrial network with the right kind of stress might not only enhance its function, but protect the supra structure represented by the brain itself.

Advanced intelligence and electro-magnetic fields; a role for the mitochondrion?

From an organism's perspective, it is important to "remember" the past, "predict" the future and therefore be "aware" of the present. Memory has been defined as the capacity of organisms to benefit from their past [94]. This process is totally dependent on energy flux to maintain structure. Without energy there can be no memory, and thus no awareness. From a thermodynamic perspective, the heat generated during ETC fulfils the basic rules of entropy, making life a dissipative structure with the ability to create order out of disorder. Enhancing the capability of the ETC not only increases its capacity to do work, but also to store information.

This suggests that the adaptive response could arise from perturbation of localised areas of coherence. In effect, maintenance of coherence is key in detecting the environment as it induces decoherence, which is a way of crystallising out information as the system is effectively *observed* the very definition of a quantum principle. Hence, the importance of electron flow and the maintenance of EM fields in life; these fields exist in prokaryotes, and of course, within their descendants, the mitochondria. In fact, it has been suggested that biological electric fields can modulate cell shape and movement, following a biphasic distribution the "hormetic electric field theory of pattern formation", with the fields following a hormetic morphogen concentration gradient [95]. The generation of the proton gradient is thus pivotal. Thus, could mitochondria, other than providing energy, help to explain awareness in more complex creatures?

One of the great unsolved mysteries of biology is consciousness, in particular, the "binding problem" – how does a large brain act coherently? There have been many theories, ranging from ones purely based on classical principles, to those that rely entirely on a quantum explanation [96]. One proposal is the Conscious Electromagnetic Information (CEMI) field theory. This suggests that EM fields could be a key in coordinating the brain, thus explaining the binding problem [97]. There is evidence that endogenous electrical fields may guide neocortical network activity [98]. Quantum information theory has also been applied to provide a model of quantum-like processing of mental information that doesn't rely on quantum physical effects, but does use the brain's electric fields [99]. In fact, quantum formalism is being used to explain the optimisation for information flows for biological and physical systems, through quantum information biology and a Darwinian approach to quantum mechanics, respectively, and could provide a quantum explanation of biological adaptation on many levels [100]. This of course suggests that quantum information theory could explain hormesis.

It has been long suggested that mitochondria and microtubules can form some kind of resonant network, with excited vibrational modes [101]. Coupled with the emerging evidence of quantum beating in biological systems by harnessing near-resonant vibrations to prolong coherence, for instance in light systems that enhance efficiency by using quantum heat engines [102], then it might make sense to suggest that apart from detecting the environment, both the source of the vibrations, and the power, could involve mitochondria. One of the most important aspects of the brain is that it stores potential energy across its membranes in the form of ion gradients, which are associated with EM fields. But the most intense fields, perhaps in the region of ~30 million V/m, are found across the mitochondrial membrane [103]. Hence, perhaps, we should not ignore the link between microscopic mitochondrial fields and the macroscopic ones associated with the brain in general. In this respect, anaesthetics may be telling us something important.

Several anaesthetics affect mitochondrial function, some directly inhibiting the ETC while others induce uncoupling [104,105]; they do seem to bind to key mitochondrial proteins, such as the voltage dependent anion channel (VDAC) [106] and critically, microtubules [107], which are also closely associated with mitochondria. Furthermore, anaesthetics are *also* being investigated as neuroprotective and cardioprotective agents, with researchers focussing on modulation of mitochondrial function as a key mode of action [108,109]. This suggests they could be activating mitohormetic mechanisms. Does this mean that their possible actions on mitochondria and loss of consciousness are linked?

There are many theories on how anaesthetics might work, including a thermodynamic one involving alterations in membrane melting points; the potency of an anaesthetic appears to be less related to its structure-activity, but more to its lipid solubility (the Meyer-Overton rule) [110]. Interestingly, when flies are anaesthetised, there are measureable changes in electron spin resonance (ESR), possibly related to electron current changes but only in intact cells. These signals could originate in mitochondria although it cannot be a purely mitochondrial effect, as classical uncoupling agents don't induce anaesthesia and there are other sources that could alter ESR [111]. However, anaesthetics can reduce the presence of detectable resting state networks in the frontal cortex, suggesting a decrease in connectivity [112]. In effect, they appear to reduce brain connectivity, which results in a loss of consciousness.

Another potentially relevant finding is mitochondrial proton leak; depending on the type of cell, between 20-50% of their energy is dissipated by uncoupling during the resting state. Much of it happens apparently non-specifically, but some is controlled by uncoupling proteins (UCPs) [113]. Some estimates suggest that 20% of the brain's energy use could be ascribed to uncoupling [114]. Other than controlling ROS or generating heat, uncoupling could therefore have another role maintaining electric fields via electron and proton flux. Interestingly, some anaesthetics, at high concentrations, start to break up mitochondrial networks [115]; this would clearly alter the EM field pattern within the cell. During anaesthesia, the brains energy consumption drops dramatically from 30-70% [116]. This would suggest that electron flow in the brain is dramatically reduced and thus its ability to maintain electric fields.

The final piece of the puzzle maybe that mitochondria are key in controlling intra-cellular ion/metabolite oscillations. They display small autonomous amplitude changes in membrane potential, over a wide range of frequencies that can scale up through resonance coupling to the whole cell, and in the heart, result in arrhythmias; altering mitochondrial function, for instance by adding inhibitors, can dramatically change these effects [117]. There is thus a clear precedent for mitochondrial resonance to enslave larger scale field oscillations.

In summary, given the importance of resonance in both the quantum world and at larger scales across the brain, anything that alters mitochondrial function, perhaps altering coherence domains within it by mildly altering protein structure, would clearly affect brain function. Searching for a kind of rhythmic entrainment of mitochondria during consciousness, and its loss during unconsciousness, may support the idea. It is possible that mitochondria could act as a kind of environmental detection/quantum resonator system, linking energy production to the generation of appropriate resonance frequencies and entrainment of larger EM fields important in consciousness. Given their potential to also damage the brain, a loss of consciousness, or even a partial reduction in cognition, could represent a feedback mechanism to prevent excessive ROS-induced damage. This of course has relevance to why we sleep, and as we discuss later, what happens when the brain gets inflamed.

The human brain versus a computer

Human brains are extremely complex, with a high capacity to store information. We have previously suggested that the brain could hold between 0.58×10^{14} to 0.58×10^{15} bytes of information, or between 58 to 580 terabytes (TB) [19]. Given that a one TB hard drive can store about 75 h of high definition (HD) video, the brain has the capacity for between 4,350 to 43,500 h of high definition film or 181 days to about 5 years of continuous watching! This is quite an achievement for something that appears to have evolved from an inorganic proton gradient. It would also help to explain why our brains require so much energy. Even at rest, about 20% of the total energy the body utilises is used by the brain. Stimulate it, and it starts to require more, however, the precise increase in energy use by action potentials from baseline in the resting states is thought to be only around 10% or so, with the rest of the energy being used on housekeeping tasks, resting potential, postsynaptic receptors, neurotransmitter recycling, vesical cycling and calcium homeostasis; the brain is thus very efficient at processing [118]. Critically, the majority of the energy is supplied by mitochondria and is consumed at the synapses [119]. Interestingly, calculations suggests that in total, the active brain can generate 27 μmol ATP/g/min, which is not too dissimilar to what a human leg muscle is generating during a marathon [120]. This means that the brain is doing *work* to process information and increases when asked to carry out tasks above basic biochemical house-keeping. In fact, it appears that it is required to do work just to keep us conscious.

However, in processing terms, the human brain is vastly more efficient than current electronic devices, and uses multiple mechanisms to do this, including miniaturisation [121]. Recent attempts to mimic the brain fall well short. Japan's K super computer, in 2013, was programmed to have 1.73 virtual billion neurons and 10.4 trillion virtual synapses, each holding 24 bytes of memory. Overall, it took 40 min to mimic one sec worth of 1% of a human brain network activity. This was achieved with a machine that could reach 10×10^{15} operations per second (10 petaflops), with one petabyte of memory. The memory was equivalent to something like 250,000 personal computers [122]. However, it required 9 MW or more of power [123]; in other words a sizable chunk of the output of a small power station. Let us not forget that our brains only use around 12-20 W. This shows that not only is any animal brain vastly more complex, but it is also millions of times more efficient. In fact this efficiency has long been recognised, and prompted Penrose to suggest that biology is perhaps using some other aspect of physics, possibly quantum principles, to enable it to produce

the necessary energy to acquire and process information [124]. Thus, if, as is becoming apparent, mitochondria are relying on basic quantum principles, then it is perhaps possible that some of this efficiency arises from harnessing the quantum world.

The Mitochondrion and the Double-Edged Sword of Inflammation

As we have discussed, lifespan seems to be limited for most species, but is modifiable to some extent via the process of hormesis that appears to control the rate of ageing. However, there is another factor that has had an enormous impact on evolution and function of the mitochondrion and which can drastically alter life expectancy and cognition; inflammation.

Inflammation is an old term, which has its roots in Latin, meaning "setting on fire" and is used to describe the protective response in a tissue: pain, heat, redness and swelling. It is vital for survival, but can also reduce longevity if inappropriately over-active. Interestingly, it uses a lot of energy and energetically it is inefficient, but the fact that it has been selected for by evolution shows it is an essential process.

The importance of uncoupling

From a thermodynamic perspective, "heat" might suggest work is being done, and quite possibly, this is associated with a redirection of electron flow but it is also indicative of a dissipative system. As we have discussed, uncoupling seems to be an essential process in mitochondrial function and could be essential in brain function. Some of the uncoupling proteins, like UCP 1, seemed to have specifically evolved to generate heat, and are key in thermogenesis, while others can be viewed as a negative feedback mechanism to reduce ROS; precisely how they work is not fully understood, but they can be activated by ROS, and fatty acids, and inhibited by certain nucleotides. Their mechanism seems to involve the redox state of coenzyme Q- a key component of the ETC [125,126].

Of particular interest in the context of this paper is that uncoupling is anti-inflammatory as it reduces ROS. Critically, in the brain, UCPs appear to play a key role in preventing inflammation-induced depression [127] suggesting a direct link between cognition and mitochondrial function. In fact, it seems that uncoupling is tightly controlled by the immune system and inflammation generally suppressing it [128,129]. One of the ways this seems to happen is that it repurposes succinate dehydrogenase, at least in macrophage mitochondria, from generating energy to producing ROS, a process associated with an increased membrane potential and decreased uncoupling and enhanced glycolysis to provide the energy [130]. This "repurposing" of mitochondria has long been observed and seems to be part of a more general inflammatory strategy [7]. Interestingly, UCP expression can be increased by the peroxisomal-proliferating activated receptors (PPARs), which generally become more active during calorie restriction, but are suppressed themselves by inflammation; increased activity of the PPARs is generally associated with longevity and resistance to oxidative stress and may have evolved to aid in fat metabolism while minimising oxidative stress [131].

Another angle to this is the role of the mitochondrial membrane potential in survival of the mitochondrion itself; if the membrane potential drops too much, for instance if the mitochondrion is damaged, it can undergo fission and be singled out for mitophagy but they can also form more resistant '*donuts*' and when the precipitating insult is removed, reform and survive. The process is modulated by generation of ROS. In this way, the mitochondrial morphology reflects their functional status [132]. Overall, uncoupling appears to be an evolved mechanism to enable a steady state of tick over, in effect, a kind of instantly adaptable dissipative system, where electron flow can be modulated according to need.

The evolutionary need to rebuild and breed; a potential downside for the brain

The obvious downside to inflammation modulating mitochondrial function, especially in the brain, could be reduced cognition. However, the modulation of uncoupling and therefore mitochondrial function, clearly serves a very important purpose. The clue as to why may lie in the observation that survival to reproduce is key in natural selection and one of the biggest challenges for any organism, apart from unavoidable environmental catastrophes, as well as famine and/or predation, is the need to resist infection and recovery from injury. Simply put, in order to survive, it may be necessary to remove parts of a larger system to resist infection and then rebuild the damaged tissue even if it limits its function for a while.

For example, the astrocyte is essential in supporting neuronal function. However during neuroinflammation they show increased mitochondrial fission, which in turn is associated with reduced oxidative phosphorylation and increased ROS [133]. Hence, continued neuroinflammation could have devastating effects on the cohesive structure of the brain. In fact astrocytes and microglial cells can end up in a reactive gliosis "vicious cycle", which is thought to be involved in the progression of neurodegenerative disorders [134] conditions known to be associated with mitochondrial "dysfunction" [135]. In fact many disorders are associated with an imbalance between mitochondrial fission and fusion, and in general, the balance is more towards fission and the loss of networks; this could reflect the shift of cells towards proliferation and glycolysis [136].

Clearly, although repair and growth are essential, the prolonged loss of networks is detrimental to the brain. However, it may well be quite a natural response to inflammatory stimuli. This therefore suggests that inflammation could play a key role in determining both the efficiency and longevity of the brain. Furthermore, although mitochondria have enabled vast increases in cognitive ability, they may be a double-edged sword as they are, ultimately, responsible for the pro-ageing senescent phenotype. Recent data suggest that removing them can slow senescence in cell lines via enhanced glycolysis [9]. But, in evolutionary terms, if an organism has managed to breed and its offspring are independent, the degradation of its brain becomes less of an issue. The price of enhanced cognitive powers as a result of mitochondria is, perhaps, a greater susceptibility to inflammatory induced loss.

Inflammation: An ancient precedent?

So just how old is the process embraced by "inflammation" and does it suggest what inflammation actually is? The term, after all, is simply a description of a process coined before the underlying mechanisms were understood. It does actually appear that resistance to infection and damage is a trait that evolved long ago, in fact, in prokaryotes; they have their own kind of innate immune system to resist viruses, based on the "CRISPR-CAS system" [137]. Moreover, this system can also induce death of some infected prokaryotes in biofilms enabling an adaptive behaviour change [138]. In short, there is a very tight relationship between an immune system and longevity of the individual and the benefit to the species as a whole, which is probably almost as old as life itself. For example, apoptosis, and other forms of PCD, including autophagy, can, ultimately, recycle cells and their constituents. Dying for the greater good is helpful if you are less efficient and more damaged, as it can recycle valuable metabolites and energy for healthier cells.

It appears that when the immune system becomes chronically activated it can result in the slow decoherence of larger structures: whether this is a purely stochastic or programmed process to ensure survival of a species is still unclear. If the latter, then is could be said that inflammation is both the protector and ultimately, the executioner. As we have mentioned previously, the concept of phenoptosis could play a role in species survival by removing damaged individuals. Certainly the concept of "cytokine induced sickness behaviour", whereby during injury and/or infection, an animal's behaviour changes, is becoming well recognised [5] and if more recent thinking is correct, it could well have evolved to the extent of removing the animal to protect related organisms from infection – in effect, kin selection [139]. Clearly, degrading brain function could be viewed as part of this effect and would be related to feeling depressed and wanting to simply "curl up in a corner". That inflammation accelerates cognitive decline is very well established [4]. Interestingly, as hormesis tends to be anti-inflammatory, it suggests that in tough times, inflammation can be suppressed to ensure the individual survives and maintain optimum robustness and intelligence; in effect, energy could be diverted away from inflammation and towards adaptation, and critically, by maintaining mitochondrial function, to keeping the brain connected.

Thinking and Hormesis

At the core of this discussion is the concept that informational transfer requires energy and the brain, in particular, is doing this all the time. This is both described by quantum and thermodynamics/information theory, and at a macro level, by the need for cells and neurons to maintain ion gradients and communicate. The interesting question, however, is whether its ability to store and manipulate information is important in itself. The main sign seems to reside with the observation that information can enhance the stability of dissipative structures and this itself is based on natural selection of self-replicating molecules that can incorporate information especially when stressed, so applying a pressure to drive natural selection. Entropy, from one perspective, simply describes the flow of energy down a gradient, and the generation of these structures accelerates this flow. The development of intelligent systems may be an inevitable consequence of hormesis.

The large size of the human brain and its energy consumption indicates how important processing information is for our survival. It enables vast amounts of readily accessible data to be stored and therefore enhances cognitive buffering against the environment, which effectively equates to a self-replicating structure that continually seeks energy. Moreover, as we suggest above, we are a pure product of entropy, as the ability to take on information drives energy seeking that accelerates the process. The ultimate expression of this is of course technology, as it is enabling each individual to use vastly more energy than they could by simply ingesting it, running about and procreating. It could therefore be said that our brains are the ultimate dissipative structure, and exist because of constant challenges. In contrast, remove the challenges and the system slowly becomes decoherent and degrades. The paradox is that the degradative process would be accelerated by the availability of unlimited energy because there would be less energy perturbation to force the requirement for brain coherence. From an evolutionary standpoint, it suggests that if the brain is "over-fed" with energy, it does not have to "think" to replenish it and the system would inevitably lose its adaptive capabilities.

Thus far we have described a process where life appears to have evolved due to fundamental quantum and thermodynamic principles, and with the evolution of the mitochondrion, it was set on a path towards greater intelligence and self-awareness. In its broadest definition, "intelligence" may have initially acted at the cellular level improving initially the prokaryotic, then the eukaryotic cell's ability to maintain homeostasis, and eventually as life got ever more complex, at the level of the brain, making the organism smarter enabling it to effectively "outwit" the environment. Cognitive science has come to the point where it is possible to map cognitive systems to various parts of the brain, leading to the ideas that these cognitive units (cell assemblies) can be integrated by "attention" to ensure optimal functioning. One suggestion in particular, concerning humans, is their improved ability to inter-link different areas of the brain, which could help explain our apparently greater intelligence than many other organisms [140]. Hence, if we consider hormesis, which is effectively a positive adaptive response to stress, having to think could also be viewed as an adaptation to stress. In effect, deciphering information and processing it requires energy use and is therefore hormetic. This would apply whether the information was external as a result of the environment or internally, by just thinking about it. The question here, however, is which kind of thinking is the most hormetic? Could reading this paper be described as hormetic? What about just thinking in the bath while drinking a cup of tea? What about exercise? And what happens when you learn?

Physical activity, hormesis, fluid and crystallised intelligence

One of the most important hormetins is physical activity (PA), but the hormetic effect of PA is not just limited to the muscles, but to the whole body as the whole body has to function well to do it and this includes the brain. Movement requires the coordinated integration of multiple bits of information. This provides a good starting point for discussing thinking and hormesis and in particular, what learning means.

Movement requires the co-ordinated firing of many neurons and the transfer of information to the muscles – and of course, transfer of information back to the brain about position, tension and other parameters, including metabolic adaptations. In particular, which movements work and are efficient and which are not. This means that learning new movements requires programming and the formation of new networks, hence, energy use. Learning new movements requires a degree of effort and thought. However, with enough practice, many movements become sub-conscious, but still require a tight integration between the brain, metabolic systems and muscles. What we describe as learnt behaviour, which barely requires conscious control, may simply represent a hard wired sub-routine that requires minimal energy to enact. So movement alone challenges the brain even if it requires less "thought". However, there may well be a hierarchy of physical activity, with more complex movement, which requires a greater part of the brain being involved, being more hormetic.

When we stop using the movements, we may not forget them, but they become less efficient – which suggests maintaining the connections requires some energy. We have to practice. This could help to explain the difference between fluid and crystallised intelligence; evolution in an energy-restricted environment would ensure that the control circuits for a particular behaviour or action would become as efficient as possible and would require minimal use of higher brain coherence and energy requiring function. As one ages, crystallised intelligence appears to be well maintained, especially if the particular skill is practiced, while fluid intelligence decreases [141], suggesting that crystallised intelligence requires less energy, so enabling it to be maintained into old age even if the brain is becoming less efficient.

The brain also has to deal with a vast amount of other bits of information, ranging from vision, sound, smell, proprioception and

balance and decide what to do with it and integrate it with movement responses. So from informational point of view, the brain is constantly being challenged by the environment. This suggests that hormetic factors induce hard wired adaptation, and with practice, require less and less conscious control of these responses. In effect, they require less conscious effort to enact, but when learning, require a lot of conscious input. So in this respect, conscious involvement in learning is part of the hormetic process, which requires effort as it requires energy; when hardwired, the energy requirement is reduced.

Thinking, hormesis and effort

The question of what thought actually is has vexed mankind for millennia, and there is still no real consensus. However, psychologists have described it as "intellectual exertion", a description that most people would relate to. It requires *effort*, which suggests that it uses energy. It is clear that the brain becomes less effective when we are tired, for instance reaction times increase, attention decreases, while working memory diminishes. It has been suggested using optimal control theory that the brain can reduce energetically expensive cognitive processes and manage them over time to optimise reward. For the individual, this tends to mean we avoid mental tasks that we find hard, but instead rely on learned habits if the reward is low, but will put much more effort if the reward is high. Biologically, this may represent the percentage of neurons that are recruited; the more, the greater the energy demand across the brain. If we think a lot for too long, what we feel is generally subjective fatigue, that is, the brain still has resources available, but provides us with an early warning. In effect, cognitive effort avoidance can be explained as resource allocation with a *look-ahead* property we can become *optimally lazy*. However, the system may adapt rather like muscle, increasing the stores of glycogen in areas that are used more often [142].

Broadly speaking it seems that there are generally two cognitive states: externally directed, for instance, diverting our attention to information coming in from the outside world (vision, hearing, sensation, etc.) and internal, where we process memories/experiences. These themselves can be split into intentional cognition, in effect voluntary control of attention and require effort, and spontaneous, which is largely involuntary and appears effortless and includes mind wandering (day dreaming). They can both occur at once, and can synergise and compete, and involve multiple parts of the brain; these are usually separate, but when they occur together, they can start to affect capacity limited areas, such as the pre-frontal cortex [143]. This therefore suggests that the kind of thinking is important, some types are actually quite pleasurable, and require little effort, in particular, the kind of spontaneous "alone with our thoughts" so not all thinking is aversive [144]; it is likely that they do serve an important function, and clearly do involve many areas of the brain [145]. But this does suggest that simply paying attention to incoming information requires energy and is thus hormetic. Certainly, the ability to undertake counter-factual reasoning (in effect, to think about different scenarios that we have not experienced, and make predictions), requires a lot brain resources [146].

Another way to view this is that hormesis is a phenomena that effectively "trains" a system, and the brain is no exception. There is plenty of evidence suggesting that we can train the brain and it has been growing field of interest for a number of years. However, recent studies have shown that some training tasks are better than others. For instance auditory perception and skill acquisition training improve everyday cognition and "far transfer", and are associated with changes of connectivity in the brain in older people [20]. Direct monitoring of cerebral hemodynamic response by near infrared spectroscopy demonstrates clear training effects associated with improvement using working memory training [147]. Blood flow to any tissue must therefore be very tightly controlled to minimise the potential toxicity of oxygen, and is reflective to some degree of metabolic demand [148]. Hence, both the fact that performance can improve with cognitive training, and this is matched to changes in blood flow, strongly links the importance of training to increased metabolism.

All of this, as would be predicted from the thermodynamics, suggests that not only is thinking hormetic, but that some forms have a stronger effect on inducing adaptability than others. Perhaps one of the simplest and most effective would be trying to maintain focus and attention, as this could represent coherence across the brain. In this regard mindfulness meditation is extremely interesting, as it has long been used to improve the ability to focus, reduce stress and perhaps, increase longevity. Although strong empirical data on how it is working biologically is still to be validated, multiple randomised controlled trials are hinting that it can reduce inflammation, in particular, nuclear factor kappa-B activity and perhaps, even increase telomerase function [149,150]. Indeed, it has been long recognised that the brain can both detect the peripheral immune system and control it, although the precise mechanisms are unclear. New data does now suggest that the activation of part of the brain's reward system can boost innate and adaptive immunity [151].

Enforced thinking

The above suggests that enforced thinking, generated by environmental circumstances, could also be powerfully hormetic. For example, calorie restriction, which is hormetic and anti-inflammatory, can activate hypothalamic Sirt1 and centrally control the adaptive response [152]. Becoming hungry is a powerful stimulus to find food, and this is a powerful incentive to think. Hunger circuits include factors associated with suppressing inflammation and up regulating anti-oxidant systems, such as the forkhead class box-O transcription factors (FOXO), endocannabinoids and mitochondria [153]; these circuits are closely associated with the underlying biochemistry of hormesis. Certainly, the link between calorie restriction and the urge to move seems obvious, and has been discussed extensively in relation to the "flee from famine" hypothesis [154]. Physical activity also falls into the same category and is often linked to the need to find food, or critically, simply to survive. Physical activity is also strongly anti-inflammatory [155] and seems to offset age-related inflammation [156]. In aged mice, physical activity may well reduce brain inflammation, enhance mitochondrial function and restore a degree of neurogenesis [157]. It is thus interesting that the FOXO group of transcription factors appear to be vital in controlling the ageing process across several species and may have evolved to do so [158]. But perhaps one of the most important things about cardiovascular fitness, and strength, is that certainly in humans, increased levels are associated with greatly reduced mortality [159-162] suggesting a generalised benefit.

So, from the point of view of physical activity, as the brain is essential in coordinating movement, the brain's control of physical activity could well be hormetic in and of itself. This is especially so for movement requiring highly coordinated action. This has been illustrated by recent studies where elderly volunteers clearly improved cognitive function with exercise [163]. Critically, exercise activates nuclear factor-E2 related-factor 2 (NRF2) in the brain [164]. The same is true for calorie restriction. It is associated with suppression of inflammation in the brain and increased mitochondrial biogenesis – and is a target for treating neurodegeneration [165-168]. Overall, this suggests that a combination of learning complex movements while exercising, and being in the moment, could synergise to maximally impact the brain. We therefore

proposed that complex, weight bearing movement requiring balance, awareness and our full attention to learn would be one of the strongest hormetic stimuli for cognitive health.

Is thinking anti-inflammatory?

Chronic inflammation is detrimental to the brain, while hormesis appears to be anti-inflammatory. Given the central role of the brain in controlling the ageing process in relation to diet and exercise [169] and the observation that hypothalamic inflammation can also control the ageing process [170], it is possible that if thinking is hormetic, it would also be anti-inflammatory. This might suggest that "thinking" may directly affect our health.

Clinical depression often goes hand in hand with inflammation. It is interesting that many studies suggest that major psychiatric conditions are associated with inflammation [171]; in particular, there appears to be a correlation between suicide and inflammatory markers [172]. It is therefore of particular relevance that many anti-depressants apparently inhibit the ETC [173], suggesting that some of their effects could be explained by hormesis. Mild inhibition of mitochondrial function could stimulate mitochondrial biogenesis, mitophagy and/or improved functionality. This is certainly supported by the benefits of exercise in treating some mental health conditions [174]. Overall, this supports the concept that actively engaging our minds in the right way induces order and stability, so prolonging our existence and reducing brain inflammation.

Thinking and cognitive reserve – the implications of the biphasic effect

"Cognitive reserve" was a term originally coined to describe how some people, despite showing a similar amount of brain pathology, could remain above a functional threshold compared to other less fortunate individuals. There is some evidence that this could be due to bigger brains and/or a higher childhood IQ and therefore more synapses. However, one of the most consistent findings in relation to improved cognitive reserve is high educational achievement and/or occupational complexity. The evidence suggests that this can offset certain brain pathologies to some degree, enabling some people to maintain good cognitive functionality into older age [175]. The conclusion from this is that thinking, or making the brain work, is indeed hormetic and can increase the cognitive reserve so an individual can stay above a functional threshold for longer. One of the effects is likely to be suppression of inflammation and maintenance of mitochondrial function.

However, implicit in the term "hormesis" is the biphasic effect, where, as the dose is increased, a Rubicon is crossed, which can be described as the "No Observed Adverse Effect Level" (NOAEL, Figure 1). A key component of hormesis is that the system has sufficient time, or capacity, for the system to adapt. For example, excessive physical activity in elite athletes can lead to the Over-Training Syndrome (OTS), which seems to have both a central and a peripheral component and can be highly debilitating. In particular, it is associated with profound tiredness, activation of the stress system, increased markers of oxidative stress and raised serotonin levels [176]. In fact, evidence is building that adult hippocampal neurogenesis does display a biphasic response to exercise, which can impact on mood, and can be explained using known molecular pathways involved in hormesis [177]. Thus, it seems that not only can excessive exercise damage the body, but it might also damage the brain. However, mainly "mental" tasks can also lead to problems. The clearest example of "overdoing it" is to work constantly without a break and particularly, without sleep.

The function of sleep is still not completely understood, but it is obviously essential and evolved for a purpose, because without it, the cognitive performance of most animals drastically degrades. One of the strongest theories involves the requirement for repair and maintenance, as well as synaptic downscaling, so in effect, restorative and information process activities, which would explain why a loss of consciousness maybe required [178,179]. In support of this, there does appear to be a correlation across mammalian species between the amount of sleep required and the number of neurons: as the ratio of cortical neurons to brain surface area decreases, less sleep is required. The reason being suggested is that this reduces the build-up of metabolites per neuron [180]. Certainly, loss of sleep can activate anti-oxidant pathways in the brain, including the Unfolded Protein Response, suggesting that it does result in oxidative stress [181]. Loss of sleep can induce neuroinflammation [182], while both too much sleep, and too little, is associated with the metabolic syndrome [183].

Overall this would suggest that not only could the occasional bout of sleep loss be hormetic, but continual sleep loss leads to excessive stress and inflammation. It might also suggest that the right amount of stress might reduce the amount of sleep we need. However, if sleep can be viewed as a time of synaptic rescaling and maintenance, it could be argued that it displays elements of inflammation, which is an essential process to rebuild it. This would begin to explain why loss of consciousness, or cognition, occurs during inflammation. Figure 2 summarises the possible control loops involved in information processing in relation to hormesis and inflammation, and the effect it has on cognitive reserve.

Summary: I Think Therefore I Am and Shall Continue to Be

Some suggest that consciousness is itself a quantum effect [96], while others invoke a half-way house theory (e.g. quantum entanglement involving sodium ion channels) [52,53]. It has even been proposed that phosphorous, via quantum entanglement of nuclear spin states, could play a role in the brain [184]. Others suggest that some quantum physical effects are important at the level of the molecule, but that a larger more "classical" level, quantum information theory is still needed [54]. The truth is that we simply do not know how important quantum mechanics is in explaining thinking and consciousness. However, it is becoming clear that life has harnessed the quantum world, for instance, via electron tunnelling in mitochondria or proton tunnelling in proteins, suggesting that life is not too warm and wet for coherence. This opens up the possibility that a constant flow of electrons, which generates a flow of protons, is a fundamental embodiment of a dissipative system that could potentially use coherent regions to detect changes in the environment. At the most basic level, this generates order of chaos due to perturbation, which embodies the hormetic principle. As mitochondria are the prime locations for this system, and are essential for higher intelligence, this suggests that not only do they provide the necessary energy, but potentially, also a source for coherent resonance that could help explain the binding problem. Figure 3 summarises the idea behind the relationship between hormesis and life as a dissipative, information-driven system.

In light of this, we propose that whenever we use our brains, either to process information stored in our memories, to learn something new (in effect, encode information) or to interpret incoming data from the environment, energy is required implying a hormetic transformation. Equally, when the structure and energy production system of the brain is threatened, for instance by inflammation, this

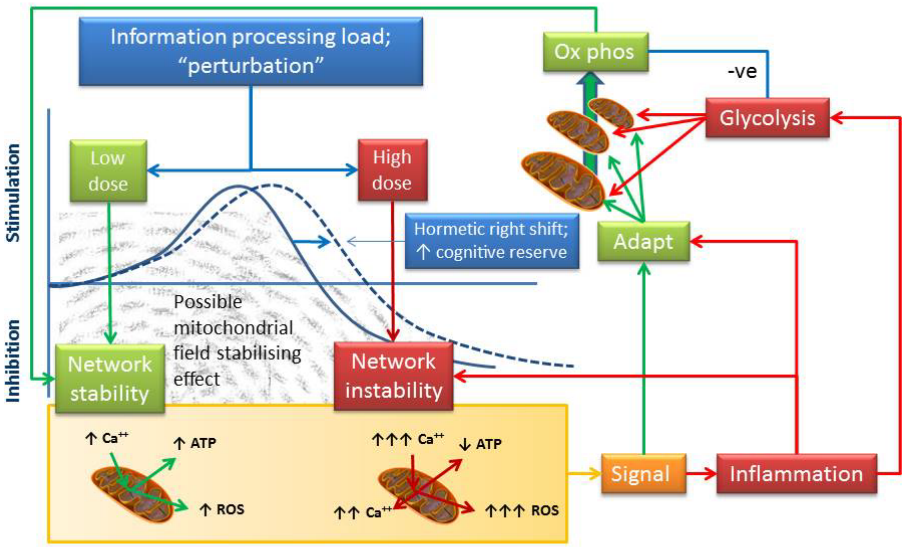

Figure 2: Summary – cognitive reserve, hormesis and inflammation.
Hormesis could lead to enhancement of brain function and improve cognitive reserve, for instance, by ensuring efficient mitochondrial function – right shifting the curve. In effect, the system is perturbed, but this information induces stabilisation and adaptation. However, inflammation may induce a switch in mitochondrial function towards glycolysis, which may have a destabilising effect on the larger structure, but also offers the opportunity for it to rebuild if short lived (in effect, acute inflammation also perturbs the system, inducing negative feedback). What may determine the threshold of this would therefore relate to prior hormetic stimuli, and exposure to inflammation. This could include excessive demands on information processing, for instance, by staying awake, or excessive physical activity, which would prevent the repair process and synaptic regeneration (scaling), leading to a decline in function. If bad enough, it is possible that a lack of sleep would become inflammatory in and of itself. Mitochondrial fields might also play a role in stabilisation.

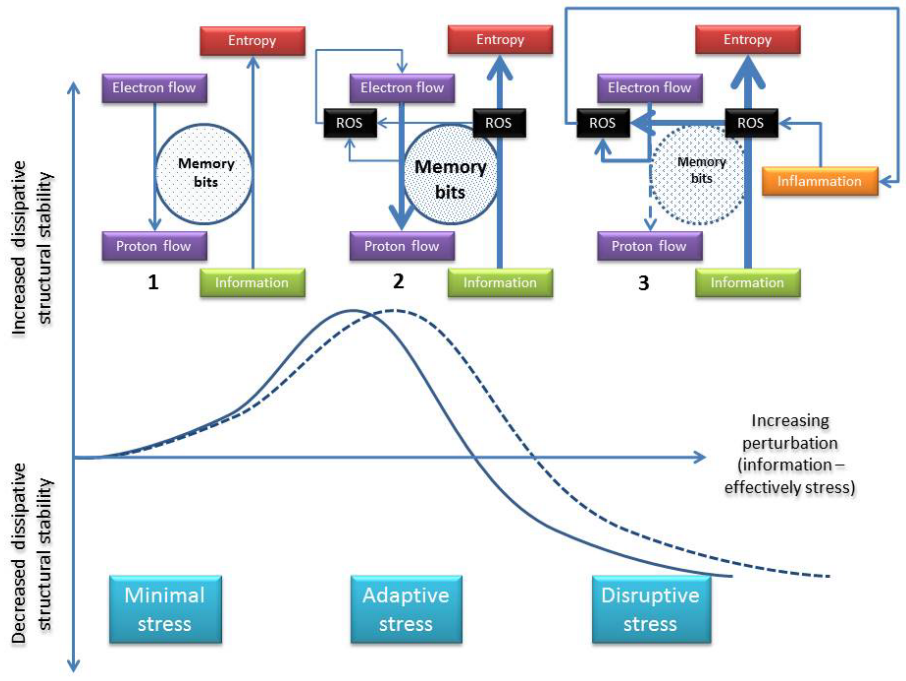

Figure 3: Electron flow and stabilisation of the dissipative structure – effect of hormesis.
1. Baseline situation, where constant electron flow is used to drive proton gradient and information storage, generating a dissipative structure; uncoupling may aid in this
2. Increase in information generates ROS signal stimulating adaptation and right shifting of curve. For example, this could be caused by environmental perturbation of a structure reliant on coherence to work (such as the ETC)
3. Too much information load, or inflammation, can induce a breakdown of the structure
In relation to memory, information can be measured in "bits" (short for binary digit). The key point here is that life can be defined by its intelligence, which is another way of saying its ability to store and use information for survival. Although information can certainly be stored in structures, for instance, DNA or a compact disc, or even a virus, these are not "alive"; it is the homodynamic adaptive response based on energy and information flow that comes from metabolism that could actually define life. The energy derived from electron flow enables the information for structure to be read from DNA, and for the information flowing from the environment to enable adaptation. If the electron flow is disturbed, it can generate free radicals that can disrupt the fluid live structure, or even damage the hard information storage system (DNA) hence they are a powerful adaptive signal.

ability is diminished and cognitive capabilities compromised. Thus there are strong thermodynamic and quantum reasons why hormetic challenges, including the processing of information ("thinking") are essential for optimal cognitive health. However, at the present time, humanity is being less than smart. For a significant percentage of the population there is a paucity of hormetic signals essential for achieving and maintaining optimal health. Our environment has become too "comfortable" [1].

Indeed, today there is little need to engage in significant physical and mental exertion in order to survive. In effect, most of the time most people do not need to learn particularly difficult and physically demanding tasks with a high degree of novelty. Many jobs do not even require people to think that hard or even move. But there is hope as evidence suggests that many forms of hormesis, including exercise and polyphenols, are associated with highly positive cognitive effects and should form the core of our daily life and any long term strategy to maintaining optimal cognitive health (Figure 3).

Acknowledgement

To the early pioneers of quantum physics that had the insight to suggest that it could be used to explain many aspects of biology, and to the current day scientists, from several different disciplines, who have taken up the quantum biology baton. To the proponents of hormesis who continue to raise awareness of this important concept.

Author Contributions

The concept of whether or not thinking could be hormetic was discussed by AVN, GWG and JDB. AVN developed the concept and wrote and edited the manuscript. GWG and JDB provided feedback on each draft of the manuscript and approved the final version.

References

1. Nunn AV, Guy GW, Bell JD (2014) The intelligence paradox; will ET get the metabolic syndrome? Lessons from and for Earth. Nutr Metab 11: 34.
2. Yau PL, Castro MG, Tagani A, Tsui WH, Convit A (2012) Obesity and metabolic syndrome and functional and structural brain impairments in adolescence. Pediatrics 130: e856-e64.
3. Jacob ME, Yee LM, Diehr PH, Arnold AM, Thielke SM, et al. (2016) Can a healthy lifestyle compress the disabled period in older adults? J Am Geriatr Soc 64: 1952-1961.
4. Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, et al. (2015) Neuroinflammation in Alzheimer's disease. Lancet Neurol 14: 388-405.
5. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW (2008) From inflammation to sickness and depression: When the immune system subjugates the brain. Nat Rev Neurosci 9: 46-56.
6. Yates KF, Sweat V, Yau PL, Turchiano MM, Convit A (2012) Impact of metabolic syndrome on cognition and brain: A selected review of the literature. Arterioscler Thromb Vasc Biol 32: 2060-2067.
7. West AP, Shadel GS, Ghosh S (2011) Mitochondria in innate immune responses. Nat Rev Immunol 1: 389-402.
8. Lane N (2015) The vital question: Why is life the way it is? Great Britain: Profile Books Ltd.
9. Correia-Melo C, Marques FD, Anderson R, Hewitt G, Hewitt R, et al. (2016) Mitochondria are required for pro-ageing features of the senescent phenotype. EMBO J 35: 724-742.
10. Collell G, Fauquet J (2015) Brain activity and cognition: A connection from thermodynamics and information theory. Front Psychol 6: 818.
11. Michel D (2013) Life is a self-organizing machine driven by the informational cycle of Brillouin. Orig Life Evol Biosph 43: 137-150.
12. Pulselli RM, Simoncini E, Tiezzi E (2009) Self-organization in dissipative structures: A thermodynamic theory for the emergence of prebiotic cells and their epigenetic evolution. Bio Systems 96: 237-241.
13. Gatenby RA, Frieden BR (2013) The critical roles of information and non-equilibrium thermodynamics in evolution of living systems. Bull Math Biol 75: 589-601.
14. Schrodinger E (1944) What is life? The physical aspect of the living cell. Cambridge University Press.
15. Arndt M, Juffmann T, Vedral V (2009) Quantum physics meets biology. HFSP J 3: 386-400.
16. Castelvecchi D (2017) Battle between quantum and thermodynamic laws heats up. Nature 543: 597-598.
17. Trevors JT (2011) Origin of microbial life: Nano- and molecular events, thermodynamics/entropy, quantum mechanisms and genetic instructions. J Microbiol Methods 84: 492-495.
18. Nunn AV, Guy GW, Bell JD (2015) Hormesis and cognitive function: An evolutionary/adaptive Arabesque leading to longevity. In: Farooqui T, Farooqui AA (edr) Diet and exercise in cognitive function and neurological diseases. Wiley-Blackwell, USA and Canada.
19. Nunn AV, Guy GW, Bell JD (2016) The quantum mitochondrion and optimal health. Biochem Soc Trans 44: 1101-1110.
20. Strenziok M, Parasuraman R, Clarke E, Cisler DS, Thompson JC, et al. (2014) Neurocognitive enhancement in older adults: Comparison of three cognitive training tasks to test a hypothesis of training transfer in brain connectivity. NeuroImage 85: 1027-1039.
21. Owen AM, Hampshire A, Grahn JA, Stenton R, Dajani S, et al. (2010) Putting brain training to the test. Nature 465: 775-778.
22. Smith GE, Housen P, Yaffe K, Ruff R, Kennison RF, et al. (2009) A cognitive training program based on principles of brain plasticity: Results from the improvement in memory with plasticity-based adaptive cognitive training (IMPACT) study. J Am Geriatr Soc 57: 594-603.
23. Northey JM, Cherbuin N, Pumpa KL, Smee DJ, Rattray B (2017) Exercise interventions for cognitive function in adults older than 50: A systematic review with meta-analysis. Br J Sports Med.
24. Khammash M (2016) An engineering viewpoint on biological robustness. BMC Biol 14: 22.
25. Medaglia JD, Pasqualetti F, Hamilton RH, Thompson-Schill SL, Bassett DS (2017) Brain and cognitive reserve: Translation via network control theory. Neurosci Biobehav Rev 75: 53-64.
26. Ball P, Clegg B, Clifford L, Close F, Hebden S, et al. (2014) 30 second quantum theory; the 50 most important thought-provoking quantum concepts, each explain in half a minute. London, UK: ICON Books Ltd.
27. Schiller C (2016) Motion Mountain - Adventures in physics, Volume IV, The quantum of change. 28 Edn. Internet: Motion Mountain.
28. Al-Khalili J, McFadden J (2014) Life on the edge: The coming of age of quantum biology. Great Britain: Transworld Publishers.
29. Tamulis A, Grigalavicius M (2011) The emergence and evolution of life in a "fatty acid world" based on quantum mechanics. Orig Life Evol Biosph 41: 51-71.
30. Tamulis A, Grigalavicius M (2014) Quantum entanglement in photoactive prebiotic systems. Syst Synth Biol 8: 117-140.
31. McFadden J (2000) Quantum Evolution: Life in the Multiverse. UK: Harper Collins.
32. Weiss CM, Sousa FL, Mrnjavac N, Neukirchen S, Roettger M, et al. (2016) The physiology and habitat of the last universal common ancestor. Nat Microbiol 1.
33. Koc I, Caetano-Anolles G (2017) The natural history of molecular functions inferred from an extensive phylogenomic analysis of gene ontology data. PloS ONE 12: e0176129.
34. Blankenship RE (2010) Early evolution of photosynthesis. Plant Physiol 154: 434-438.
35. Szent-Gyorgyi A (1941) Towards a new biochemistry? Science 93: 609-611.
36. DeVault D, Chance B (1966) Studies of photosynthesis using a pulsed laser. I. Temperature dependence of cytochrome oxidation rate in chromatium. Evidence for tunneling. Biophys J 6: 825-847.
37. Sutcliffe MJ, Masgrau L, Roujeinikova A, Johannissen LO, Hothi P, et al. (2006) Hydrogen tunnelling in enzyme-catalysed H-transfer reactions: flavoprotein and quinoprotein systems. Philos Trans R Soc Lond B Biol Sci 361: 1375-1386.

38. Engel GS, Calhoun TR, Read EL, Ahn TK, Mancal T, Cheng YC, et al. (2007) Evidence for wavelike energy transfer through quantum coherence in photosynthetic systems. Nature 446: 782-786.

39. Fassioli F, Dinshaw R, Arpin PC, Scholes GD (2014) Photosynthetic light harvesting: Excitons and coherence. J R Soc 11: 20130901.

40. Lim J, Palecek D, Caycedo-Soler F, Lincoln CN, Prior J, et al. (2015) Vibronic origin of long-lived coherence in an artificial molecular light harvester. Nat Commun 6: 7755.

41. Weber S, Ohmes E, Thurnauer MC, Norris JR, Kothe G (1995) Light-generated nuclear quantum beats: A signature of photosynthesis. Proc Natl Acad Sci U S A 92: 7789-793.

42. Vattay G, Salahub D, Csabai I, Nassimi A, Kaufmann SA (2015) Quantum criticality at the origin of life. J Phys: Conf Ser 626: 012023.

43. Craddock TJ, Friesen D, Mane J, Hameroff S, Tuszynski JA (2014) The feasibility of coherent energy transfer in microtubules. J R Soc 11: 20140677.

44. Craddock TJ, Priel A, Tuszynski JA (2014) Keeping time: Could quantum beating in microtubules be the basis for the neural synchrony related to consciousness? J Integr Neurosci 13: 293-311.

45. Winkler JR, Gray HB (2014) Long-range electron tunneling. J Am Chem Soc 136: 2930-2939.

46. Hayashi T, Stuchebrukhov AA (2011) Quantum electron tunneling in respiratory complex I. J Phys Chem B 115: 5354-5364.

47. Moser CC, Farid TA, Chobot SE, Dutton PL (2006) Electron tunneling chains of mitochondria. Biochim Biophys Acta 1757: 1096-1109.

48. de Vries S, Dorner K, Strampraad MJ, Friedrich T (2015) Electron tunneling rates in respiratory complex I are tuned for efficient energy conversion. Angewandte Chemie 54: 2844-2848.

49. Lundholm IV, Rodilla H, Wahlgren WY, Duelli A, Bourenkov G, et al. (2015) Terahertz radiation induces non-thermal structural changes associated with Frohlich condensation in a protein crystal. Struct Dyn 2: 054702.

50. Pokorny J, Pokorny J, Kobilkova J (2013) Postulates on electromagnetic activity in biological systems and cancer. Integr Biol 5: 1439-1446.

51. Vattay G, Kauffman S, Niiranen S (2014) Quantum biology on the edge of quantum chaos. PloS ONE 9: e89017.

52. Moradi N, Scholkmann F, Salari V (2015) A study of quantum mechanical probabilities in the classical Hodgkin-Huxley model. J Integr Neurosci 14: 1-17.

53. Summhammer J, Salari V, Bernroider G (2012) A quantum-mechanical description of ion motion within the confining potentials of voltage-gated ion channels. J Int Neurosci 11: 123-135.

54. Melkikh AV, Khrennikov A (2015) Non-trivial quantum and quantum-like effects in biosystems: Unsolved questions and paradoxes. Prog Biophys Mol Biol 119: 137-161.

55. Harman D (1956) Aging: A theory based on free radical and radiation chemistry. J Gerontol 11: 298-300.

56. Barja G (2013) Updating the mitochondrial free radical theory of aging: An integrated view, key aspects and confounding concepts. Antioxid Redox Signal 19: 1420-1445.

57. Hayflick L (2007) Biological aging is no longer an unsolved problem. Ann N Y Acad Sci 1100: 1-13.

58. Vijg J, Kennedy BK (2016) The essence of aging. Gerontology 62: 381-385.

59. Werfel J, Ingber de, bar-yam y (2015) programed death is favored by natural selection in spatial systems. Phys Rev Lett 114: 238103.

60. Skulachev VP (1999) Phenoptosis: Programmed death of an organism. Biochemy (Mosc) 64: 1418-1426.

61. Allocati N, Masulli M, Di Ilio C, De Laurenzi V (2015) Die for the community: An overview of programmed cell death in bacteria. Cell Death Dis 6: e1609.

62. Lane N (2011) Mitonuclear match: Optimizing fitness and fertility over generations drives ageing within generations. Bioessays 33: 860-869.

63. Drechsel DA, Patel M (2010) Respiration-dependent H_2O_2 removal in brain mitochondria via the thioredoxin/peroxiredoxin system. J Biol Chem 285: 27850-27858.

64. Kembro JM, Cortassa S, Aon MA (2014) Complex oscillatory redox dynamics with signaling potential at the edge between normal and pathological mitochondrial function. Front Physiol 5: 257.

65. Marais A, Sinayskiy I, Petruccione F, van Grondelle R (2015) A quantum protective mechanism in photosynthesis. Sci Rep 5: 8720.

66. Zhang YB, Kais S (2015) The radical pair mechanism and the avian chemical compass: Quantum coherence and entanglement. ArXiv: 150200671v2.

67. Magistretti PJ, Allaman I (2015) A cellular perspective on brain energy metabolism and functional imaging. Neuron 86: 883-901.

68. Hayakawa K, Esposito E, Wang X, Terasaki Y, Liu Y, et al. (2016) Transfer of mitochondria from astrocytes to neurons after stroke. Nature 535: 551-555.

69. Wang X, Gerdes HH (2015) Transfer of mitochondria via tunnelling nanotubes rescues apoptotic PC12 cells. Cell Death Differ 22: 1181-1191.

70. Speijer D (2014) How the mitochondrion was shaped by radical differences in substrates: What carnitine shuttles and uncoupling tell us about mitochondrial evolution in response to ROS. Bioessays 36: 634-643.

71. Speijer D, Manjeri GR, Szklarczyk R (2014) How to deal with oxygen radicals stemming from mitochondrial fatty acid oxidation. Philos Trans R Soc Lond B Biol Sci 369: 20130446.

72. Bravo-Sagua R, Parra V, Lopez-Crisosto C, Diaz P, Quest AF, et al. (2017) Calcium transport and signaling in mitochondria. Compr Physiol 7: 623-634.

73. Calabrese EJ, Baldwin LA (1998) Hormesis as a biological hypothesis. Environ Health Perspect 1: 357-362.

74. Ristow M, Zarse K (2010) How increased oxidative stress promotes longevity and metabolic health: The concept of mitochondrial hormesis (mitohormesis). ExpGerontol 45: 410-418.

75. Tapia PC (2006) Sub lethal mitochondrial stress with an attendant stoichiometric augmentation of reactive oxygen species may precipitate many of the beneficial alterations in cellular physiology produced by caloric restriction, intermittent fasting, exercise and dietary phytonutrients: “Mitohormesis” for health and vitality. Med Hypotheses 66: 832-843.

76. Scarpulla RC (2008) Transcriptional paradigms in mammalian mitochondrial biogenesis and function. Physiol Rev 88: 611-638.

77. Allen JF (1993) Control of gene expression by redox potential and the requirement for chloroplast and mitochondrial genomes. J Theor Biol 165: 609-631.

78. Allen JF (2015) Why chloroplasts and mitochondria retain their own genomes and genetic systems: Colocation for redox regulation of gene expression. Proc Natl Acad Sci U S A 112: 10231-10238.

79. Sousa FL, Thiergart T, Landan G, Nelson-Sathi S, Pereira IA, et al. (2013) Early bioenergetic evolution. Philos Trans R Soc Lond B Biol Sci 368: 20130088.

80. Roland-Mieskowski M (1994) Life on earth- flow of energy and entropy. Digital Recordings.

81. Lane N, Martin W (2010) The energetics of genome complexity. Nature 467: 929-934.

82. Rosenfeld S (2009) Patterns of stochastic behaviour in dynamically unstable high-dimensional biochemical networks. Gene Regul Syst Biol 3: 1-10.

83. Rosenfeld S (2011) Mathematical descriptions of biochemical networks: Stability, stochasticity, evolution. Prog Biophys Mol Biol 106: 400-409.

84. Whitacre JM (2012) Biological robustness: paradigms, mechanisms and systems principles. Front Genet 3: 67.

85. Glancy B, Hartnell LM, Malide D, Yu ZX, Combs CA, et al. (2015) Mitochondrial reticulum for cellular energy distribution in muscle. Nature 523: 617-620.

86. Szabadkai G, Simoni AM, Chami M, Wieckowski MR, Youle RJ, et al. (2004) Drp-1-dependent division of the mitochondrial network blocks intraorganellar $Ca2^+$ waves and protects against $Ca2^+$-mediated apoptosis. Mol Cell 16: 59-68.

87. Rambold AS, Kostelecky B, Elia N, Lippincott-Schwartz J (2011) Tubular network formation protects mitochondria from autophagosomal degradation during nutrient starvation. Proc Natl Acad Sci USA 108: 10190-10195.

88. Han XJ, Tomizawa K, Fujimura A, Ohmori I, Nishiki T, et al. (2011) Regulation of mitochondrial dynamics and neurodegenerative diseases. Acta Med Okayama 65: 1-10.

89. Sheridan C, Martin SJ (2010) Mitochondrial fission/fusion dynamics and apoptosis. Mitochondrion 10: 640-648.

90. Shutt TE, McBride HM (2012) Staying cool in difficult times: Mitochondrial dynamics, quality control and the stress response. Biochim Biophys Acta 1833: 417-424.

91. Vedel S, Nunns H, Kosmrlj A, Semsey S, Trusina A (2016) Asymmetric damage segregation constitutes an emergent population-level stress response. Cell Syst 3: 187-198.

92. Szalay MS, Kovacs IA, Korcsmaros T, Bode C, Csermely P (2007) Stress-induced rearrangements of cellular networks: Consequences for protection and drug design. FEBS Lett 581: 3675-3680.

93. Lapuente-Brun E, Moreno-Loshuertos R, Acin-Perez R, Latorre-Pellicer A, Colas C, et al. (2013) Super complex assembly determines electron flux in the mitochondrial electron transport chain. Science 340: 1567-1570.

94. Tulving E (1985) How many memory systems are there? Am Psychol 40: 385-398.

95. Fosslien E (2010) Hormetic electric field theory of pattern formation. Dose Response 8: 518-526.

96. Hameroff S, Penrose R (2014) Consciousness in the universe: A review of the 'Orch OR' theory. Phys Life Rev 11: 39-78.

97. McFadden J (2013) The CEMI field theory: Closing the loop. J Conscious Stud 20: 153-168.

98. Frohlich F, McCormick DA (2010) Endogenous electric fields may guide neocortical network activity. Neuron 67: 129-143.

99. Khrennikov A (2011) Quantum-like model of processing of information in the brain based on classical electromagnetic field. Biosystems 105: 250-262.

100. Baladron C, Khrennikov A (2016). Quantum formalism as an optimisation procedure of information flows for physical and biological systems. Biosystems 150: 13-21.

101. Srobar F (2012) Frohlich systems in cellular physiology. Prague Med Rep 113: 95-104.

102. Killoran N, Huelga SF, Plenio MB (2015) Enhancing light-harvesting power with coherent vibrational interactions: A quantum heat engine picture. J Chem Phys 143: 155102.

103. Tyner KM, Kopelman R, Philbert MA (2007) "Nanosized voltmeter" enables cellular-wide electric field mapping. Biophys J 93: 1163-1174.

104. Morissette G, Bawolak MT, Marceau F (2011) Dissociation of the vacuolar and macroautophagic cytopathology from the cytotoxicity induced by the lipophilic local anesthetic bupivacaine. Can J Physiol Pharmacol 89: 505-512.

105. Bains R, Moe MC, Vinje ML, Berg-Johnsen J (2009) Sevoflurane and propofol depolarize mitochondria in rat and human cerebrocortical synaptosomes by different mechanisms. Acta Anaesthesiol Scand 53: 1354-1360.

106. Weiser BP, Bu W, Wong D, Eckenhoff RG (2014) Sites and functional consequence of VDAC-alkyl phenol anesthetic interactions. FEBS Lett 588: 4398-4403.

107. Craddock TJ, St George M, Freedman H, Barakat KH, Damaraju S, et al. (2012) Computational predictions of volatile anesthetic interactions with the microtubule cytoskeleton: Implications for side effects of general anesthesia. PloS ONE 7: e37251.

108. Kitano H, Kirsch JR, Hurn PD, Murphy SJ (2007) Inhalational anesthetics as neuroprotectants or chemical preconditioning agents in ischemic brain. J Cereb Blood Flow Metab 27: 1108-1128.

109. Agarwal B, Stowe DF, Dash RK, Bosnjak ZJ, Camara AK (2014) Mitochondrial targets for volatile anesthetics against cardiac ischemia-reperfusion injury. Front Physiol 5: 341.

110. Heimburg T, Jackson AD (2007) The thermodynamics of general anesthesia. Biophys J 92: 3159-3165.

111. Turin L, Skoulakis EM, Horsfield AP (2014) Electron spin changes during general anesthesia in Drosophila. Proc Natl Acad Sci U S A 111: E3524-3533.

112. Guldenmund P, Gantner IS, Baquero K, Das T, Demertzi A, et al. (2016) Propofol-induced frontal cortex disconnection: A study of resting-state networks, total brain connectivity and mean BOLD signal oscillation frequencies. Brain Connect 6: 225-237.

113. Stuart JA, Brindle KM, Harper JA, Brand MD (1999) Mitochondrial proton leak and the uncoupling proteins. J Bioenerg Biomembr 31: 517-525.

114. Engl E, Attwell D (2015) Non-signalling energy use in the brain. J Physiol 593: 3417-3429.

115. Twaroski DM, Yan Y, Zaja I, Clark E, Bosnjak ZJ, et al. (2015) Altered mitochondrial dynamics contributes to propofol-induced cell death in human stem cell-derived neurons. Anesthesiology 123: 1067-1083.

116. Hudetz AG (2012) General anesthesia and human brain connectivity. Brain Connect 2: 291-302.

117. Aon MA, Cortassa S, O'Rourke B (2008) Mitochondrial oscillations in physiology and pathophysiology. Adv Exp Med Biol 641: 98-117.

118. Howarth C, Gleeson P, Attwell D (2012) Updated energy budgets for neural computation in the neocortex and cerebellum. J Cereb Blood Flow Metab 32: 1222-1232.

119. Harris JJ, Jolivet R, Attwell D (2012) Synaptic energy use and supply. Neuron 75: 762-777.

120. Hochachka PW (1994) Solving the common problem: matching ATP synthesis to ATP demand during exercise. Advances in Veterinary Science and Comparative Medicine 38A: 41-56.

121. Sengupta B, Friston KJ, Penny WD (2014) Efficient gradient computation for dynamical models. NeuroImage 98: 521-527.

122. (2013) Largest neuronal network simulation achieved using K computer. Website: Riken.

123. http://www.aics.riken.jp/en/overview/opsdiv/fac_ops_dev/

124. Penrose R (1994) Shadows of the mind; a search for the missing science of consciousness. Great Britain: Oxford University Press.

125. Mailloux RJ, Harper ME (2011) Uncoupling proteins and the control of mitochondrial reactive oxygen species production. Free Radic Biol Med 51:106-115.

126. Woyda-Ploszczyca AM, Jarmuszkiewicz W (2016) The conserved regulation of mitochondrial uncoupling proteins: From unicellular eukaryotes to mammals. Biochimica et Biophysica Acta 1858: 21-33.

127. Du RH, Wu FF, Lu M, Shu XD, Ding JH, et al. (2016) Uncoupling protein 2 modulation of the NLRP3 inflammasome in astrocytes and its implications in depression. Redox Biol 9: 178-87.

128. Bae J, Ricciardi CJ, Esposito D, Komarnytsky S, Hu P, et al. (2014) Activation of pattern recognition receptors in brown adipocytes induces inflammation and suppresses uncoupling protein 1 expression and mitochondrial respiration. Am J Physiol Cell Physiol 306: C918-930.

129. Emre Y, Nubel T (2010) Uncoupling protein UCP2: When mitochondrial activity meets immunity. FEBS Lett 584: 1437-1442.

130. Mills EL, Kelly B, Logan A, Costa AS, Varma M, et al. (2016) Succinate dehydrogenase supports metabolic repurposing of mitochondria to drive inflammatory macrophages. Cell 167: 457-470 e13.

131. Nunn AV, Bell J, Barter P (2007) The integration of lipid-sensing and anti-inflammatory effects: How the PPARs play a role in metabolic balance. Nucl Recept 5: 1.

132. Galloway CA, Lee H, Yoon Y (2012) Mitochondrial morphology-emerging role in bioenergetics. Free Radic Biol Med 53: 2218-2228.

133. Motori E, Puyal J, Toni N, Ghanem A, Angeloni C, et al. (2013) Inflammation-induced alteration of astrocyte mitochondrial dynamics requires autophagy for mitochondrial network maintenance. Cell Metab 18: 844-859.

134. Steardo L Jr., Bronzuoli MR, Iacomino A, Esposito G, Steardo L, et al. (2015) Does neuroinflammation turn on the flame in Alzheimer's disease? Focus on astrocytes. Front Neurosci 9: 259.

135. Cabezas-Opazo FA, Vergara-Pulgar K, Perez MJ, Jara C, Osorio-Fuentealba C, et al. (2015) Mitochondrial dysfunction contributes to the pathogenesis of Alzheimer's disease. Oxid Med Cell Longev 2015: 509654.

136. Archer SL (2013) Mitochondrial dynamics--mitochondrial fission and fusion in human diseases. N Engl J Med 369: 2236-2251.

137. Marraffini LA (2015) CRISPR-Cas immunity in prokaryotes. Nature 526: 55-61.

138. Heussler GE, Cady KC, Koeppen K, Bhuju S, Stanton BA, et al. (2015)

Clustered regularly interspaced short palindromic repeat-dependent, biofilm-specific death of *Pseudomonas aeruginosa* mediated by increased expression of phage-related genes. mBio 6: e00129-15.

139. Shakhar K, Shakhar G (2015) Why do we feel sick when infected--Can altruism play a role? PLoS Biol 13: e1002276.

140. Pulvermuller F, Garagnani M, Wennekers T (2014) Thinking in circuits: Toward neurobiological explanation in cognitive neuroscience. Biol Cybern 108: 573-593.

141. Hartshorne JK, Germine LT (2015) When does cognitive functioning peak? The asynchronous rise and fall of different cognitive abilities across the life span. Psychol Sci 26: 433-443.

142. Christie ST, Schrater P (2015) Cognitive cost as dynamic allocation of energetic resources. Front Neurosci 9: 289.

143. Dixon ML, Fox KC, Christoff K (2014) A framework for understanding the relationship between externally and internally directed cognition. Neuropsychologia 62: 321-330.

144. Fox KC, Thompson E, Andrews-Hanna JR, Christoff K (2014) Is thinking really aversive? A commentary on Wilson et al.'s "Just think: The challenges of the disengaged mind". Front Psychol 5: 1427.

145. Fox KC, Spreng RN, Ellamil M, Andrews-Hanna JR, Christoff K (2015) The wandering brain: Meta-analysis of functional neuroimaging studies of mind-wandering and related spontaneous thought processes. NeuroImage 111: 611-621.

146. Van Hoeck N, Watson PD, Barbey AK (2015) Cognitive neuroscience of human counterfactual reasoning. Front Hum Neurosci 9: 420.

147. McKendrick R, Ayaz H, Olmstead R, Parasuraman R (2014) Enhancing dual-task performance with verbal and spatial working memory training: Continuous monitoring of cerebral hemodynamics with NIRS. NeuroImage 85: 1014-1026.

148. Lane N (2002) Oxygen - The Molecule that made the world. Great Britain: Oxford University Press, Great Clarendon Street, Oxford OX2 6DP.

149. Epel ES, Puterman E, Lin J, Blackburn EH, Lum PY, et al. (2016) Meditation and vacation effects have an impact on disease-associated molecular phenotypes. Transl Psychiatry 6: e880.

150. Black DS, Slavich GM (2016) Mindfulness meditation and the immune system: A systematic review of randomized controlled trials. Ann N Y Acad Sci 1373: 13-24.

151. Ben-Shaanan TL, Azulay-Debby H, Dubovik T, Starosvetsky E, Korin B, et al. (2016) Activation of the reward system boosts innate and adaptive immunity. Nat Med 22: 940-944.

152. Satoh A, Brace CS, Rensing N, Cliften P, Wozniak DF, et al. (2013) Sirt1 extends life span and delays aging in mice through the regulation of Nk2 homeobox 1 in the DMH and LH. Cell Metab 18: 416-430.

153. Nunn AV, Guy GW, Bell JD (2010) Endocannabinoids, FOXO and the metabolic syndrome: Redox, function and tipping point - The view from two systems. Immunobiol 215: 617-628.

154. Guisinger S (2003) Adapted to flee famine: Adding an evolutionary perspective on anorexia nervosa. Psychol Rev 110: 745-761.

155. Petersen AM, Pedersen BK (2005) The anti-inflammatory effect of exercise. J Appl Physiol 98: 1154-1162.

156. Woods JA, Wilund KR, Martin SA, Kistler BM (2012) Exercise, inflammation and aging. Aging Dis 3: 130-140.

157. Lezi E, Burns JM, Swerdlow RH (2014) Effect of high-intensity exercise on aged mouse brain mitochondria, neurogenesis and inflammation. Neurobiol Aging 35: 2574-2583.

158. Webb AE, Kundaje A, Brunet A (2016) Characterization of the direct targets of FOXO transcription factors throughout evolution. Aging Cell.

159. Despres JP (2016) Physical activity, sedentary behaviours and cardiovascular health: When will cardiorespiratory fitness become a vital sign? Can J Cardiol 32: 505-513.

160. Leong DP, Teo KK, Rangarajan S, Lopez-Jaramillo P, Avezum A Jr., et al. (2015) Prognostic value of grip strength: Findings from the prospective urban rural epidemiology (PURE) study. Lancet 386: 266-273.

161. Metter EJ, Talbot LA, Schrager M, Conwit R (2002) Skeletal muscle strength as a predictor of all-cause mortality in healthy men. J Gerontol A Biol Sci Med Sci 57: B359-B65.

162. Newman AB, Kupelian V, Visser M, Simonsick EM, Goodpaster BH, et al. (2006) Strength, but not muscle mass, is associated with mortality in the health, aging and body composition study cohort. J Gerontol A Biol Sci Med Sci 61: 72-77.

163. Vidoni ED, Johnson DK, Morris JK, Van Sciver A, Greer CS, et al. (2015) Dose-response of aerobic exercise on cognition: A community-based, pilot randomized controlled trial. PloS ONE 10: e0131647.

164. Tsou YH, Shih CT, Ching CH, Huang JY, Jen CJ, et al. (2015) Treadmill exercise activates Nrf2 antioxidant system to protect the nigrostriatal dopaminergic neurons from MPP+ toxicity. Exp Neurol 263: 50-62.

165. Johnson DA, Johnson JA (2015) Nrf2-a therapeutic target for the treatment of neurodegenerative diseases. Free Radic Biol Med 88: 253-267.

166. Lopez-Lluch G, Hunt N, Jones B, Zhu M, Jamieson H, et al. (2006) Calorie restriction induces mitochondrial biogenesis and bioenergetic efficiency. Proc Natl Acad Sci U S A 103: 1768-1773.

167. Nisoli E, Tonello C, Cardile A, Cozzi V, Bracale R, et al. (2005) Calorie restriction promotes mitochondrial biogenesis by inducing the expression of eNOS. Science 310: 314-317.

168. Martin-Montalvo A, Villalba JM, Navas P, de Cabo R (2011) NRF2, cancer and calorie restriction. Oncogene 30: 505-520.

169. Tabarean I, Morrison B, Marcondes MC, Bartfai T, Conti B (2010) Hypothalamic and dietary control of temperature-mediated longevity. Ageing Res Rev 9: 41-50.

170. Zhang G, Li J, Purkayastha S, Tang Y, Zhang H, et al. (2013) Hypothalamic programming of systemic ageing involving IKK-beta, NF-kappaB and GnRH. Nature 497: 211-216.

171. Robson PJ, Guy GW, Di Marzo V (2014) Cannabinoids and schizophrenia: Therapeutic prospects. Curr Pharm Des 20: 2194-2204.

172. Black C, Miller BJ (2015) Meta-analysis of cytokines and chemokines in suicidality: Distinguishing suicidal versus non-suicidal patients. Biol Psychiatry 78: 28-37.

173. Hroudova J, Fisar Z (2012) *In vitro* inhibition of mitochondrial respiratory rate by anti-depressants. Toxicol Lett 213: 345-352.

174. Holley J, Crone D, Tyson P, Lovell G (2011) The effects of physical activity on psychological well-being for those with schizophrenia: A systematic review. Br J Clin Psychol 50: 84-105.

175. Whalley LJ, Staff RT, Fox HC, Murray AD (2016) Cerebral correlates of cognitive reserve. Psychiatry Res 247: 65-70.

176. Purvis D, Gonsalves S, Deuster PA (2010) Physiological and psychological fatigue in extreme conditions: Overtraining and elite athletes. PM R 2: 442-450.

177. Gradari S, Palle A, McGreevy KR, Fontan-Lozano A, Trejo JL (2016) Can exercise make you smarter, happier and have more neurons? A hormetic perspective. Front Neurosci 10: 93.

178. Krueger JM, Frank MG, Wisor JP, Roy S (2015) Sleep function: Toward elucidating an enigma. Sleep Med Rev 28: 42-50.

179. de Vivo L, Bellesi M, Marshall W, Bushong EA, Ellisman MH, et al. (2017) Ultra-structural evidence for synaptic scaling across the wake/sleep cycle. Science 355: 507-510.

180. Herculano-Houzel S (2015) Decreasing sleep requirement with increasing numbers of neurons as a driver for bigger brains and bodies in mammalian evolution. Proc Biol Sci 282: 20151853.

181. Brown MK, Naidoo N (2010) The UPR and the anti-oxidant response: Relevance to sleep and sleep loss. Mol Neurobiol 42: 103-113.

182. Zhu B, Dong Y, Xu Z, Gompf HS, Ward SA, et al. (2012) Sleep disturbance induces neuroinflammation and impairment of learning and memory. Neurobiol Dis 48: 348-355.

183. Choi KM, Lee JS, Park HS, Baik SH, Choi DS, et al. (2008) Relationship between sleep duration and the metabolic syndrome: Korean National Health and Nutrition Survey 2001. Int J Obes 32: 1091-1097.

184. Fisher MP (2015) Quantum cognition: The possibility of processing with nuclear spins in the brain. arXiv: 150805929v2 362: 593-602.