BRAIN AGEING — SCIENCE AND SOCIETY

Recruiting adaptive cellular stress responses for successful brain ageing

Alexis M. Stranahan and Mark P. Mattson

Abstract | Successful ageing is determined in part by genetic background, but also by experiential factors associated with lifestyle and culture. Dietary, behavioural and pharmacological interventions have been identified as potential means to slow brain ageing and forestall neurodegenerative disease. Many of these interventions recruit adaptive cellular stress responses to strengthen neuronal networks and enhance plasticity. In this Science and Society article, we describe several determinants of healthy and pathological brain ageing, with insights into how these processes are accelerated or prevented. We also describe the mechanisms underlying the neuroprotective actions of exercise and nutritional interventions, with the goal of recruiting these molecular targets for the treatment and prevention of neurodegenerative disease.

Ageing is associated with numerous physiological alterations across multiple organ systems, including the brain. In the CNS, the effects of ageing can be partly attributed to intrinsic responses to accumulated 'wear and tear', but may also be a result of ageing in other organ systems, including ageing of the reproductive system[1] and muscle loss[2]. Some changes that occur in the context of ageing are adaptive. For example, despite increased physical ailments, the elderly self-report higher levels of happiness relative to middle-aged and younger populations[3] and, presumably, the increased rate of contentment in older adults has some neuronal correlate. Other age-related alterations, such as declining executive function and motor impairment, are more pernicious; ideally, these changes could be delayed or prevented by targeted CNS interventions. Many of these interventions, including exercise and dietary moderation, resemble the dictates of common sense. In this article we describe mechanisms underlying neuroprotective 'common sense' manipulations, with the goal of harnessing these mechanisms to protect against the deleterious consequences of brain ageing.

Salient features of brain ageing

The ageing process leads to an increase in the variability associated with cognitive and motor capabilities in humans[4] and rodent models[5]. Just as some humans maintain cognitive function into their eighth decade and beyond, a subset of aged rodents retains the capacity for performance across a range of cognitive tasks[5–7]. In this regard, it is possible to distinguish among healthy ageing with preserved cognition, age-related cognitive impairment and neuropathology (FIG. 1). As described in the remaining sections of this article, these general functional features of brain ageing are caused by cells becoming less able to respond to stress. In other words, neurons become impaired in their ability to adapt to and rebound from potentially damaging alterations to the local environment and the endocrine milieu.

Regardless of genetic background, there are several major cellular and molecular changes that occur in the CNS during normal ageing that are shared, to a certain extent, with age-related alterations in other organ systems. These fundamental aspects of brain ageing, which are common across the spectrum of cognitive performance, include increased oxidative stress, impaired cellular energy metabolism, perturbed cellular calcium signalling and the abnormal accumulation of damaged proteins and organelles[8]. Superoxide anion radicals, hydroxyl radicals, nitric oxide and peroxynitrite are major oxygen free radicals that have been implicated in normal brain ageing and cognitive impairment[9]. Protein oxidation and modification by lipid peroxidation products and peroxynitrite increases progressively during ageing, and is particularly prominent in the neurons that degenerate in Alzheimer's disease. Likewise, normal ageing is associated with increased immunoreactivity for indices of oxidative stress in humans[10], and pathological ageing further exacerbated this effect[11]. Oxidative damage to membrane lipids occurs more severely in aged, cognitively impaired animals[12] and to an even greater extent in experimental models of neurodegenerative diseases[13,14]. For example, membrane-associated oxidative stress results in neuronal dysfunction and degeneration by a mechanism involving the lipid peroxidation product 4-hydroxynonenal, which covalently modifies proteins that are crucial for cellular ion homeostasis, including Na^+ and Ca^{2+} motive ATPases and glucose and glutamate transport proteins[15]. Such aberrant oxidative damage is likely to contribute to an excitatory imbalance that may presage the onset of age-related cognitive impairment and Alzheimer's disease[16].

With advancing age, neurons may suffer from reduced production of the molecular energy couriers ATP and NAD^+, with impaired mitochondrial function being a principal reason for such a cellular energy deficit[17]. Changes that lead to cellular energy deficits include oxidative damage to mitochondrial DNA, electron transport chain proteins[18] and the plasma membrane redox system[19]. Disease-specific factors may also compromise energy metabolism; such factors include amyloid-β (Aβ) in Alzheimer's disease, α-synuclein in Parkinson's disease, huntingtin in Huntington's disease and Cu/Zn-superoxide dismutase (SOD) in amyotrophic lateral sclerosis (ALS)[17]. Ageing is also accompanied by the accumulation of damaged proteins, nucleic acids and organelles[20,21]. Deficits in proteasomal

© 2012 Macmillan Publishers Limited. All rights reserved

degradation and molecular repair processes are increasingly recognized as central to age-related CNS dysfunction, particularly following physiological challenges to homeostasis[22,23]. As with oxidative stress, cellular energy deficits and accumulation of damaged molecules and organelles tip the balance of activity in neuronal circuits towards uncontrolled excitation[24].

The impact of energy on brain ageing

Studies of human subjects and animal models support a bidirectional relationship between energy intake and brain function; excessive intake impairs function, whereas dietary energy restriction enhances function[25]. The underlying mechanisms for this relationship converge on changes in synaptic plasticity and neurogenesis. Diabetes and obesity are common consequences of excessive energy intake that accelerate brain ageing by compromising hippocampal neurogenesis and long-term potentiation (LTP), which is a candidate cellular model for the synaptic changes underlying learning and memory[26]. Excessive caloric intake may also increase the risk for neurodegenerative diseases and stroke, possibly by compromising the integrity of the blood–brain barrier[27], resulting in deficient neurovascular coupling. Through these mechanisms and others, conditions arising from excessive energy intake have an impact on brain regions implicated in various facets of cognition.

Perturbation of the levels and rhythmicity of a number of hormones in the context of obesity and the metabolic syndrome (BOX 1) leads to maladaptive alterations in circuit function that are not restricted to regions that are traditionally associated with feeding and metabolism. Ghrelin, a hormone produced in the stomach, is one example of a metabolically relevant peptide that influences cognition and neuroplasticity. Ghrelin acts on the hypothalamic arcuate nucleus to stimulate feeding and promote the deposition of adipose tissue[28]. Ghrelin administration enhances hippocampal synaptic density, whereas loss-of-function results in decreased synapse numbers and impaired Schaffer collateral LTP[29]. Targeted disruption of the gene encoding ghrelin compromises synaptic function and is associated with behavioural deficits in learning and memory[29]. In addition to regulating synaptic density, LTP and learning, ghrelin promotes adult neurogenesis in rats[30]. These findings support a role for

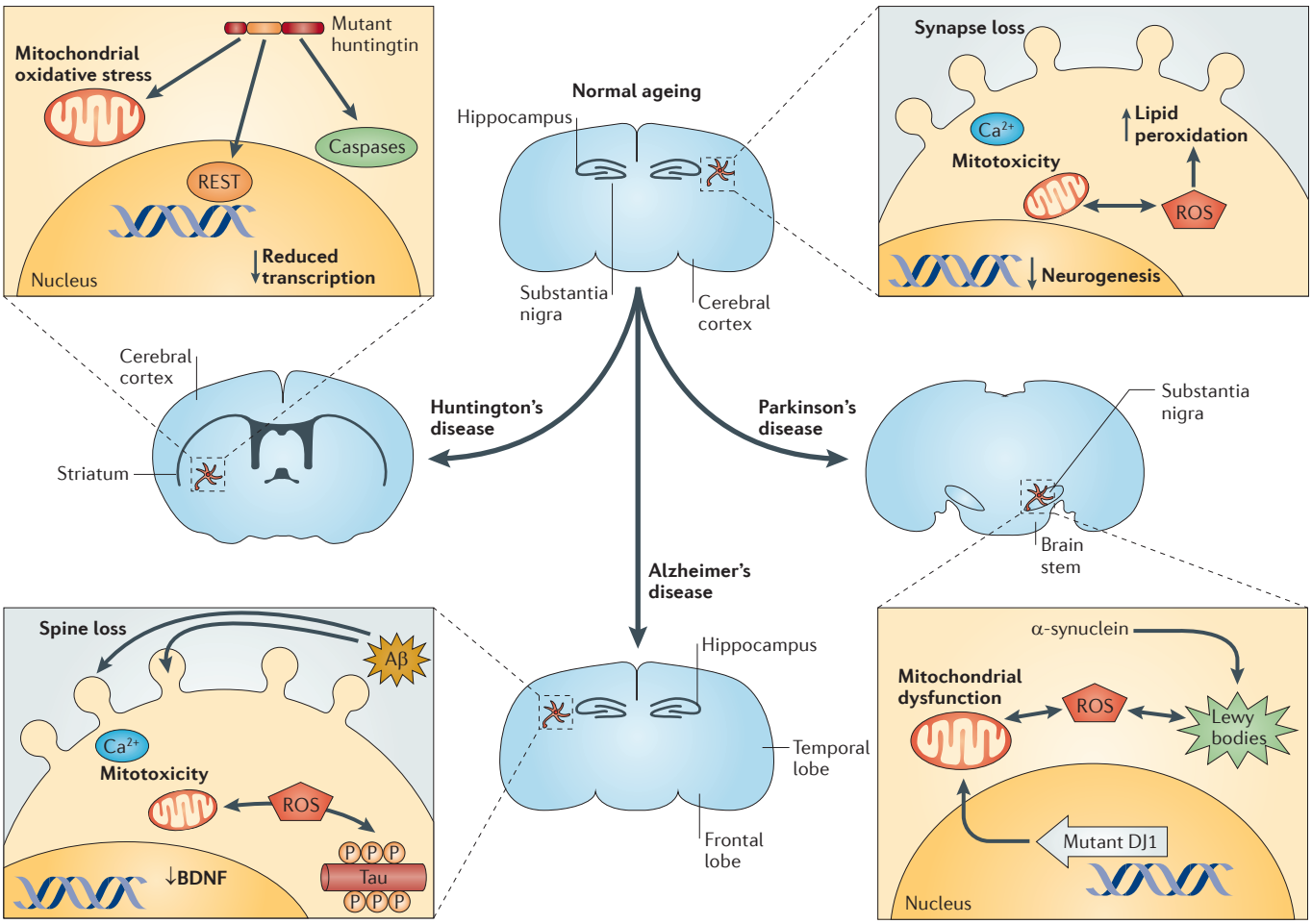

Figure 1 | **Intrinsic features of normal and pathological ageing.** Normal ageing is accompanied by alterations in neuronal calcium handling and changes in lipid peroxidation, leading to increased generation of reactive oxygen species (ROS) and damage to mitochondria. These changes are permissive or instructive for the suppression of adult neurogenesis beginning in middle age. Successful ageing is characterized by the implementation of alternative plasticity mechanisms to compensate for changes in the local microenvironment. Age-related pathologies such as Alzheimer's disease, Parkinson's disease and Huntington's disease arise from a combination of genetic and environmental factors, but each disease shares a common feature in that age is a risk factor for disease onset. In this respect, ageing sets the stage for the onset of pathology. Aβ, amyloid-β; BDNF, brain-derived neurotrophic factor; DJ1, Parkinson's disease protein 7; P, phosphorylation site; REST, repressor element 1-silencing transcription factor.

© 2012 Macmillan Publishers Limited. All rights reserved

Box 1 | **The metabolic syndrome**

The metabolic syndrome is a constellation of risk factors that increase the probability of developing diabetes, stroke and cardiovascular diseases. Individuals with the metabolic syndrome have: a high waist-to-hip ratio that is indicative of central adiposity; elevated fasting glucose levels that, although they may not meet the criteria for type 2 diabetes, indicate that insulin sensitivity may be compromised; elevated triglycerides; and increased blood pressure. The most effective treatment for the metabolic syndrome is weight loss. The endocrine consequences of the metabolic syndrome are not restricted to insulin signalling, but also involve perturbation of leptin levels and sensitivity, changes in corticosteroid synthesis and rhythmicity, and alterations in ghrelin secretion. Because these endocrine factors have each been shown to influence neuronal function[26,75,76], particularly in the hippocampus, it is likely that the metabolic syndrome could accelerate age-related cognitive deficits. Indeed, recent studies in animal models and human subjects have demonstrated improvements in cognitive performance in response to interventions that increase insulin sensitivity, including dietary energy restriction, exercise and pharmacological agents such as glucagon-like peptide 1 analogues[77–80].

ghrelin in hippocampal plasticity and raise the possibility that disruption of ghrelin signalling in the context of obesity could lead to impairment of hippocampal function.

Owing to pre-existing societal prejudice against obese individuals, studies on the mechanisms related to cognition in obesity should be interpreted cautiously. The perception of obesity as a condition arising from lack of discipline, rather than a disease that, like certain psychiatric conditions, arises from a mixture of environmental pressures and genetic predisposition, often facilitates negative bias among the general public, and could potentially influence opinions among the scientific and health-care providers. It is also important to recognize that experimental observations in genetically homogenous rodent populations may not always translate to humans. Given these precautions, it should be noted that, for both humans and animal models, there is evidence for and against cognitive dysfunction in the context of obesity (TABLE 1).

The results of human studies reveal a critical time window in which obesity, and the metabolic syndrome more generally, has the potential to affect cognitive ageing (TABLE 1). Exposure to the direct oxidative and indirect endocrine consequences of excessive energy intake during the fourth and fifth decade of life increases the likelihood of cognitive decline during later years[31], whereas higher body mass indices may not cause cognitive impairment later in life[32]. One interpretation is that the middle-aged brain is most susceptible to the endocrine adversities of the metabolic syndrome, whereas another hypothesis would suggest that other factors that are correlated with the prevalence of obesity, such as socioeconomic status, exert their effects on cognition during this same window. External variables, such as socioeconomic status and level of education, are controlled for by some, but not all, studies examining cognitive changes in relationship to obesity, so the degree to which obesity has an impact on cognition remains an open question.

Research in animal models demonstrates more consistent impairments on various measures associated with learning and memory in rodents exposed to excessive caloric intake. Diets high in fats and simple sugars impair spatial learning in the water maze[33,34], spatial recognition in the Y-maze[35], complex maze learning[36] and operant discrimination[37,38]. However, the time course for memory impairment in rats fed Western diets varies. Some studies report memory impairment after 2 to 3 months of diet exposure[33,35,37] using diets that range from 20% fat to 45% fat; by contrast, another study did not detect cognitive impairment using a diet that was 45% fat until after 8 months of diet exposure[34]. Other researchers have failed to detect any impairment at all when feeding mice diets comparably enriched with fats and simple sugars[39]. Understanding the time course, and the underlying cellular and molecular mechanisms, of memory impairment caused by diets that elicit features of the metabolic syndrome is crucial in light of evidence for a critical time window in humans. However, the question of when, and how, cognitive impairment develops in the context of the metabolic syndrome remains unanswered.

Dietary energy restriction can protect the brain against ageing. Early studies in mice showed that lifelong energy restriction through an alternate-day fasting regimen improves learning in a complex maze[40]. Intermittent energy restriction also improves memory and Schaffer collateral LTP in young mice[41] and enhances neurogenesis through a brain-derived neurotrophic factor (BDNF)-dependent mechanism[42]. Dietary moderation is also positively associated with successful ageing (healthy rather than pathological ageing) in human populations[25]. Interestingly, age-related impairments in cellular energy metabolism can be reversed by dietary energy restriction[19], as can pathological deficits in learning and memory in Alzheimer's disease model mice[43,44]. Dietary energy restriction was also effective in protecting dopaminergic neurons and improving motor function in mouse[45] and monkey[46]

Table 1 | **Recent studies of cognitive function in relationship to obesity**

Study	Age group	Cognitive outcome	Refs
Human studies			
Roriz-Cruz *et al.* (2007)	Aged	↓	87
Gunstad *et al.* (2007)	Adult	↓	88
van den Berg *et al.* (2007)	Aged	↑	89
Sturman *et al.* (2008)	Aged	No change	32
Li *et al.* (2008)	Young	↓	90
Huizinga *et al.* (2008)	Adult	↓	91
Sabia *et al.* (2009)	Adult	↓	92
Volkow *et al.* (2009)	Adult	↓	93
Fergenbaum *et al.* (2009)	Adult	↓	94
Animal models			
Morrison *et al.* (2010)	Aged	↓	36
McNay *et al.* (2010)	Adult	↓	35
Granholm *et al.* (2008)	Adult	↓	95
Kanoski *et al.* (2007)	Adult	↓	38
Mielke *et al.* (2006)	Aged	No change	39

© 2012 Macmillan Publishers Limited. All rights reserved

models of Parkinson's disease, protecting striatal and cortical neurons, and extending survival in a mouse model of Huntington's disease[47]. A major mechanism by which energy restriction protects neurons against ageing and disease is by engaging adaptive cellular stress response pathways that result in the production of a range of cytoprotective proteins, including neurotrophic factors, protein chaperones, DNA repair enzymes and mitochondrial uncoupling proteins, among others[48–50] (FIG. 2).

Influence of specific dietary components

Epidemiological data from human populations and mechanistic data from animal models support a protective role for certain dietary phytochemicals[51] and a deleterious effect of saturated fats and refined sugars[52]. Specific macro- and micro-nutrients counteract brain ageing by protecting against impairment and promoting adaptive plasticity, or by acting in a permissive or instructive fashion for deficits in neuronal function. For example, regular consumption of refined sugars and saturated fats accelerates age-related deficits in spatial learning[34], whereas consuming relatively high amounts of vegetables and fruits may counteract the ageing process[53]. Emerging evidence suggests that some neuroprotective phytochemicals engage adaptive cellular stress response pathways in neurons to upregulate the expression of neurotrophic factors, antioxidant enzymes and proteins involved in cellular energy metabolism[51]. In this regard, the biological framework for nutritional neuroprotection conforms to the theory of hormesis (BOX 2). Phytochemicals that have been shown to protect neurons against dysfunction and degeneration in animal models of neurodegenerative disorders include folic acid[54], thiamine[55], curcumin[56], epigallocatechin-3-gallate[57], plumbagin[58] and resveratrol[59]. Signalling pathways activated by these phytochemicals include the nuclear regulatory factor 2 (NRF2)–antioxidant response element (ARE) pathway, the Ca^{2+}–cyclic AMP response element-binding protein (CREB) pathway, and the sirtuin–forkhead box O (FOXO) pathway (FIG. 2). Neuroprotective genes induced by the Ca^{2+}–CREB and sirtuin–FOXO pathways include those encoding neurotrophic factors (for example, BDNF), protein chaperones (for example, heat shock protein 70 and glucose-regulated protein 78), antioxidant enzymes (for example, MnSOD, haem oxygenase 1 and NADH quinone oxidoreductase 1), energy-regulating proteins (for example, mitochondrial uncoupling proteins) and DNA repair proteins (for

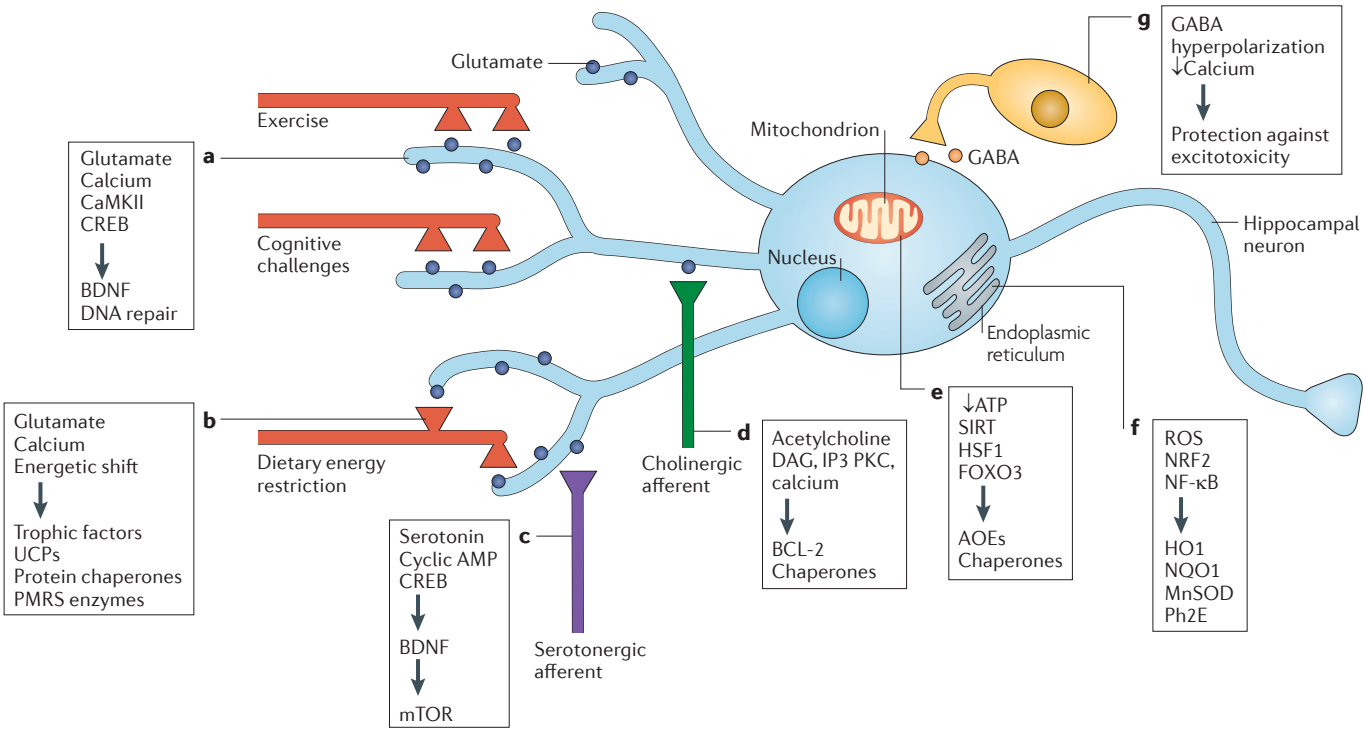

Figure 2 | **Adaptive cellular stress response signalling mediates the beneficial effects of environmental challenges on neuroplasticity and vulnerability to degeneration.** A typical glutamatergic neuron in the hippocampus is depicted receiving excitatory inputs (red) from neurons activated in response to exercise, cognitive challenges and dietary energy restriction. Examples of seven different adaptive stress response signalling pathways that protect neurons against degeneration and promote synaptic plasticity are shown. During exercise and cognitive challenges, postsynaptic receptors for glutamate (**a**,**b**), serotonin (**c**) and acetylcholine (**d**) are activated to engage intracellular signalling cascades and transcription factors that induce the expression of neuroprotective proteins including brain-derived neurotrophic factor (BDNF), mitochondrial uncoupling proteins (UCPs) and anti-apoptotic proteins (for example, BCL-2). BDNF promotes neuronal growth, in part, by activating mammalian target of rapamycin (mTOR). Mild cellular stress resulting from reduced energy substrates (**e**) and reactive oxygen species (ROS) (**f**) engages adaptive stress response pathways, including those that upregulate antioxidant enzymes (AOEs) and protein chaperones. Release of GABA from interneurons (**g**) in response to activity in excitatory circuits (as occurs during exercise and cognitive challenges) hyperpolarizes excitatory neurons protecting them from Ca^{2+} overload and excitotoxicity. CaMKII, calcium/calmodulin kinase II; CREB, cyclic AMP response element-binding protein; DAG, diacylglycerol; FOXO3, forkhead box protein O3; HO1, haem oxygenase 1; HSF1, heat shock factor 1; IP3 PKC, inositol-trisphosphate 3 protein kinase C; MnSOD, manganese superoxide dismutase; NF-κB, nuclear factor-κB; NQO1, NAD(P)H-quinone oxidoreductase 1; NRF2, nuclear regulatory factor 2; Ph2E, phase 2 enzyme; PMRS, plasma membrane redox system; SIRT, sirtuin.

© 2012 Macmillan Publishers Limited. All rights reserved

example, AP endonuclease 1). Based on these natural products, medicinal chemists may be able to develop therapeutic agents with greater specificity for a stress response pathway and reduced toxicity.

Physical and cognitive exercise

Evidence in favour of experiential neuroprotection is compelling, and emerging data suggest that lifestyle factors can be harnessed to prevent or treat neurological disease. Physical and mental activities can protect neurons against age-related dysfunction and disease through a variety of mechanisms, including upregulation of neurotrophic factors, enhanced synaptic plasticity and stimulation of neurogenesis. Lifestyle factors such as cognitive stimulation[60] and aerobic exercise[61] engage a variety of signalling cascades to maintain transcriptional profiles that are more commonly observed in the structurally dynamic developing brain. Such lifestyle factors could, in principle, enhance the efficacy of pharmacological treatments designed to forestall neurodegenerative diseases.

One example of a synergistic interaction between exercise and pharmacological neuroprotection involves the neurotransmitter noradrenaline (FIG. 3). Noradrenergic innervation of the hippocampus is necessary for exercise-induced upregulation of BDNF expression[62]. The locus coeruleus is the origin of noradrenergic fibres, and depletion of locus coeruleus noradrenaline exacerbates amyloid plaque deposition and cognitive impairment in Alzheimer's disease model mice[63]. Both of these studies used loss-of-function pharmacological approaches, but it remains to be seen whether synergistic gain-of-function could be detected through the concomitant treatment of Alzheimer's disease model mice with exercise and selective noradrenaline reuptake inhibitors (SNRIs) (FIG. 3).

Whereas healthy ageing is accompanied by increased variability in cognitive performance[5–7], aged rats are uniformly more susceptible to memory deficits following an immune challenge[64]. Increased vulnerability to infection-induced learning deficits is accompanied by exacerbation of hippocampal inflammatory responses. Although aged rats run far less than their younger counterparts, even a limited amount of voluntary wheel running was sufficient to prevent impaired learning following *Escherichia coli* infection and attenuate neuroinflammation in the hippocampus[64]. Although this study demonstrates that exercise is indeed neuroprotective, no studies to date have addressed whether late-onset physical activity can ameliorate cognitive deficits in a naturally occurring model of age-related cognitive impairment, such as the aged-impaired rat model[5]. Possible interactions between exercise and ageing of the noradrenergic system in healthy individuals also remain uncharacterized.

Box 2 | **Successful brain ageing through hormesis**

Intermittent exposure to mild cognitive or physiological stress can increase neuronal resistance to the degenerative disorders of ageing[48]. Hormesis — the process through which exposure to low levels of a stressor activates biological repair mechanisms[81] — occurs during exercise, in response to dietary energy restriction and when neurons are stimulated with certain phytochemicals. Hormetic stress stimulates signalling pathways that enhance the abilities of neurons to resist oxidative stress, DNA damage, mitochondrial impairment, and protein misfolding and aggregation. Some of the major proteins involved in such adaptive stress responses include neurotrophic factors, protein chaperones and proteins involved in mitochondrial biogenesis, protein degradation and autophagy (FIG. 2). The cellular signalling pathways that mediate hormetic responses in neurons are being identified. For example, cognitive stimulation and exercise involve the activation of glutamate receptors (resulting in Ca^{2+} influx), Ca^{2+}/calmodulin-dependent kinases and the transcription factor cyclic AMP response element-binding protein (CREB), as well as the induction of genes encoding brain-derived neurotrophic factor (BDNF) and the DNA repair enzyme apurinic-apyrimidinic endonuclease 1 (APE1), among others[60,61]. Dietary energy restriction has been reported to activate genes encoding proteins involved in synaptic plasticity, cellular energy metabolism and cell survival[82]. It has been proposed that there is an evolutionarily conserved network of genes that orchestrate hormetic responses of cells and organisms to various stressful challenges. These so-called 'vitagenes' encode proteins that are crucial for the control of protein quality, redox balance, ion homeostasis, membrane integrity and energy metabolism[83]. Examples of phytochemicals that act via hormesis are: sulphoraphane (which is present in relatively high amounts in broccoli) and plumbagin, which activate the nuclear regulatory factor 2 (NRF2) –antioxidant response element (ARE) pathway, resulting in the expression of the antioxidant enzymes haem oxygenase 1 and NAD(P)H-quinone oxidoreductase 1 (also known as NAD(P)H dehydrogenase [quinone] 1 (REF. 84); curcumin (curry spice), which stimulates adult hippocampal neurogenesis by inducing a mild cellular stress response involving the extracellular signal-regulated kinases (ERKs)[85]; and flavonoids from fruits such as grapes and blueberries, which enhance learning and memory, possibly by activating sirtuins and CREB[86]. A better understanding of the mechanisms by which phytochemicals stimulate or stress neurons in ways that enhance CNS function and resilience may lead to the development of novel interventions for neurodegenerative disorders.

Late-life resilience

During the past few decades, there has been increased interest in regenerative medicine, largely as the result of major advances in research on stem cells and neurotrophic factors. Here, we briefly describe the mechanisms that regulate neurogenesis, as well as advances in the development of therapeutic interventions that either stimulate endogenous neural stem cells or involve transplantation of neural progenitors derived from embryonic stem cells or autologous induced pluripotent stem (iPS) cells. Several environmental factors and chemical agents have been shown to stimulate neurogenesis in one or both of the two major populations of neural progenitors in the adult brain, which are located in the hippocampal dentate gyrus and the subventricular zone. Exercise, dietary energy restriction and enriched environments enhance neurogenesis by a mechanism involving the upregulation of BDNF expression[65]. The ability of these lifestyle-related factors to enhance neurogenesis is retained during ageing, although their efficacy may be attenuated. Conversely, chronic adverse stressors (for example, psychosocial stress and depression) and metabolic derangements (for example, diabetes and insulin resistance) impair neurogenesis by elevating glucocorticoid levels and reducing BDNF expression[66–68]. Unfortunately, because there may not be neural progenitors that are capable of supplying new neurons to the vast majority of neuronal circuits in the brain, it is unlikely that stimulating endogenous progenitors will be sufficient to repair all damaged circuits in neurodegenerative disorders.

Neuronal replacement by transplantation of neural progenitors, embryonic stem cells or autologous iPS cells is being pursued in preclinical and translational research projects. Several studies have documented the restorative effects of transplanted stem or progenitor cells in animal models of brain injury or neurodegenerative disorders[69]. Human studies in which human fetal neural progenitors have been transplanted into patients with Parkinson's disease have yielded mixed results[70]. Nevertheless, emerging findings with iPS cells generated from fibroblasts or other cell types suggest that

© 2012 Macmillan Publishers Limited. All rights reserved

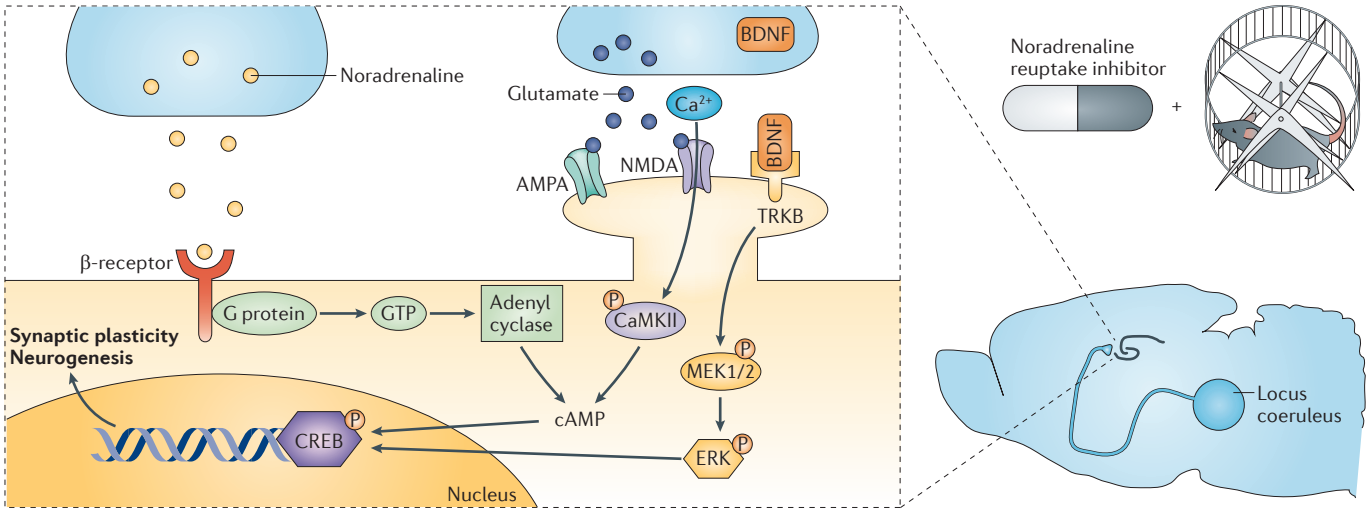

Figure 3 | **Potential for mechanistic synergy between exercise and pharmacological treatments designed to maintain cognition in an ageing population.** The locus coeruleus projection to the hippocampus is essential for exercise-induced brain-derived neurotrophic factor (BDNF) expression. Exercise enhances hippocampal BDNF synthesis, leading to activation of the extracellular signal-related kinase (ERK) pathway, which converges on the transcription factor cyclic AMP response element-binding protein (CREB). Treatment with drugs that block noradrenaline reuptake enhance noradrenergic neurotransmission, leading to activation of adenyl cyclase and cAMP, which also activates CREB, leading to transcription of a number of different genes associated with synaptic plasticity and neurogenesis. Concurrent exercise and noradrenaline reuptake inhibitor treatment could additively enhance hippocampal BDNF production and be neuroprotective. CaMKII, calcium/calmodulin kinase II; MEK, mitogen-activated protein kinase; P, phosphorylation site; TRKB, high-affinity BDNF receptor.

the transplantation of these cells has beneficial effects in a rodent model of Parkinson's disease[71]. Some of the hurdles encountered in transplantation studies (such as immune rejection, insufficient trophic support or an 'unfriendly' cellular niche) might be circumvented by inducing endogenous glial cells to become multipotent neural progenitors, which could then be coaxed towards neuronal phenotypes using one or more of the environmental factors described above or by co-treatment with a neurotrophic factor (see below). For example, glial cells could be infected with an innocuous virus expressing two or three genes that encode proteins that change the phenotype of the cells to that of iPS cells or neurons.

Neurotrophic factor replacement via infusion or gene therapy is another promising approach for halting and reversing age-related CNS dysfunction[72]. A long and rich history of preclinical research in animal models, together with considerable clinical experience in Alzheimer's disease and Parkinson's disease, suggests that neurotrophic factor-based therapies are likely to counteract disease processes in patients. However, to be successful, it is likely that the treatment must be initiated early in the disease process. In addition, such neurotrophic factor therapy assumes that neurons will be responsive (that is, express functional neurotrophic factor receptors), which in some cases may not be so[73] (for example, defects were found in insulin-like growth factor 1 and insulin receptors in Alzheimer's disease). Because neurotrophic factors may not readily cross the blood–brain barrier, there are efforts to develop low-molecular-weight agonists of neurotrophic factors with high specificity and potency[74], although the potential for adverse effects of such agents on peripheral neurons may hinder their development.

Lifestyle-based neuroprotection

A major implication of the research described above is that successful brain ageing is possible for most individuals if they maintain healthy diets and lifestyles throughout their adult life. Unfortunately, this is currently one of the major conundrums in modern societies, where high-energy food is readily available, exercise is unnecessary in daily routines and preventive medicine is being suppressed by the actions of the food and pharmaceutical industries. Healthy lifestyle choices should be implemented and incentivized through the coordinated efforts of government, medical schools and health-care providers. Moreover, additional research into the mechanisms underlying nutritional and experiential neuroprotection is warranted in order to harness these mechanisms through pharmacomimetic strategies. Greater awareness of the extent to which physiological ageing conforms to a hormetic framework will aid in this effort.

Alexis M. Stranahan is at the Physiology Department, Georgia Health Sciences University, Augusta, Georgia 30912, USA.

Mark P. Mattson is at the Laboratory of Neurosciences, National Institute on Ageing Intramural Research Program, National Institutes of Health, Baltimore, Maryland 21224, USA.

Correspondence to M.P.M.
e-mail: mattsonm@grc.nia.nih.gov

doi:10.1038/nrn3151
Published online18 January 2012

1. Behl, C. Oestrogen as a neuroprotective hormone. *Nature Rev. Neurosci.* **3**, 433–442 (2002).
2. Burns, J. M., Johnson, D. K., Watts, A., Swerdlow, R. H. & Brooks, W. M. Reduced lean mass in early Alzheimer disease and its association with brain atrophy. *Arch. Neurol.* **67**, 428–433 (2010).
3. Stone, A. A., Schwartz, J. E., Broderick, J. E. & Deaton, A. A snapshot of the age distribution of psychological well-being in the United States. *Proc. Natl Acad. Sci. USA* **107**, 9985–9990 (2010).
4. Albert, M. S. The ageing brain: normal and abnormal memory. *Phil. Trans. R. Soc. Lond. B* **352**, 1703–1709 (1997).
5. Gallagher, M., Burwell, R. & Burchinal, M. Severity of spatial learning impairment in ageing: development of a learning index for performance in the Morris water maze. *Behav. Neurosci.* **107**, 618–626 (1993).
6. Robitsek, R. J., Fortin, N. J., Koh, M. T., Gallagher, M. & Eichenbaum, H. Cognitive ageing: a common decline of episodic recollection and spatial memory in rats. *J. Neurosci.* **28**, 8945–8954 (2008).
7. Zyzak, D. R., Otto, T., Eichenbaum, H. & Gallagher, M. Cognitive decline associated with normal ageing in rats: a neuropsychological approach. *Learn. Mem.* **2**, 1–16 (1995).
8. Mattson, M. P. & Magnus, T. Ageing and neuronal vulnerability. *Nature Rev. Neurosci.* **7**, 278–294 (2006).
9. Floyd, R. A. & Hensley, K. Oxidative stress in brain ageing. Implications for therapeutics of neurodegenerative diseases. *Neurobiol. Ageing* **23**, 795–807 (2002).
10. Dei, R. *et al.* Lipid peroxidation and advanced glycation end products in the brain in normal ageing and in Alzheimer's disease. *Acta Neuropathol.* **104**, 113–122 (2002).

© 2012 Macmillan Publishers Limited. All rights reserved

11. Lovell, M. A., Ehmann, W. D., Mattson, M. P. & Markesbery, W. R. Elevated 4-hydroxynonenal in ventricular fluid in Alzheimer's disease. *Neurobiol. Ageing* **18**, 457–461 (1997).
12. Nicolle, M. M. *et al*. Signatures of hippocampal oxidative stress in aged spatial learning-impaired rodents. *Neuroscience* **107**, 415–431 (2001).
13. Mattson, M. P. Modification of ion homeostasis by lipid peroxidation: roles in neuronal degeneration and adaptive plasticity. *Trends Neurosci.* **21**, 53–57 (1998).
14. Guo, Q. *et al*. Increased vulnerability of hippocampal neurons to excitotoxic necrosis in presenilin-1 mutant knock-in mice. *Nature Med.* **5**, 101–106 (1999).
15. Mattson, M. P. Roles of the lipid peroxidation product 4-hydroxynonenal in obesity, the metabolic syndrome, and associated vascular and neurodegenerative disorders. *Exp. Gerontol.* **44**, 625–633 (2009).
16. Kapogiannis, D. & Mattson, M. P. Disrupted energy metabolism and neuronal circuit dysfunction in cognitive impairment and Alzheimer's disease. *Lancet Neurol.* **10**, 187–198 (2011).
17. Mattson, M. P., Gleichmann, M. & Cheng, A. Mitochondria in neuroplasticity and neurological disorders. *Neuron* **60**, 748–766 (2008).
18. Gibson, G. E., Starkov, A., Blass, J. P., Ratan, R. R. & Beal, M. F. Cause and consequence: mitochondrial dysfunction initiates and propagates neuronal dysfunction, neuronal death and behavioral abnormalities in age-associated neurodegenerative diseases. *Biochim. Biophys. Acta* **1802**, 122–134 (2010).
19. Hyun, D. H., Emerson, S. S., Jo, D. G., Mattson, M. P. & de Cabo, R. Calorie restriction up-regulates the plasma membrane redox system in brain cells and suppresses oxidative stress during ageing. *Proc. Natl Acad. Sci. USA* **103**, 19908–19912 (2006).
20. Weissman, L. *et al*. Defective DNA base excision repair in brain from individuals with Alzheimer's disease and amnestic mild cognitive impairment. *Nucleic Acids Res.* **35**, 5545–5555 (2007).
21. Wong, E. & Cuervo, A. M. Autophagy gone awry in neurodegenerative diseases. *Nature Neurosci.* **13**, 805–811 (2010).
22. Naidoo, N., Ferber, M., Master, M., Zhu, Y. & Pack, A. I. Ageing impairs the unfolded protein response to sleep deprivation and leads to proapoptotic signaling. *J. Neurosci.* **28**, 6539–6548 (2008).
23. Bingol, B. & Sheng, M. Deconstruction for reconstruction: the role of proteolysis in neural plasticity and disease. *Neuron* **69**, 22–32 (2011).
24. Gleichmann, M., Chow, V. W. & Mattson, M. P. Homeostatic disinhibition in the ageing brain and Alzheimer's disease. *J. Alzheimers Dis.* **24**, 15–24 (2011).
25. Stranahan, A. M. & Mattson, M. P. Impact of energy intake and expenditure on neuronal plasticity. *Neuromolecular Med.* **10**, 209–218 (2008).
26. Stranahan, A. M. *et al*. Diabetes impairs hippocampal function through glucocorticoid-mediated effects on new and mature neurons. *Nature Neurosci.* **11**, 309–317 (2008).
27. Kanoski, S. E., Zhang, Y., Zheng, W. & Davidson, T. L. The effects of a high-energy diet on hippocampal function and blood-brain barrier integrity in the rat. *J. Alzheimers Dis.* **21**, 207–219 (2010).
28. Inui, A. Ghrelin: an orexigenic and somatotrophic signal from the stomach. *Nature Rev. Neurosci.* **2**, 551–560 (2001).
29. Diano, S. *et al*. Ghrelin controls hippocampal spine synapse density and memory performance. *Nature Neurosci.* **9**, 381–388 (2006).
30. Johansson, I. *et al*. Proliferative and protective effects of growth hormone secretagogues on adult rat hippocampal progenitor cells. *Endocrinology* **149**, 2191–2199 (2008).
31. Debette, S. *et al*. Midlife vascular risk factor exposure accelerates structural brain ageing and cognitive decline. *Neurology* **77**, 461–468 (2011).
32. Sturman, M. T. *et al.* Body mass index and cognitive decline in a biracial community population. *Neurology* **70**, 360–367 (2008).
33. Molteni, R., Barnard, R. J., Ying, Z., Roberts, C. K. & Gómez-Pinilla, F. A high-fat, refined sugar diet reduces hippocampal brain-derived neurotrophic factor, neuronal plasticity, and learning. *Neuroscience* **112**, 803–814 (2002).
34. Stranahan, A. M. *et al*. Diet-induced insulin resistance impairs hippocampal synaptic plasticity and cognition in middle-aged rats. *Hippocampus* **18**, 1085–1088 (2008).
35. McNay, E. C. *et al*. Hippocampal memory processes are modulated by insulin and high-fat-induced insulin resistance. *Neurobiol. Learn. Mem.* **93**, 546–553 (2010).
36. Morrison, C. D. *et al*. High fat diet increases hippocampal oxidative stress and cognitive impairment in aged mice: implications for decreased Nrf2 signaling. *J. Neurochem.* **114**, 1581–1589 (2010).
37. Greenwood, C. E. & Winocur, G. Learning and memory impairment in rats fed a high saturated fat diet. *Behav. Neural. Biol.* **53**, 74–87 (1990).
38. Kanoski, S. E., Meisel, R. L, Mullins, A. J. & Davidson, T. L. The effects of energy-rich diets on discrimination reversal learning and on BDNF in the hippocampus and prefrontal cortex of the rat. *Behav. Brain Res.* **182**, 57–66 (2007).
39. Mielke, J. G. *et al*. Longitudinal study of the effects of a high-fat diet on glucose regulation, hippocampal function, and cerebral insulin sensitivity in C57BL/6 mice. *Behav. Brain Res.* **175**, 374–382 (2006).
40. Goodrick, C. L. Effects of lifelong restricted feeding on complex maze performance in rats. *Age* **7**, 1–2 (1984).
41. Fontán-Lozano, A. *et al*. Caloric restriction increases learning consolidation and facilitates synaptic plasticity through mechanisms dependent on NR2B subunits of the NMDA receptor. *J. Neurosci.* **27**, 10185–10195 (2007).
42. Lee, J., Duan, W. & Mattson, M. P. Evidence that brain-derived neurotrophic factor is required for basal neurogenesis and mediates, in part, the enhancement of neurogenesis by dietary restriction in the hippocampus of adult mice. *J. Neurochem.* **82**, 1367–1375 (2002).
43. Halagappa, V. K. *et al*. Intermittent fasting and caloric restriction ameliorate age-related behavioral deficits in the triple-transgenic mouse model of Alzheimer's disease. *Neurobiol. Dis.* **26**, 212–220 (2007).
44. Wu, P. *et al*. Calorie restriction ameliorates neurodegenerative phenotypes in forebrain-specific presenilin-1 and presenilin-2 double knockout mice. *Neurobiol. Ageing* **29**, 1502–1511 (2008).
45. Duan, W. & Mattson, M. P. Dietary restriction and 2-deoxyglucose administration improve behavioral outcome and reduce degeneration of dopaminergic neurons in models of Parkinson's disease. *J. Neurosci. Res.* **57**, 195–206 (1999).
46. Maswood, N. *et al*. Caloric restriction increases neurotrophic factor levels and attenuates neurochemical and behavioral deficits in a primate model of Parkinson's disease. *Proc. Natl Acad. Sci. USA* **101**, 18171–18176 (2004).
47. Duan, W. *et al*. Dietary restriction normalizes glucose metabolism and BDNF levels, slows disease progression, and increases survival in huntingtin mutant mice. *Proc. Natl Acad. Sci. USA* **100**, 2911–2916 (2003).
48. Mattson, M. P. Hormesis defined. *Ageing Res. Rev.* **7**, 1–7 (2008).
49. Arumugam, T. V. *et al*. Age and energy intake interact to modify cell stress pathways and stroke outcome. *Ann. Neurol.* **67**, 41–52 (2010).
50. Yang, J. L., Tadokoro, T., Keijzers, G., Mattson, M. P. & Bohr, V. A. Neurons efficiently repair glutamate-induced oxidative DNA damage by a process involving CREB-mediated up-regulation of apurinic endonuclease 1. *J. Biol. Chem.* **285**, 28191–28199 (2010).
51. Son, T. G., Camandola, S. & Mattson, M. P. Hormetic dietary phytochemicals. *Neuromolecular Med.* **10**, 236–246 (2008).
52. Kanoski, S. E. & Davidson, T. L. Western diet consumption and cognitive impairment: links to hippocampal dysfunction and obesity. *Physiol. Behav.* **103**, 59–68 (2011).
53. Parachikova, A., Green, K. N., Hendrix, C. & LaFerla, F. M. Formulation of a medical food cocktail for Alzheimer's disease: beneficial effects on cognition and neuropathology in a mouse model of the disease. *PLoS ONE* **5**, e14015 (2010).
54. Kruman, I. I. *et al*. Folic acid deficiency and homocysteine impair DNA repair in hippocampal neurons and sensitize them to amyloid toxicity in experimental models of Alzheimer's disease. *J. Neurosci.* **22**, 1752–1762 (2002).
55. Karuppagounder, S. S. *et al*. Thiamine deficiency induces oxidative stress and exacerbates the plaque pathology in Alzheimer's mouse model. *Neurobiol. Ageing* **30**, 1587–1600 (2009).
56. Ma, Q. L. *et al*. β-amyloid oligomers induce phosphorylation of tau and inactivation of insulin receptor substrate via c-Jun N-terminal kinase signaling: suppression by omega-3 fatty acids and curcumin. *J. Neurosci.* **29**, 9078–9089 (2009).
57. Obregon, D. F. *et al*. ADAM10 activation is required for green tea (–)-epigallocatechin-3-gallate-induced α-secretase cleavage of amyloid precursor protein. *J. Biol. Chem.* **281**, 16419–16427 (2006).
58. Son, T. G. *et al.* Plumbagin, a novel Nrf2/ARE activator, protects against cerebral ischemia. *J. Neurochem.* **112**, 1316–1326 (2010).
59. Vingtdeux, V. *et al*. AMP-activated protein kinase signaling activation by resveratrol modulates amyloid-β peptide metabolism. *J. Biol. Chem.* **285**, 9100–9113 (2010).
60. Park, S. S. *et al*. Cortical gene transcription response patterns to water maze training in aged mice. *BMC Neurosci.* **12**, 63 (2011).
61. Stranahan, A. M. *et al*. Hippocampal gene expression patterns underlying the enhancement of memory by running in aged mice. *Neurobiol. Ageing* **31**, 1937–1949 (2010).
62. Garcia, C., Chen, M. J., Garza, A. A., Cotman, C. W. & Russo-Neustadt, A. The influence of specific noradrenergic and serotonergic lesions on the expression of hippocampal brain-derived neurotrophic factor transcripts following voluntary physical activity. *Neuroscience* **119**, 721–732 (2003).
63. Heneka, M. T. *et al*. Locus ceruleus degeneration promotes Alzheimer pathogenesis in amyloid precursor protein 23 transgenic mice. *J. Neurosci.* **26**, 1343–1354 (2006).
64. Barrientos, R. M. *et al*. Little exercise, big effects: reversing ageing and infection-induced memory deficits, and underlying processes. *J. Neurosci.* **31**, 11578–11586 (2011).
65. Lazarov, O., Mattson, M. P., Peterson, D. A., Pimplikar, S. W. & van Praag, H. When neurogenesis encounters ageing and disease. *Trends Neurosci.* **33**, 569–579 (2010).
66. Bremner, J. D. Stress and brain atrophy. *CNS Neurol. Disord. Drug Targets.* **5**, 503–512 (2006).
67. Stranahan, A. M., Khalil, D. & Gould, E. Social isolation delays the positive effects of running on adult neurogenesis. *Nature Neurosci.* **9**, 526–533 (2006).
68. Rothman, S. M. *et al.* 3xTgAD mice exhibit altered behavior and elevated Aβ after chronic mild social stress. *Neurobiol. Ageing* 19 Aug 2011 (doi:10.1016/j.neurobiolaging.2011.07.005).
69. Lindvall, O. & Kokaia, Z. Stem cells in human neurodegenerative disorders — time for clinical translation? *J. Clin. Invest.* **120**, 29–40 (2010).
70. Olanow, C. W., Kordower, J. H., Lang, A. E. & Obeso, J. A. Dopaminergic transplantation for Parkinson's disease: current status and future prospects. *Ann. Neurol.* **66**, 591–596 (2009).
71. Hargus, G. *et al*. Differentiated Parkinson patient-derived induced pluripotent stem cells grow in the adult rodent brain and reduce motor asymmetry in Parkinsonian rats. *Proc. Natl Acad. Sci. USA* **107**, 15921–15926 (2010).
72. Nagahara, A. H. & Tuszynski, M. H. Potential therapeutic uses of BDNF in neurological and psychiatric disorders. *Nature Rev. Drug Discov.* **10**, 209–219 (2011).
73. Moloney, A. M. *et al*. Defects in IGF-1 receptor, insulin receptor and IRS-1/2 in Alzheimer's disease indicate possible resistance to IGF-1 and insulin signalling. *Neurobiol. Ageing* **31**, 224–243 (2010).
74. Massa, S. M. *et al*. Small molecule BDNF mimetics activate TrkB signaling and prevent neuronal degeneration in rodents. *J. Clin. Invest.* **120**, 1774–1785 (2010).
75. *Harvey*, J. Leptin regulation of neuronal excitability and cognitive function. *Curr. Opin. Pharmacol.* **7**, 643–647 (2007).
76. Mirescu, C. & Gould, E. Stress and adult neurogenesis. *Hippocampus* **16**, 233–238 (2006).
77. Mattson, M. P., Perry, T. & Greig, N. H. Learning from the gut. *Nature Med.* **9**, 1113–1115 (2003).
78. Stranahan, A. M. *et al*. Voluntary exercise and caloric restriction enhance hippocampal dendritic spine density and BDNF levels in diabetic mice. *Hippocampus* **19**, 951–961 (2009).
79. Witte, A. V., Fobker, M., Gellner, R., Knecht, S. & Flöel, A. Caloric restriction improves memory in elderly humans. *Proc. Natl Acad. Sci. USA* **106**, 1255–1260 (2009).
80. Porter, D. W., Kerr, B. D., Flatt, P. R., Holscher, C. & Gault, V. A. Four weeks administration of Liraglutide improves memory and learning as well as glycaemic control in mice with high fat dietary-induced obesity and insulin resistance. *Diabetes Obes. Metab.* **12**, 891–899 (2010).

© 2012 Macmillan Publishers Limited. All rights reserved

81. Calabrese, E. J. *et al*. Biological stress response terminology: integrating the concepts of adaptive response and preconditioning stress within a hormetic dose–response framework. *Toxicol. Appl. Pharmacol.* **222**, 122–128 (2007).
82. Xu, X. *et al*. Gene expression atlas of the mouse central nervous system: impact and interactions of age, energy intake and gender. *Genome Biol.* **8**, R234 (2007).
83. Calabrese, V., Cornelius, C., Dinkova-Kostova, A. T., Calabrese, E. J. & Mattson, M. P. Cellular stress responses, the hormesis paradigm, and vitagenes: novel targets for therapeutic intervention in neurodegenerative disorders. *Antioxid. Redox Signal.* **13**, 1763–1811 (2010).
84. Kraft, A. D., Johnson, D. A. & Johnson, J. A. Nuclear factor E2-related factor 2-dependent antioxidant response element activation by tert-butylhydroquinone and sulforaphane occurring preferentially in astrocytes conditions neurons against oxidative insult. *J. Neurosci.* **24**, 1101–1112 (2004).
85. Kim, S. J. *et al.* Curcumin stimulates proliferation of embryonic neural progenitor cells and neurogenesis in the adult hippocampus. *J. Biol. Chem.* **283**, 14497–14505 (2008).
86. Spencer, J. P. The impact of fruit flavonoids on memory and cognition. *Br. J. Nutr.* **104** (Suppl. 3), 40–47 (2010).
87. Roriz-Cruz, M. *et al*. Cognitive impairment and frontal-subcortical geriatric syndrome are associated with metabolic syndrome in a stroke-free population. *Neurobiol. Ageing* **28**, 1723–1736 (2007).
88. Gunstad, J. *et al*. Elevated body mass index is associated with executive dysfunction in otherwise healthy adults. *Compr. Psychiatry* **48**, 57–61 (2007).
89. van den Berg, E., Biessels, G. J., de Craen, A. J., Gussekloo, J. & Westendorp, R. G. The metabolic syndrome is associated with decelerated cognitive decline in the oldest old. *Neurology* **69**, 979–985 (2007).
90. Li, Y., Dai, Q., Jackson, J. C. & Zhang, J. Overweight is associated with decreased cognitive functioning among school-age children and adolescents. *Obesity (Silver Spring)* **16**, 1809–1815 (2008).
91. Huizinga, M. M., Beech, B. M., Cavanaugh, K. L., Elasy, T. A. & Rothman, R. L. Low numeracy skills are associated with higher BMI. *Obesity (Silver Spring)* **16**, 1966–1968 (2008).
92. Sabia, S., Kivimaki, M., Shipley, M. J., Marmot, M. G. & Singh-Manoux, A. Body mass index over the adult life course and cognition in late midlife: the Whitehall II Cohort Study. *Am. J. Clin. Nutr.* **89**, 601–607 (2009).
93. Volkow, N. D. *et al*. Inverse association between BMI and prefrontal metabolic activity in healthy adults. *Obesity (Silver Spring)* **17**, 60–65 (2009).
94. Fergenbaum, J. H. *et al*. Obesity and lowered cognitive performance in a Canadian First Nations population. *Obesity (Silver Spring)* **17**, 1957–1963 (2009).
95. Granholm, A. C. *et al*. Effects of a saturated fat and high cholesterol diet on memory and hippocampal morphology in the middle-aged rat. *J. Alzheimers Dis.* **14**, 133–145 (2008).

Acknowledgements
This work was supported by the Intramural Research Program of the National Institute on Aging.

Competing interests statement
The authors declare no competing financial interests.

© 2012 Macmillan Publishers Limited. All rights reserved