Published Online July 24, 2012

Nutrition, adult hippocampal neurogenesis and mental health

Muhammad Syahrul Anwar Zainuddin and **Sandrine Thuret***

Institute of Psychiatry, Centre for the Cellular Basis of Behaviour, The James Black Centre, King's College London, 125 Coldharbour Lane, London SE5 9NU, UK

Introduction: Over the last 8 years, emerging studies bridging the gap between nutrition and mental health have resolutely established that learning and memory abilities as well as mood can be influenced by diet. However, the mechanisms by which diet modulates mental health are still not well understood.

Sources of data: In this article, a review of the literature was conducted using PubMed to identify studies that provide functional implications of adult hippocampal neurogenesis (AHN) and its modulation by diet.

Areas of agreement: One of the brain structures associated with learning and memory as well as mood is the hippocampus. Importantly, the hippocampus is one of the two structures in the adult brain where the formation of newborn neurons, or neurogenesis, persists.

Areas of controversy: The exact roles of these newborn neurons in learning, memory formation and mood regulation remain elusive.

Growing points: Nevertheless, there has been accumulating evidence linking cognition and mood to neurogenesis occurring in the adult hippocampus. Therefore, modulation of AHN by diet emerges as a possible mechanism by which nutrition impacts on mental health.

Areas timely for developing research: This area of investigation is new and needs attention because a better understanding of the neurological mechanisms by which nutrition affect mental health may lead to novel dietary approaches for disease prevention, healthier ageing and discovery of new therapeutic targets for mental illnesses.

Keywords: adult hippocampal neurogenesis/neural stem cells/diet/nutrition/learning and memory/mood

Accepted: July 2, 2012

**Correspondence address.*
E-mail: sandrine.1.thuret@kcl.ac.uk

British Medical Bulletin 2012; **103**: 89–114
DOI:10.1093/bmb/lds021

Introduction

Recently, diet has emerged as important for mental health as it is for cardiovascular health, cancer risks and longevity. Undeniably, learning and memory abilities as well as mood can be influenced by diet, not only during development, but also during adulthood (reviewed in Gomez-Pinilla[1]). Indeed, a large number of epidemiological studies have suggested a relationship between diet and mental illnesses where inverse associations between diet quality and the common mental disorders, depression and anxiety have been identified and reported in adults.[2–6] Similarly, there is a large body of epidemiological evidence linking diet to cognitive abilities, especially in the ageing population (reviewed in Solfrizzi *et al.*,[7] Kanoski and Davidson[8] and Gu and Scarmeas[9]). Although these studies emphasize an important role of diet on mental health, further work is necessary to establish the mechanisms underlying these behavioural effects.

One of the brain structures associated with learning and memory as well as mood is the hippocampus. Interestingly, the hippocampus is one of the two structures in the adult brain where the formation of newborn neurons, or neurogenesis, persists. Adult hippocampal neurogenesis (AHN) has been linked directly to cognition and mood (reviewed in Zhao *et al.*[10]); therefore, modulation of AHN by diet could emerge as a possible mechanism by which nutrition impacts on mental health. In this article, we give an overview of the functional implications of AHN and we summarize recent findings regarding AHN modulation by diet.

Adult hippocampal neurogenesis

Newborn neurons have been consistently found derived from two privileged areas of the adult brain: the subgranular zone (SGZ) in the dentate gyrus of the hippocampus[11] and the subventricular zone (SVZ) of the lateral ventricles[12] (Fig. 1). Adult neurogenesis has been found in all mammals studied to date, including humans.[13] The process of adult neurogenesis encompasses the proliferation of resident neural progenitor cells and their subsequent differentiation, migration and functional integration into the pre-existing circuitry. During AHN (Fig. 1), neural progenitor cells proliferate in the SGZ and give rise to immature neurons. Many die within 2 weeks, but the surviving neurons then migrate into the molecular layer.[14] The surviving neurons then send axons to the CA3 region and the hilus to form functional synapses with hilar interneurons and CA3 neurons within 3 weeks.[15] Next,

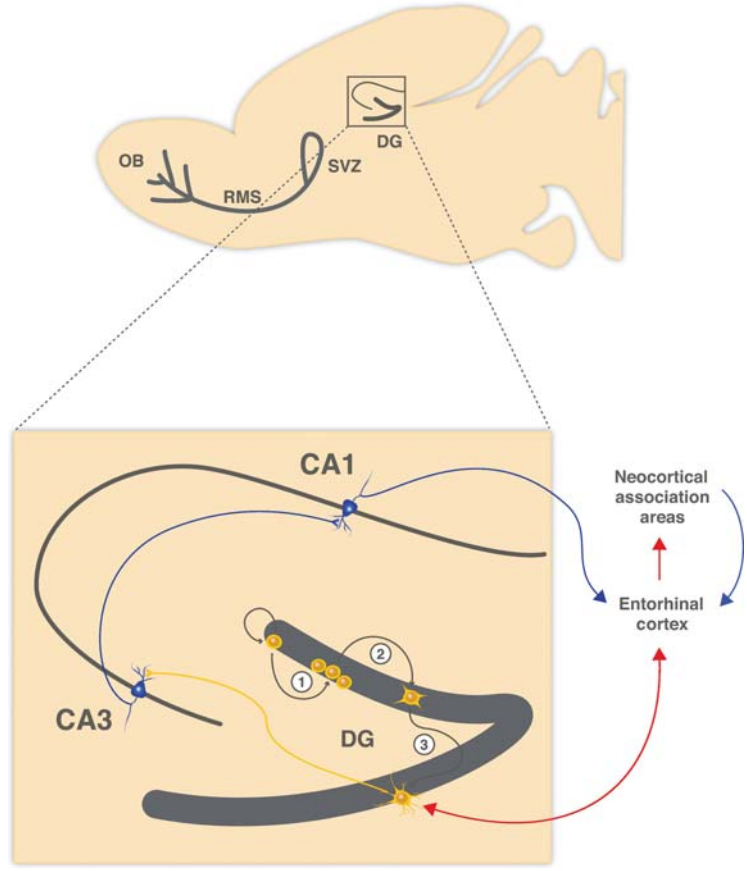

Fig. 1 Schematic illustration of the sagittal view of a rodent brain highlighting the two neurogenic zones of the adult mammalian brain: the SVZ of the lateral ventricles and the SGZ of the dentate gyrus (DG) in the hippocampus. Neurons generated in the SVZ migrate through the rostral migratory stream (RMS) and are incorporated into the olfactory bulb. The hippocampal region contained in the black square is enlarged showing in yellow (1) neural progenitor cells in the SGZ of the dentate gyrus proliferating, (2) migrating into the granule cell layer and (3) maturing into new granule neurons, integrating into the hippocampal circuitry by receiving inputs from the entorhinal cortex, and extend projections into the CA3.

these new neurons start also to receive synaptic inputs from the cortex and are capable of firing action potentials.[16] Therefore, these newly generated neurons become physiologically mature and functionally integrated in the circuit.

The molecular control of AHN is very complex and remains to be fully elucidated. Over the last 10 years, many signals have been implicated in the regulation of AHN. They intervene at the stages of proliferation, differentiation, survival, migration and integration. Growth factors, cytokines, neurotransmitters and hormones are the types of extrinsic factors that have been found to play a role in regulating AHN

and have been reviewed by Mu *et al.*[17] Moreover, AHN is also subject to intrinsic epigenetic regulation such as DNA methylation, histone acetylation and non-coding RNAs. These intrinsic factors controlling AHN have been recently reviewed by Sun *et al.*[18]

Functionality of AHN

As described above, adult-born hippocampal neurons are functional and integrated into the hippocampal circuitry. However, the incorporation of adult-born hippocampal neurons into current concepts of hippocampal network function and behaviour is complex.

Learning and memory

The implication of AHN in learning and memory is supported by some correlative and ablation studies (reviewed in Koehl *et al.*[19]), as well as by computational modelling (reviewed in Aimone *et al.*[20]). AHN varies among different genetic backgrounds in mice and a correlation between the level of hippocampal neurogenesis and the performance in hippocampal-dependent learning tasks is observed between mice of different strains.[21,22] Environment also has a major impact on AHN (this will be discussed in detail later) and changes in neurogenesis induced by the environment correlates with performance in hippocampal-dependent learning tasks. These studies establish only a correlation; therefore, it is possible that other factors such as structural plasticity, neurotrophin or hormone levels also contribute to genetically and environmentally induced changes in hippocampus-dependent learning and memory.

Newborn neurons represent only a small cell population within the adult hippocampus. It is therefore difficult to imagine how such a small number of cells can influence the function of the hippocampus. In order to investigate whether hippocampal neurogenesis is required for hippocampus-dependent learning tasks, a variety of approaches have been taken to reduce or even ablate completely dividing cells in the hippocampus. Blockade of neurogenesis has been achieved with pharmacological, radiological and genetic strategies (reviewed in Koehl *et al.*[19]). Despite mixed results, behavioural evaluation of rodents with reduced AHN has consistently suggested an involvement of hippocampal adult-born neurons in learning and memory (reviewed in Deng *et al.*[23]). Nevertheless, the exact function of hippocampal adult-born neurons in learning and memory process remains elusive and many hypotheses have been proposed: (i) data have already suggested that

hippocampal neurogenesis is involved in pattern separation as it has been shown that new hippocampal neurons are required for discrimination of proximal spatial locations[24] and similar contexts,[25] where pattern separation can be modulated by pattern integration.[26] (ii) The constant turn-over of immature hippocampal neurons suggest that adult-born hippocampal neurons could have a role in temporal association and separation during learning and memory (reviewed in Deng *et al.*[23]), but experimental evidence is needed to support that hypothesis. (iii) Moreover, adult-born hippocampal neurons show enhanced plasticity at 4–6 weeks of age,[27] which make them well suited to encoding new information, as predicted by computational studies (reviewed in Aimone *et al.*[20]). Importantly, it remains unclear whether AHN is involved in the encoding, the consolidation or the recall of memory. Therefore, developing techniques to study the physiology of AHN in awaken behaving animals will be crucial to answer this question. Moreover, the recent non-invasive imaging techniques developed for monitoring AHN in humans[28,29] need to be refined and reproduced to allow the function of AHN to be investigated in humans.

Mood regulation

Recently, it has been proposed that AHN might play a role in mood regulation and in the aetiology of major depression.[30,31] This idea arises from two lines of evidence. The first is that AHN is reduced by stressful experiences, a causal factor in the pathogenesis of major depression. Moreover, AHN is reduced in animal models of depression.[32] The second line of evidence indicates that many treatments for depression have been shown to enhance neurogenesis in laboratory animals; these factors include electroconvulsive therapy[33] and common antidepressant drugs, such as selective serotonin reuptake inhibitors (SSRIs).[34] It was also shown that antidepressants increase AHN in the human dentate gyrus.[35] Notably, other environmental interventions conferring antidepressant-like behaviour such as running, exercise and environmental enrichment also increase AHN (as discussed in detail later). It is also important to note that the effects of SSRIs on neurogenesis are selective for the hippocampus, leaving the ongoing stem-cell proliferation in the SVZ unchanged,[36] suggesting a specificity of the antidepressants to regulate adult neurogenesis in the hippocampus. Finally, in several animal models of depression, disruption of neurogenesis blocks the behavioural efficacy of some antidepressants (reviewed in Samuels and Hen[37]).

One of the mechanisms thought to mediate the reduction in AHN by stress is the elevation of corticosterone by an activated hypothalamic–

pituitary–adrenal (HPA) axis. Indeed, corticosterone decreases cell proliferation, whereas adrenalectomy increases AHN. Moreover, glucocorticoid levels are increased in a variety of stress paradigms, adrenalectomy prevents the stress-induced suppression of AHN (reviewed in Mirescu and Gould[38]) and mice with ablation of AHN showed and increased HPA axis response to an acute stress.[39] Finally, we have recently shown that antidepressants increase human hippocampal neurogenesis by activating the glucocorticoid receptor.[40] Because stimulation of the dentate gyrus can yield an inhibitory effect on the HPA axis,[41] it is possible that adult newborn neurons contribute to hippocampal-dependent negative feedback of the HPA axis.

While there is requirement for AHN in mediating some of the effect of antidepressants, decreasing AHN alone is not sufficient to drive a depression-like phenotype (reviewed in Samuels and Hen[37]) and whether specific manipulations that increase AHN alone results in a non-depressed phenotype remains to be tested. Therefore, the current AHN hypothesis of depression can only be retained as at least partially true. It will be critical for future work to determine how the addition of new neurons to the dentate gyrus is involved in mediating the effect of antidepressant.

AHN in CNS pathologies

AHN responds to neurodegenerative diseases such as Alzheimer's, Parkinson's and Huntington's diseases. Conflicting observations have been reported on the level of AHN in Alzheimer's disease various mouse models and human studies. Data can be found for both increased and decreased AHN depending on the model and stage of the disease studied (reviewed in Mu and Gage[42]). Mouse models of Parkinson's disease over-expressing the wild-type human α-synuclein show a decrease in the survival rate of newborn hippocampal neurons (reviewed in Thompson *et al.*[43]), and studies have reported a decrease in AHN in rodent models of Huntington's disease (reviewed in Winner *et al.*[44]). AHN is also influenced by many other pathological conditions and is increased, for example, in epilepsy[45] and stroke.[46] Whereas it is decreased in HIV infection[47] and the integration of newborn neurons is disrupted by CNS inflammation.[48] It is apparent that AHN is influenced by neurological diseases or/and that disruption of AHN might contribute to their progression. However, further studies are needed to understand the roles and consequences of AHN changes in pathological events. Realistically, taking into account the low number of newly generated adult-born neuron in the dentate gyrus compared with the large number of dying neurons in such CNS pathology in different

brain regions, it is unlikely that these newly generated neurons in the dentate gyrus will be able to achieve total repair. However, given the crucial role of AHN in mood as well as in learning and memory, it is possible that stimulating AHN might have some therapeutic effects.

Environmental modulation of AHN

The environment and diverse physiological conditions can significantly alter AHN (Fig. 2). Ageing is associated with a decreased AHN, and aged rodents display impaired learning and memory abilities (reviewed in Klempin and Kempermann[49]), and it has been recently suggested that decline in AHN and cognitive impairments observed during ageing in mice are in part attributed to changes in blood-borne factors.[50] Stress is also a major negative modulator of AHN, which can induce depressive behaviour (reviewed in Mirescu and Gould[38]). Accordingly, social isolation is a stressful experience in rodents and has been shown to negatively regulate AHN and learning abilities.[51]

Likewise, sleep has recently appeared as another important modulator of AHN. Prolonged restriction or disruption of sleep leads to a

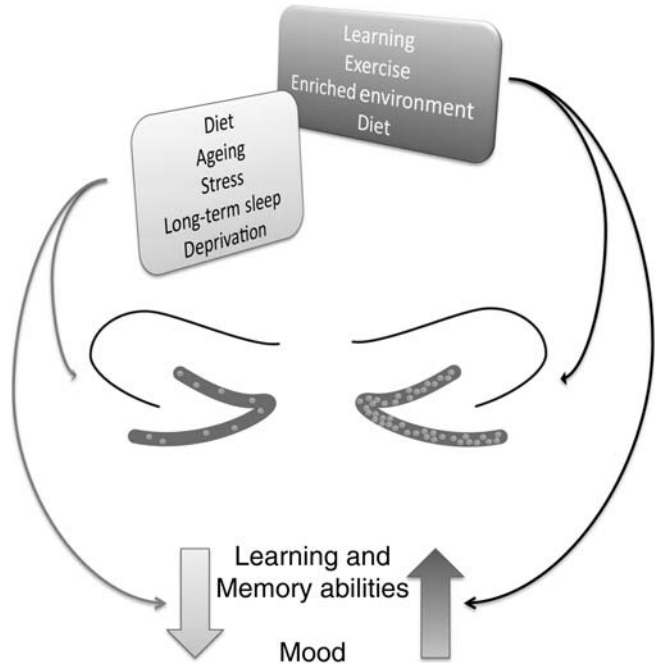

Fig. 2 Overview of physiological and environmental modulation of AHN and its impact on learning and memory abilities and mood. The grey dots represent newborn neurons in the dentate gyrus of the hippocampus.

major decrease in AHN (reviewed in Meerlo *et al.*[52]). Stress and glucocorticoids have initially been proposed to be the mediators of the harmful effects of sleep disruption and deprivation. However, a number of studies clearly show that prolonged sleep loss can inhibit AHN independently of adrenal stress hormones (reviewed in Meerlo *et al.*[52]), circadian disruption or melatonin suppression.[53] Interestingly, sleep deprivation (SD) also disturbs memory formation (reviewed in Stickgold[54]) and this could suggest that promoting AHN may be a mechanism by which sleep supports learning and memory processes. Conversely, while prolonged disruption of sleep decrease AHN, short-term or acute 1-night (12 h) SD up-regulates AHN by significantly increasing cell proliferation and the total number of surviving cells.[55] Interestingly, one night SD has been clinically proven to produce transient antidepressogenic effect and has been used in the treatment of patients with primary depression and bipolar disorders (reviewed in Wu and Bunney[56]). However, a recent report concluded that this short-term (12 h) SD only transiently increases hippocampal progenitor cells proliferation by altering the cell cycle and that the negative effect of SD on AHN begins shortly after more than 12 h of SD.[57] In addition, sustained sleep fragmentation has also been found to reduce AHN and caused delayed changes in cognitive function in rats.[58]

Equally, pregnancy[59] and maternal experiences[60] in rodent also have a negative impact on AHN. These are associated with a decline in performance in hippocampus-dependent tasks during pregnancy. Interestingly, the reduced AHN may be an outcome of pregnancy-induced changes in the immune response rather than of hormonal changes.[59] Whereas during the postpartum period, the decrease in AHN is dependent on elevated basal glucocorticoid levels;[60] it is therefore attractive to postulate that decreased AHN during the postpartum period could be a link to postpartum depression experienced by some women.

On the contrary, voluntary running and enriched environment are associated with enhanced AHN and spatial learning abilities. Running increases the proliferation,[61] whereas enriched environment increase the survival rate of newborn neurons.[62,63] Both enriched environment and running lead to increased synaptic formation and up-regulation of neurotrophins; however, they most likely act via dissociable pathways. Olson *et al.*[64] suggest that exercise leads to the convergence of key somatic and cerebral factors in the dentate gyrus to induce cell proliferation, whereas enriched environment-induced cell survival by cortical restructuring as a means of promoting survival. The regulation of AHN by neural activity suggests that learning might also induce the activation of newborn neurons and enhance their survival and incorporation into circuits. Indeed, AHN is increased upon learning, but only

by learning tasks that depend on the hippocampus (reviewed in Leuner *et al.*[65]).

Conveniently, the detrimental effect of many negative regulators of AHN can be offset by running or enriched environment in rodents, including ageing,[21] stress/depression (reviewed in Brene *et al.*[66]) and pregnancy.[59] However, the molecular mechanisms by which physiological and environmental changes modulate AHN are currently poorly understood.

Dietary modulation of AHN

Diet is another important environmental factor that significantly modulates AHN. Nutrition can impact on AHN at four different levels: calorie intake, meal frequency, meal texture and meal content (Fig. 3). Not only do these four parameters modulate AHN in rodents (reviewed in Table 1), but independent rodent studies and intervention or epidemiological studies in humans have shown that these same dietary parameters modulate cognitive performance and mood (reviewed in Table 2).

Calorie intake, meal frequency and texture

Calorie restriction (CR) has been suggested to extend lifespan, improve behavioural outcomes in some experimental animal models of neurodegenerative disorders and enhance spatial learning (reviewed in Mattson[67]). It has been shown in rodents that a reduction in calorie intake of 30–40% increases AHN.[68] Further rodent studies have postulated that, as a type of metabolic stress, CR creates favourable environment for facilitating neuronal plasticity, enhancing cognitive function, stimulating AHN and regulating inflammatory response (reviewed in

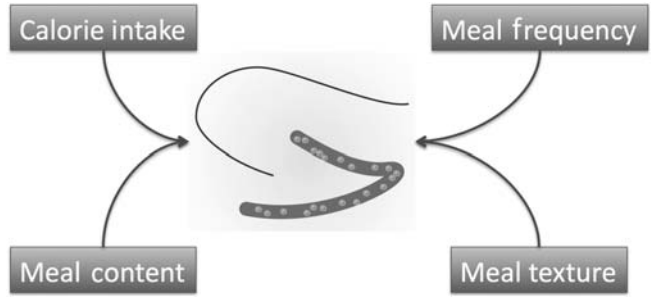

Fig. 3 Overview of the four different levels at which diet impacts on AHN. The grey dots represent newborn neurons in the dentate gyrus of the hippocampus.

Table 1 Modulation of AHN by diet

Diet	Effect on AHN	Study models	References
Calorie restriction	Increased survival	Mouse	68–70,125–127
Omega 3 fatty acids	Increased	Rat	77,87,128–130
Flavonoids	Increased proliferation	Rat chronically stressed	88
	Increased proliferation	Mice	131,132
Blueberry	Increased proliferation	Rat	133
Curcumin low concentrations	Increased proliferation	Mouse	91,93–95
Retinoic acid excess	Decreased proliferation	Mouse	106
Vitamin A deficiency	Decreased proliferation (rescued with RA)	Rat	108
Thiamine deficiency	Decreased proliferation/survival	Mouse	134,135
Zinc deficiency	Decreased proliferation/survival	Rat male	100,103,136
Folic acid	Increased proliferation	Rat	137
Folate deficiency	Inhibited proliferation	Mouse	138
Increased homocystein	Inhibited proliferation	Mouse	139,140
High fat	Decreased proliferation No change	Rat male Rat female	115,116
Soft diet	Decreased proliferation	Rat	73,76
Caffeine at physiologically relevant doses	Decreased proliferation	Mouse	114
Caffeine at supraphysiological doses	Increased proliferation/ decreased survival	Mouse	113
Caffeine low doses chronically	Decreased proliferation	Rat	
Ethanol	Decreased proliferation	Rat	141,142
	Decreased proliferation	Mouse	143
Capsaicin	Decreased proliferation	Mice	144
Resveratrol	Increased proliferation	Mice	97,98
High sugar (fructose)	Decreased proliferation	Male rat	117
Vitamin E deficiency	Increased proliferation	Rat	145–147
Vitamin E high doses	Increased survival	Rat	148

Park and Lee[69]). These distinct effects of CR on the brain were attributed to CR-induced expressions of factors such as heat shock protein, neurotrophic factors, cytokines and Sirtuin1 (SIRT1) (reviewed in Qiu *et al.*[70]). Interestingly, neurothrophic factors such as brain-derived neurotrophic factor (BDNF) through its signalling pathway involving TrkB has been implicated in the control of cell proliferation and survival. Other neurotrophic factor such as neurotrophin-3 (NT-3) and cytokines such as interferon-γ have also been suggested to up-regulate neurogenesis upon CR by promoting neuronal differentiation (reviewed in Park and Lee[69]). Noticeably, an interventional trial on memory performance in healthy human elderly subjects has demonstrated the beneficial effects of caloric restriction at 30% for 3 months, although the serum level of BDNF remained unchanged.[71]

Table 2 Modulation of learning and memory and depressive behaviour by diet

Diet	Effect on depressive behaviour	Effect on learning and memory	Study models	References
Caloric/dietary restriction		Enhanced spatial learning	Rat (aged)	149
intermittent fasting		Increased learning and motor performance	Mouse	150
		Increased learning consolidation	Mouse	151
		Enhanced verbal memory	Human (healthy elderly)	71
		Improved spatial learning	Rat (traumatic brain injury)	152
	Improved		Mice (depression model)	153
Omega 3 fatty acids	Improved		Human (bipolar)	85,86
	Delayed onset		Human (bipolar)	154
	Improved		Human (bipolar)	155
	No benefit		Human (bipolar)	156
		Improved spatial memory	Mouse (Alzheimer's model)	157
		Improved acquisition and retention	Mouse (aged)	158
		Improved learning performance	Rat (diabetic)	159
	Improved mood state	No effect	Human (recovered from depression)	160
Flavonoids	Improved		Rat	89
		Improved	Various Species	For review[161,162]
		Improved	Rodent Species	For review[162–164]
		Improved	Rat	165–169
Blueberry		Increased spatial memory	Rat	90
		Improved	Human (old age)	170
		Improved	Mice	171
Curcurmin		Improved cognitive performance	Human	92
		Improved cognitive performance	Rat	94,172
		Improve spatial memory and learning	Rat	173,174
		Improved	Mice	175,176
		Improved	Rat (Alzheimer's disease)	177
	Improved		Rat	96,178–180
	Improved		Mice	181
Retinoic acid excess	Improved		Mouse	107
Vitamin A/retinoid deficiency		Impaired spatial learning and memory	Rat	182
		Impaired relational memory	Mouse	183
Zinc	Improved		Rodent, human	For review[102]

Continued

Table 2 *Continued*

Diet	Effect on depressive behaviour	Effect on learning and memory	Study models	References
High fat		Decreased spatial learning	Rat	118
		Decreased learning and memory and Increased risk for dementia	Rat	184
		Impair spatial learning	Mice	185
	Exacerbates		Rat (depression model)	186
		Increased susceptibility to spatial learning deficit	Rat	187,188
		Impaired memory	Rat	189
High sugar		Impaired spatial learning	Rat	190
		Impaired spatial learning	Rat	191
		Impaired	Rat	192
Low glucose (extracellular)		Impaired memory	Rat (aged)	193
Soft diet		Impaired	Rat (Alzheimer's model)	74
		Impaired learning and memory	Aged animals	For review[194]
		Impaired spatial learning and memory	Mice (female albino)	195
Caffeine		Improved object recognition	Mouse	196
	Reduced risk		Human	197
	Reduced risk		Human	198
		Improved cognitive function	Rat	199
Ethanol		Improved associative learning with moderate chronic consumption	Mouse	200
		Impaired	Human	201
	Induced depressive behaviour		Rat	202
Capsaicin		No effect	Mice (young)	144
Resveratrol	Improved		Mice (despair test)	99
		Improved cognitive function	Mice	98
Vitamin E deficiency	Associated risk		Human (depression)	203
	Associated risk		Human (depression)	204
	No association		Human (aged adult with depression)	205
Vitamin E		Protective effect	Rat (brain injury)	206
		Delayed memory loss	Mouse	99

More recently, we have found that independently of calorie intake, meal frequency is a key player in modulating AHN. Indeed, without modifying significantly calorie intake, extending time between meals increases AHN in mice. It also changes extensively the level of expression of specific genes expressed in the hippocampus and correlates with performance in hippocampus-dependent tasks and mood.[72] However, further studies are ongoing to understand the mechanisms by which meal frequency modulates AHN and mental health.

Intriguingly, food texture also has an effect on AHN; rats fed with a soft diet, as opposed to a solid/hard diet, exhibit decreased proliferation of hippocampal progenitor cells. The authors hypothesize that chewing resulting in cell proliferation is related to corticosterone levels.[73] Interestingly, independent studies have shown impairment in learning and memory abilities in rodent consuming similar soft diets.[74,75] Another study in mice indicated that insufficient mastication activity during development as well as ageing restrains AHN in adulthood.[76] Indeed, if chewing plays a role in modulating AHN, these data could be particularly relevant to the ageing population with cognitive decline where dental weakening might limit chewing ability.

Omega-3 polyunsaturated fatty acids

Meal content offers the most flexibility to regulate AHN as a variety of bioactives/nutrients have been identified as potential modulators. For example, the Omega-3 polyunsaturated fatty acids (PUFA) docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), mostly available from oily fish, have long been associated with significant neuroprotective effects in ageing.[77–79] Indeed, a diet rich in Omega-3 fatty acids is associated with a prevention of cognitive decline,[80] whereas low intake of Omega-3 fatty acids is associated with several forms of cognitive decline in the elderly.[81] Moreover, rodents deficient for Omega-3 fatty acids have shown impaired performance in spatial memory tasks that could be rescued after dietary replenishment with Omega-3 fatty acids.[82] Su suggested that AHN is one of the mediators of the effects of DHA on learning and memory. Indeed, DHA treated aged-rat had enhanced long-term potentiation and synaptic protein expression as well as increased dendritic spine density and neurogenesis in the hippocampus.[83] Interestingly, the omega-3 fatty acids EPA and DHA are known endogenous ligands of retinoid X receptors (RXRs). RXRs are transcription factors involved in many cellular processes, such as proliferation and neuronal differentiation. Therefore, retinoid signalling might mediate the effects of DHA on AHN.[77]

Furthermore, it has been reported that Omega-3 fatty acid concentrations are lower in patients with depression,[84] and Omega-3 fatty acid supplementation has even emerged as a potential treatment for depression.[85,86] In rodents, a mix of PUFA diet normalizes AHN and ameliorates anxiety-related symptoms.[87] However, further studies are needed to confirm that the effects of Omega-3 fatty acids on mood are mediated by AHN.

Polyphenols

Another well-studied family of nutrients are polyphenols. Among them are flavonoids, which are enriched in foods such as cocoa and blueberries. Flavonoids have been shown to increase AHN in chronically stressed rats, and the authors hypothesized that this is mediated by BDNF.[88] Moreover, independent studies have shown that treatment with flavonoids improves symptoms of depression[89] and improves spatial working memory in ageing rats via the activation of transcription factor CREB and production of BDNF in the hippocampus.[90]

Other dietary polyphenols such as curcumin and resveratrol have also been found to regulate AHN. Curcumin, which is a natural non-flavonoid phenolic component of the turmeric plant (*Curcuma longa*), has been widely used as spice and cooking ingredient such in yellow curry as well as a food preservative. Recently, curcumin has been associated with increased AHN in rodents[91] and epidemiological studies have reported better cognitive performance from curry consumption in ageing populations.[92] Moreover, *in vitro* studies have shown that curcumin exerted biphasic effects on progenitor cells; high concentrations were cytotoxic, whereas low concentrations stimulated cell proliferation. Curcumin also activates extracellular signal-regulated kinases (ERKs) and p38 kinases, cellular signal transduction pathways known to be involved in the regulation of neuronal plasticity and stress responses.[91] More recently, the effects of curcumin on AHN and cognition were attributed to up-regulation of a transcriptional network regulating neuronal progenitor cells proliferation and survival as well as neuronal differentiation.[93] Curcumin has also been shown to reverse impaired AHN, cognition, memory deficits and neuronal plasticity induced by chronic stress in rats. These effects were as potent as the antidepressant imipramine and could be partly mediated by normalizing the corticosterone response, resulting in down-regulation of the ρCamKII and glutamate receptor levels.[94,95] It is also interesting to note that in a chronic unpredictable mild stress study on rats, curcumin also exert antidepressant-like effect on serotonergic receptor-coupled AC-cAMP pathway.[96]

Resveratrol, another non-flavonoid polyphenols found abundance in red wine, nut and berries, has been reported to improve hippocampal atrophy in chronic fatigue mice model by enhancing AHN, improving BDNF-mRNA expression in the hippocampus and inhibiting neuronal as well as expression of hippocampal acetylated ρ53.[97] It is also suggested that resveratrol improves cognitive function in mice by increasing hippocampal insulin-like growth factor-1 (IGF-1) via sensory neuron stimulation in the gastrointestinal tract.[98] Another rodent study reported that resveratrol significantly increase serotonin and noradrenaline levels and dose-dependently inhibited monoamine oxidase A activity indicating an antidepressant-like effect involving serotonergic and noradrenergic activation.[99]

Minerals and vitamins

Minerals also play an important role in modulating AHN. For example, dietary zinc deficiency has been shown to inhibit AHN[100] and to induce depression in rodents,[101] whereas independent intervention studies have shown efficacy of zinc supplement to improve symptoms of depression (for review, see Szewczyk *et al.*[102]). Corniola *et al.*[100] hypothesized that zinc plays a role in AHN by regulating p53-dependent molecular mechanisms that control neuronal precursor cell proliferation and survival. Meanwhile, it has been reported that the apoptosis proteins, including Fas, Fas ligand (FasL), apoptosis-inducing factor and caspase-3 were significantly activated in zinc-deficient mouse hippocampus.[103] It is therefore suggested that chronic zinc-deficient diet impaired AHN by reducing neural precursor cell proliferation and differentiation as well as increasing neuronal apoptosis (reviewed in Levenson and Morris[104]). In addition, ERK1/2 has also been implicated to the disruptions in neurodevelopment associated with zinc deficiency. Indeed, ERK1/2 deficits in mice lead to impairment in neurogenesis and performance of learning and memory via perturbation of neural progenitor cell proliferation and cell death regulation (reviewed in Nuttall and Oteiza[105]).

Unbalanced vitamins intake can have a detrimental effect on AHN and mental health. For instance, retinoic acid (RA), the active form of the nutrient vitamin A, causes negative effects in excess but also by its absence: excess in RA will diminish AHN, lead to depressive behaviour and impaired spatial learning in rodents.[106,107] Similarly, a deficiency in RA will lead to similar negative effects on AHN and mental health, but importantly these effects can be reversed by re-establishing a normal level of RA.[108] RA effect on AHN are mediated via specific RA receptors (RARs) and RXR which are strongly expressed in the adult

hippocampus.[109] RA has also been found to induce the differentiation of embryonic stem cells into neuronal lineages *in vitro*.[110,111] In another study using adult mice, Jacobs *et al*. reported that the depletion of RA leads to a significant decrease in neuronal differentiation within the granular cell layer of the dentate gyrus and reduced cell survival. Metabolic targets of retinoid-induced genes have been identified and it has been suggested that lipid transporters, CD-36 and ABCA-1, the lipogenic master regulator SREBP1c as well as components of the Wnt signalling pathway may play a role in down-regulating AHN.[112] Further studies are needed to differentiate the molecular mechanisms leading to the dose–response of RA on AHN.

Caffeine, fat and sugar intake

Caffeine consumed at low doses chronically decreases AHN and performance in hippocampus-dependent learning tasks in rodents.[113] Whereas at supra-physiological doses, there is an increase in proliferation of neuronal precursors. However, neurons induced in response to supra-physiological levels of caffeine have a lower survival rate than control cells and increased proliferation does not yield an increase in AHN.[114]

Diets with high-fat content, independent of calorie intake, impair AHN in male rats. The authors hypothesize that high dietary fat intake disrupt AHN through an increase in serum corticosterone levels, and that males would be more vulnerable than females.[115] In addition, another study reported that high-fat diet adversely affected neural progenitor cells proliferation and AHN by increasing the level of malondialdehyde (MDA) and decreasing BDNF level in the hippocampus. High level of MDA indicated a higher lipid peroxidation rate, thus resulted in toxic effect on progenitor cells reducing their proliferation.[116] In accordance with high-fat diet, high sugar diet has also been reported to reduce AHN in rats. A reduction in AHN was accompanied by increased apoptosis and increased circulating level of tumour necrosis factor-α (TNF-α); hence, it was suggested that impairment of AHN was mediated by TNF-α-induced apoptosis.[117] Rat fed on a diet high in saturated fats and refined sugar performed significantly worse on spatial learning and has been associated with high oxidative stress and decreased BDNF levels.[118]

All together, corticosterone and BDNF levels as well as ERKs activation emerge as common denominators of dietary modulated AHN; however, there are likely to be additional mediators. For example, further studies will need to be done to investigate if diet modulates AHN by modifying its environment. Indeed, the microenvironments of

the SGZ and SVZ, known as the neurogenic niche, provide specific factors that are permissive for the differentiation and integration of new neurons (reviewed in Zhao *et al.*[10]). The vasculature[119] and astrocytes[120] are important constituents of the neurogenic niche and interestingly flavanol-rich foods can positively enhance cortical blood flow[121,122] and are regulators of astrocytic signalling pathways and gene expression.[123] Such changes in the neurogenic niche in response to flavanols might underpin cognitive improvements through the promotion of AHN. Future studies will not only have to refine the molecular and cellular mechanisms by which food intake influences AHN, but also consider the role of epigenetic mechanisms. Undeniably, there is evidence that epigenetic mechanisms underlie both changes in AHN[45] and in gene expression in response to diet.[124] Forthcoming research will require investigating whether diet can modulate AHN through epigenetic changes, such as DNA methylation, histone acetylation and non-coding RNAs.

Conclusion and perspectives

It is now firmly established that nutrition has an impact on mental health. It is also becoming more evident that AHN affects cognition and mood. Therefore, AHN is rising as a likely mediator of the effect of diet on cognition and mood. However, further studies are required to confirm that AHN does mediate the effect of certain diet on mental health, and additional investigations are essential to understand the mechanisms by which diet modulate AHN. Thereafter, modulating AHN by diet could be a strategy of choice to prevent cognitive decline during ageing as well as to counteract the effect of stress and prevent depression.

Acknowledgements

The author would like to thank Gisele Dias for her contribution to the bibliography and Clemens Hackl for his contribution to the original illustrations.

Funding

This work was supported by the Research Councils UK, the Psychiatry Research Trust, the Welton Foundation and the Malaysian trust Council MARA.

References

1 Gomez-Pinilla F. Brain foods: the effects of nutrients on brain function. *Nat Rev Neurosci* 2008;**9**:568–78.
2 Jacka FN, Kremer PJ, Berk M *et al*. A prospective study of diet quality and mental health in adolescents. *PLoS One* 2011;**6**:e24805.
3 Jacka FN, Pasco JA, Mykletun A *et al*. Association of Western and traditional diets with depression and anxiety in women. *Am J Psychiatry* 2010;**167**:305–11.
4 Nanri A, Kimura Y, Matsushita Y *et al*. Dietary patterns and depressive symptoms among Japanese men and women. *Eur J Clin Nutr* 2010;**64**:832–9.
5 Sanchez-Villegas A, Delgado-Rodriguez M, Alonso A *et al*. Association of the Mediterranean dietary pattern with the incidence of depression: the Seguimiento Universidad de Navarra/University of Navarra follow-up (SUN) cohort. *Arch Gen Psychiatry* 2009;**66**:1090–8.
6 Akbaraly TN, Brunner EJ, Ferrie JE *et al*. Dietary pattern and depressive symptoms in middle age. *Br J Psychiatry* 2009;**195**:408–13.
7 Solfrizzi V, Frisardi V, Seripa D *et al*. Mediterranean diet in predementia and dementia syndromes. *Curr Alzheimer Res* 2011;**8**:520–42.
8 Kanoski SE, Davidson TL. Western diet consumption and cognitive impairment: links to hippocampal dysfunction and obesity. *Physiol Behav* 2011;**103**:59–68.
9 Gu Y, Scarmeas N. Dietary patterns in Alzheimer's disease and cognitive aging. *Curr Alzheimer Res* 2011;**8**:510–9.
10 Zhao C, Deng W, Gage FH. Mechanisms and functional implications of adult neurogenesis. *Cell* 2008;**132**:645–60.
11 Kempermann G, Gage FH. Neurogenesis in the adult hippocampus. *Novartis Found Symp* 2000;**231**:220–35; discussion 235–41, 302–6.
12 Alvarez-Buylla A, Seri B, Doetsch F. Identification of neural stem cells in the adult vertebrate brain. *Brain Res Bull* 2002;**57**:751–8.
13 Eriksson PS, Perfilieva E, Bjork-Eriksson T *et al*. Neurogenesis in the adult human hippocampus. *Nat Med* 1998;**4**:1313–7.
14 Kempermann G, Gast D, Kronenberg G *et al*. Early determination and long-term persistence of adult-generated new neurons in the hippocampus of mice. *Development* 2003;**130**:391–9.
15 Toni N, Laplagne DA, Zhao C *et al*. Neurons born in the adult dentate gyrus form functional synapses with target cells. *Nat Neurosci* 2008;**11**:901–7.
16 van Praag H, Schinder AF, Christie BR *et al*. Functional neurogenesis in the adult hippocampus. *Nature* 2002;**415**:1030–4.
17 Mu Y, Lee SW, Gage FH. Signaling in adult neurogenesis. *Curr Opin Neurobiol* 2010;**20**:416–23.
18 Sun J, Sun J, Ming GL *et al*. Epigenetic regulation of neurogenesis in the adult mammalian brain. *Eur J Neurosci* 2011;**33**:1087–93.
19 Koehl M, Abrous DN. A new chapter in the field of memory: adult hippocampal neurogenesis. *Eur J Neurosci* 2011;**33**:1101–14.
20 Aimone JB, Gage FH. Modeling new neuron function: a history of using computational neuroscience to study adult neurogenesis. *Eur J Neurosci* 2011;**33**:1160–9.
21 Kempermann G, Gast D, Gage FH. Neuroplasticity in old age: sustained fivefold induction of hippocampal neurogenesis by long-term environmental enrichment. *Ann Neurol* 2002;**52**:135–43.
22 Thuret S, Toni N, Aigner S *et al*. Hippocampus-dependent learning is associated with adult neurogenesis in MRL/MpJ mice. *Hippocampus* 2009;**19**:658–69.
23 Deng W, Aimone JB, Gage FH. New neurons and new memories: how does adult hippocampal neurogenesis affect learning and memory? *Nat Rev Neurosci* 2010;**11**:339–50.
24 Clelland CD, Choi M, Romberg C *et al*. A functional role for adult hippocampal neurogenesis in spatial pattern separation. *Science* 2009;**325**:210–3.
25 Tronel S, Belnoue L, Grosjean N *et al*. Adult-born neurons are necessary for extended contextual discrimination. *Hippocampus* 2010;**22**:292–8.

26 Aimone JB, Wiles J, Gage FH. Computational influence of adult neurogenesis on memory encoding. *Neuron* 2009;**61**:187–202.
27 Ge S, Yang CH, Hsu KS *et al*. A critical period for enhanced synaptic plasticity in newly generated neurons of the adult brain. *Neuron* 2007;**54**:559–66.
28 Kesner RP. A behavioral analysis of dentate gyrus function. *Prog Brain Res* 2007;**163**:567–76.
29 Manganas LN, Zhang X, Li Y *et al*. Magnetic resonance spectroscopy identifies neural progenitor cells in the live human brain. *Science* 2007;**318**:980–5.
30 Becker S, Wojtowicz JM. A model of hippocampal neurogenesis in memory and mood disorders. *Trends Cogn Sci* 2007;**11**:70–6.
31 Vollmayr B, Mahlstedt MM, Henn FA. Neurogenesis and depression: what animal models tell us about the link. *Eur Arch Psychiatry Clin Neurosci* 2007;**257**:300–3.
32 Dranovsky A, Hen R. Hippocampal neurogenesis: regulation by stress and antidepressants. *Biol Psychiatry* 2006;**59**:1136–43.
33 Scott BW, Wojtowicz JM, Burnham WM. Neurogenesis in the dentate gyrus of the rat following electroconvulsive shock seizures. *Exp Neurol* 2000;**165**:231–6.
34 Malberg JE, Eisch AJ, Nestler EJ *et al*. Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. *J Neurosci* 2000;**20**:9104–10.
35 Boldrini M, Underwood MD, Hen R *et al*. Antidepressants increase neural progenitor cells in the human hippocampus. *Neuropsychopharmacology* 2009;**34**:2376–89.
36 Encinas JM, Vaahtokari A, Enikolopov G. Fluoxetine targets early progenitor cells in the adult brain. *Proc Natl Acad Sci USA* 2006;**103**:8233–8.
37 Samuels BA, Hen R. Neurogenesis and affective disorders. *Eur J Neurosci* 2011;**33**:1152–9.
38 Mirescu C, Gould E. Stress and adult neurogenesis. *Hippocampus* 2006;**16**:233–8.
39 Schloesser RJ, Manji HK, Martinowich K. Suppression of adult neurogenesis leads to an increased hypothalamo–pituitary–adrenal axis response. *Neuroreport* 2009;**20**:553–7.
40 Anacker C, Zunszain PA, Cattaneo A *et al*. Antidepressants increase human hippocampal neurogenesis by activating the glucocorticoid receptor. *Mol Psychiatry* 2011;**16**:738–50.
41 Dunn JD, Orr SE. Differential plasma corticosterone responses to hippocampal stimulation. *Exp Brain Res* 1984;**54**:1–6.
42 Mu Y, Gage FH. Adult hippocampal neurogenesis and its role in Alzheimer's disease. *Mol Neurodegener* 2011;**6**:85.
43 Thompson A, Boekhoorn K, Van Dam AM *et al*. Changes in adult neurogenesis in neurodegenerative diseases: cause or consequence? *Genes Brain Behav* 2008;**7**(Suppl. 1):28–42.
44 Winner B, Kohl Z, Gage FH. Neurodegenerative disease and adult neurogenesis. *Eur J Neurosci* 2011;**33**:1139–51.
45 Jessberger S, Nakashima K, Clemenson GD Jr *et al*. Epigenetic modulation of seizure-induced neurogenesis and cognitive decline. *J Neurosci* 2007;**27**:5967–75.
46 Urbach A, Redecker C, Witte OW. Induction of neurogenesis in the adult dentate gyrus by cortical spreading depression. *Stroke* 2008;**39**:3064–72.
47 Okamoto S, Kang YJ, Brechtel CW *et al*. HIV/gp120 decreases adult neural progenitor cell proliferation via checkpoint kinase-mediated cell-cycle withdrawal and G1 arrest. *Cell Stem Cell* 2007;**1**:230–6.
48 Jakubs K, Bonde S, Iosif RE *et al*. Inflammation regulates functional integration of neurons born in adult brain. *J Neurosci* 2008;**28**:12477–88.
49 Klempin F, Kempermann G. Adult hippocampal neurogenesis and aging. *Eur Arch Psychiatry Clin Neurosci* 2007;**257**:271–80.
50 Villeda SA, Luo J, Mosher KI *et al*. The ageing systemic milieu negatively regulates neurogenesis and cognitive function. *Nature* 2011;**477**:90–4.
51 Lu L, Bao G, Chen H *et al*. Modification of hippocampal neurogenesis and neuroplasticity by social environments. *Exp Neurol* 2003;**183**:600–9.
52 Meerlo P, Mistlberger RE, Jacobs BL *et al*. New neurons in the adult brain: the role of sleep and consequences of sleep loss. *Sleep Med Rev* 2009;**13**:187–94.
53 Mueller AD, Mear RJ, Mistlberger RE. Inhibition of hippocampal neurogenesis by sleep deprivation is independent of circadian disruption and melatonin suppression. *Neuroscience* 2011;**193**:170–81.
54 Stickgold R. Sleep-dependent memory consolidation. *Nature* 2005;**437**:1272–8.

55 Grassi Zucconi G, Cipriani S, Balgkouranidou I *et al*. 'One night' sleep deprivation stimulates hippocampal neurogenesis. *Brain Res Bull* 2006;**69**:375–81.
56 Wu JC, Bunney WE. The biological basis of an antidepressant response to sleep deprivation and relapse: review and hypothesis. *Am J Psychiatry* 1990;**147**:14–21.
57 Junek A, Rusak B, Semba K. Short-term sleep deprivation may alter the dynamics of hippocampal cell proliferation in adult rats. *Neuroscience* 2010;**170**:1140–52.
58 Sportiche N, Suntsova N, Methippara M *et al*. Sustained sleep fragmentation results in delayed changes in hippocampal-dependent cognitive function associated with reduced dentate gyrus neurogenesis. *Neuroscience* 2010;**170**:247–58.
59 Rolls A, Schori H, London A *et al*. Decrease in hippocampal neurogenesis during pregnancy: a link to immunity. *Mol Psychiatry* 2008;**13**:468–9.
60 Leuner B, Mirescu C, Noiman L *et al*. Maternal experience inhibits the production of immature neurons in the hippocampus during the postpartum period through elevations in adrenal steroids. *Hippocampus* 2007;**17**:434–42.
61 van Praag H, Kempermann G, Gage FH. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nat Neurosci* 1999;**2**:266–70.
62 Kempermann G, Kuhn HG, Gage FH. More hippocampal neurons in adult mice living in an enriched environment. *Nature* 1997;**386**:493–5.
63 Tashiro A, Makino H, Gage FH. Experience-specific functional modification of the dentate gyrus through adult neurogenesis: a critical period during an immature stage. *J Neurosci* 2007;**27**:3252–9.
64 Olson AK, Eadie BD, Ernst C *et al*. Environmental enrichment and voluntary exercise massively increase neurogenesis in the adult hippocampus via dissociable pathways. *Hippocampus* 2006;**16**:250–60.
65 Leuner B, Gould E, Shors TJ. Is there a link between adult neurogenesis and learning? *Hippocampus* 2006;**16**:216–24.
66 Brene S, Bjornebekk A, Aberg E *et al*. Running is rewarding and antidepressive. *Physiol Behav* 2007;**92**:136–40.
67 Mattson MP. Neuroprotective signaling and the aging brain: take away my food and let me run. *Brain Res* 2000;**886**:47–53.
68 Lee J, Seroogy KB, Mattson MP. Dietary restriction enhances neurotrophin expression and neurogenesis in the hippocampus of adult mice. *J Neurochem* 2002;**80**:539–47.
69 Park HR, Lee J. Neurogenic contributions made by dietary regulation to hippocampal neurogenesis. *Ann N Y Acad Sci* 2011;**1229**:23–8.
70 Qiu G, Liu S, So KF. Dietary restriction and brain health. *Neurosci Bull* 2010;**26**:55–65.
71 Witte AV, Fobker M, Gellner R *et al*. Caloric restriction improves memory in elderly humans. *Proc Natl Acad Sci USA* 2009;**106**:1255–60.
72 Stangl D, Thuret S. Impact of diet on adult hippocampal neurogenesis. *Genes Nutr* 2009;**4**:271–82.
73 Aoki H, Kimoto K, Hori N *et al*. Cell proliferation in the dentate gyrus of rat hippocampus is inhibited by soft diet feeding. *Gerontology* 2005;**51**:369–74.
74 Kushida S, Kimoto K, Hori N *et al*. Soft-diet feeding decreases dopamine release and impairs aversion learning in Alzheimer model rats. *Neurosci Lett* 2008;**439**:208–11.
75 Tsutsui K, Kaku M, Motokawa M *et al*. Influences of reduced masticatory sensory input from soft-diet feeding upon spatial memory/learning ability in mice. *Biomed Res* 2007;**28**:1–7.
76 Yamamoto T, Hirayama A, Hosoe N *et al*. Soft-diet feeding inhibits adult neurogenesis in hippocampus of mice. *Bull Tokyo Dent Coll* 2009;**50**:117–24.
77 Dyall SC, Michael GJ, Michael-Titus AT. Omega-3 fatty acids reverse age-related decreases in nuclear receptors and increase neurogenesis in old rats. *J Neurosci Res* 2010;**88**:2091–102.
78 Morris MC, Evans DA, Bienias JL *et al*. Dietary fats and the risk of incident Alzheimer disease. *Arch Neurol* 2003;**60**:194–200.
79 Kalmijn S, Launer LJ, Ott A *et al*. Dietary fat intake and the risk of incident dementia in the Rotterdam Study. *Ann Neurol* 1997;**42**:776–82.

80 van Gelder BM, Tijhuis M, Kalmijn S *et al*. Fish consumption, n-3 fatty acids, and subsequent 5-y cognitive decline in elderly men: the Zutphen Elderly Study. *Am J Clin Nutr* 2007;**85**:1142–7.

81 Freemantle E, Vandal M, Tremblay-Mercier J *et al*. Omega-3 fatty acids, energy substrates, and brain function during aging. *Prostaglandins Leukot Essent Fatty Acids* 2006;**75**:213–20.

82 Fedorova I, Salem N Jr. Omega-3 fatty acids and rodent behavior. *Prostaglandins Leukot Essent Fatty Acids* 2006;**75**:271–89.

83 Su HM. Mechanisms of n-3 fatty acid-mediated development and maintenance of learning memory performance. *J Nutr Biochem* 2010;**21**:364–73.

84 Logan AC. Omega-3 fatty acids and 6 major depression: a primer for the mental health professional. *Lipids Health Dis* 2004;**3**:25.

85 Frangou S, Lewis M, McCrone P. Efficacy of ethyl-eicosapentaenoic acid in bipolar depression: randomised double-blind placebo-controlled study. *Br J Psychiatry* 2006;**188**:46–50.

86 Jazayeri S, Tehrani-Doost M, Keshavarz SA *et al*. Comparison of therapeutic effects of omega-3 fatty acid eicosapentaenoic acid and fluoxetine, separately and in combination, in major depressive disorder. *Aust N Z J Psychiatry* 2008;**42**:192–8.

87 Schipper P, Kiliaan AJ, Homberg JR. A mixed polyunsaturated fatty acid diet normalizes hippocampal neurogenesis and reduces anxiety in serotonin transporter knockout rats. *Behav Pharmacol* 2011;**22**:324–34.

88 An L, Zhang YZ, Yu NJ *et al*. The total flavonoids extracted from Xiaobuxin-Tang up-regulate the decreased hippocampal neurogenesis and neurotrophic molecules expression in chronically stressed rats. *Prog Neuropsychopharmacol Biol Psychiatry* 2008;**32**:1484–90.

89 Dimpfel W. Rat electropharmacograms of the flavonoids rutin and quercetin in comparison to those of moclobemide and clinically used reference drugs suggest antidepressive and/or neuroprotective action. *Phytomedicine* 2009;**16**:287–94.

90 Williams CM, El Mohsen MA, Vauzour D *et al*. Blueberry-induced changes in spatial working memory correlate with changes in hippocampal CREB phosphorylation and brain-derived neurotrophic factor (BDNF) levels. *Free Radic Biol Med* 2008;**45**:295–305.

91 Kim SJ, Son TG, Park HR *et al*. Curcumin stimulates proliferation of embryonic neural progenitor cells and neurogenesis in the adult hippocampus. *J Biol Chem* 2008;**283**:14497–505.

92 Ng TP, Chiam PC, Lee T *et al*. Curry consumption and cognitive function in the elderly. *Am J Epidemiol* 2006;**164**:898–906.

93 Dong S, Zeng Q, Mitchell ES *et al*. Curcumin enhances neurogenesis and cognition in aged rats: implications for transcriptional interactions related to growth and synaptic plasticity. *PLoS One* 2012;**7**:e31211.

94 Xu Y, Lin D, Li S *et al*. Curcumin reverses impaired cognition and neuronal plasticity induced by chronic stress. *Neuropharmacology* 2009;**57**:463–71.

95 Xu Y, Ku B, Cui L *et al*. Curcumin reverses impaired hippocampal neurogenesis and increases serotonin receptor 1A mRNA and brain-derived neurotrophic factor expression in chronically stressed rats. *Brain Res* 2007;**1162**:9–18.

96 Li YC, Wang FM, Pan Y *et al*. Antidepressant-like effects of curcumin on serotonergic receptor-coupled AC-cAMP pathway in chronic unpredictable mild stress of rats. *Prog Neuropsychopharmacol Biol Psychiatry* 2009;**33**:435–49.

97 Moriya J, Chen R, Yamakawa J *et al*. Resveratrol improves hippocampal atrophy in chronic fatigue mice by enhancing neurogenesis and inhibiting apoptosis of granular cells. *Biol Pharm Bull* 2011;**34**:354–9.

98 Harada N, Zhao J, Kurihara H *et al*. Resveratrol improves cognitive function in mice by increasing production of insulin-like growth factor-I in the hippocampus. *J Nutr Biochem* 2011;**22**:1150–9.

99 Xu Y, Wang Z, You W *et al*. Antidepressant-like effect of trans-resveratrol: involvement of serotonin and noradrenaline system. *Eur Neuropsychopharmacol* 2010;**20**:405–13.

100 Corniola RS, Tassabehji NM, Hare J *et al*. Zinc deficiency impairs neuronal precursor cell proliferation and induces apoptosis via p53-mediated mechanisms. *Brain Res* 2008;**1237**:52–61.

101 Tassabehji NM, Corniola RS, Alshingiti A *et al*. Zinc deficiency induces depression-like symptoms in adult rats. *Physiol Behav* 2008;**95**:365–9.

102 Szewczyk B, Poleszak E, Sowa-Kucma M *et al*. Antidepressant activity of zinc and magnesium in view of the current hypotheses of antidepressant action. *Pharmacol Rep* 2008;**60**:588–9.

103 Gao HL, Zheng W, Xin N *et al*. Zinc deficiency reduces neurogenesis accompanied by neuronal apoptosis through caspase-dependent and -independent signaling pathways. *Neurotox Res* 2009;**16**:416–25.

104 Levenson CW, Morris D. Zinc and neurogenesis: making new neurons from development to adulthood. *Adv Nutr* 2011;**2**:96–100.

105 Nuttall JR, Oteiza PI. Zinc and the ERK kinases in the developing brain. *Neurotox Res* 2012;**21**:128–41.

106 Crandall J, Sakai Y, Zhang J *et al*. 13-cis-retinoic acid suppresses hippocampal cell division and hippocampal-dependent learning in mice. *Proc Natl Acad Sci USA* 2004;**101**:5111–6.

107 O'Reilly KC, Shumake J, Bailey SJ *et al*. Chronic 13-cis-retinoic acid administration disrupts network interactions between the raphe nuclei and the hippocampal system in young adult mice. *Eur J Pharmacol* 2009;**605**:68–77.

108 Bonnet E, Touyarot K, Alfos S *et al*. Retinoic acid restores adult hippocampal neurogenesis and reverses spatial memory deficit in vitamin A deprived rats. *PLoS One* 2008;**3**:e3487.

109 Fragoso YD, Shearer KD, Sementilli A *et al*. High expression of retinoic acid receptors and synthetic enzymes in the human hippocampus. *Brain Struct Funct* 2012;**217**:473–83.

110 Kotasova H, Vesela I, Kucera J *et al*. Phosphoinositide 3-kinase inhibition enables retinoic acid-induced neurogenesis in monolayer culture of embryonic stem cells. *J Cell Biochem* 2012;**113**:563–70.

111 Engberg N, Kahn M, Petersen DR *et al*. Retinoic acid synthesis promotes development of neural progenitors from mouse embryonic stem cells by suppressing endogenous, Wnt-dependent nodal signaling. *Stem Cells* 2010;**28**:1498–509.

112 Jacobs S, Lie DC, DeCicco KL *et al*. Retinoic acid is required early during adult neurogenesis in the dentate gyrus. *Proc Natl Acad Sci USA* 2006;**103**:3902–7.

113 Han ME, Park KH, Baek SY *et al*. Inhibitory effects of caffeine on hippocampal neurogenesis and function. *Biochem Biophys Res Commun* 2007;**356**:976–80.

114 Wentz CT, Magavi SS. Caffeine alters proliferation of neuronal precursors in the adult hippocampus. *Neuropharmacology* 2009;**56**:994–1000.

115 Lindqvist A, Mohapel P, Bouter B *et al*. High-fat diet impairs hippocampal neurogenesis in male rats. *Eur J Neurol* 2006;**13**:1385–8.

116 Park HR, Park M, Choi J *et al*. A high-fat diet impairs neurogenesis: involvement of lipid peroxidation and brain-derived neurotrophic factor. *Neurosci Lett* 2010;**482**:235–9.

117 van der Borght K, Kohnke R, Goransson N *et al*. Reduced neurogenesis in the rat hippocampus following high fructose consumption. *Regul Pept* 2011;**167**:26–30.

118 Molteni R, Barnard RJ, Ying Z *et al*. A high-fat, refined sugar diet reduces hippocampal brain-derived neurotrophic factor, neuronal plasticity, and learning. *Neuroscience* 2002;**112**:803–14.

119 Palmer TD, Willhoite AR, Gage FH. Vascular niche for adult hippocampal neurogenesis. *J Comp Neurol* 2000;**425**:479–94.

120 Song H, Stevens CF, Gage FH. Astroglia induce neurogenesis from adult neural stem cells. *Nature* 2002;**417**:39–44.

121 Fisher ND, Sorond FA, Hollenberg NK. Cocoa flavanols and brain perfusion. *J Cardiovasc Pharmacol* 2006;**47**(Suppl. 2):S210–4.

122 Francis ST, Head K, Morris PG *et al*. The effect of flavanol-rich cocoa on the fMRI response to a cognitive task in healthy young people. *J Cardiovasc Pharmacol* 2006;**47**(Suppl. 2):S215–20.

123 Bahia PK, Rattray M, Williams RJ. Dietary flavonoid (-)epicatechin stimulates phosphatidylinositol 3-kinase-dependent anti-oxidant response element activity and up-regulates glutathione in cortical astrocytes. *J Neurochem* 2008;**106**:2194–204.

124 Mathers JC. Nutritional modulation of ageing: genomic and epigenetic approaches. *Mech Ageing Dev* 2006;**127**:584–9.

125 Bondolfi L, Ermini F, Long JM *et al*. Impact of age and caloric restriction on neurogenesis in the dentate gyrus of C57BL/6 mice. *Neurobiol Aging* 2004;**25**:333–40.

126 Kitamura T, Mishina M, Sugiyama H. Dietary restriction increases hippocampal neurogenesis by molecular mechanisms independent of NMDA receptors. *Neurosci Lett* 2006;**393**:94–6.

127 Lee J, Duan W, Mattson MP. 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* 2002;**82**:1367–75.

128 Kawakita E, Hashimoto M, Shido O. Docosahexaenoic acid promotes neurogenesis in vitro and in vivo. *Neuroscience* 2006;**139**:991–7.

129 Crupi R, Cambiaghi M, Deckelbaum R *et al*. n-3 fatty acids prevent impairment of neurogenesis and synaptic plasticity in B-cell activating factor (BAFF) transgenic mice. *Prev Med* 2011;**54**:S103–8.

130 Valente T, Hidalgo J, Bolea I *et al*. A diet enriched in polyphenols and polyunsaturated fatty acids, LMN diet, induces neurogenesis in the subventricular zone and hippocampus of adult mouse brain. *J Alzheimers Dis* 2009;**18**:849–65.

131 Yoo KY, Choi JH, Hwang IK *et al*. (-)-Epigallocatechin-3-gallate increases cell proliferation and neuroblasts in the subgranular zone of the dentate gyrus in adult mice. *Phytother Res* 2010;**24**:1065–70.

132 Lee S, Kim DH, Lee DH *et al*. Oroxylin A, a flavonoid, stimulates adult neurogenesis in the hippocampal dentate gyrus region of mice. *Neurochem Res* 2010;**35**:1725–32.

133 Casadesus G, Shukitt-Hale B, Stellwagen HM *et al*. Modulation of hippocampal plasticity and cognitive behavior by short-term blueberry supplementation in aged rats. *Nutr Neurosci* 2004;**7**:309–16.

134 Zhao N, Zhong C, Wang Y *et al*. Impaired hippocampal neurogenesis is involved in cognitive dysfunction induced by thiamine deficiency at early pre-pathological lesion stage. *Neurobiol Dis* 2008;**29**:176–85.

135 Zhao Y, Pan X, Zhao J *et al*. Decreased transketolase activity contributes to impaired hippocampal neurogenesis induced by thiamine deficiency. *J Neurochem* 2009;**111**:537–46.

136 Suh SW, Won SJ, Hamby AM *et al*. Decreased brain zinc availability reduces hippocampal neurogenesis in mice and rats. *J Cereb Blood Flow Metab* 2009;**29**:1579–88.

137 Xumei Z, Guowei H, Huan L *et al*. Folic acid enhances Notch signaling, hippocampal neurogenesis, and cognitive function in a rat model of cerebral ischemia. *Nutr Neurosci* 2012;**15**:55–61.

138 Kronenberg G, Harms C, Sobol RW *et al*. Folate deficiency induces neurodegeneration and brain dysfunction in mice lacking uracil DNA glycosylase. *J Neurosci* 2008;**28**:7219–30.

139 Kruman II, Mouton PR, Emokpae R Jr *et al*. Folate deficiency inhibits proliferation of adult hippocampal progenitors. *Neuroreport* 2005;**16**:1055–9.

140 Rabaneda LG, Carrasco M, Lopez-Toledano MA *et al*. Homocysteine inhibits proliferation of neuronal precursors in the mouse adult brain by impairing the basic fibroblast growth factor signaling cascade and reducing extracellular regulated kinase 1/2-dependent cyclin E expression. *FASEB J* 2008;**22**:3823–35.

141 He J, Nixon K, Shetty AK *et al*. Chronic alcohol exposure reduces hippocampal neurogenesis and dendritic growth of newborn neurons. *Eur J Neurosci* 2005;**21**:2711–20.

142 Nixon K, Crews FT. Binge ethanol exposure decreases neurogenesis in adult rat hippocampus. *J Neurochem* 2002;**83**:1087–93.

143 Stevenson JR, Schroeder JP, Nixon K *et al*. Abstinence following alcohol drinking produces depression-like behavior and reduced hippocampal neurogenesis in mice. *Neuropsychopharmacology* 2008;**34**:1209–22.

144 Kong KH, Kim HK, Song KS *et al*. Capsaicin impairs proliferation of neural progenitor cells and hippocampal neurogenesis in young mice. *J Toxicol Environ Health A* 2010;**73**:1490–501.

145 Cecchini T, Ciaroni S, Ferri P *et al*. Alpha-tocopherol, an exogenous factor of adult hippocampal neurogenesis regulation. *J Neurosci Res* 2003;**73**:447–55.

146 Ciaroni S, Cecchini T, Ferri P *et al*. Neural precursor proliferation and newborn cell survival in the adult rat dentate gyrus are affected by vitamin E deficiency. *Neurosci Res* 2002;**44**:369–77.

147 Ciaroni S, Cuppini R, Cecchini T *et al*. Neurogenesis in the adult rat dentate gyrus is enhanced by vitamin E deficiency. *J Comp Neurol* 1999;**411**:495–502.
148 Cuppini R, Ciaroni S, Cecchini T *et al*. Tocopherols enhance neurogenesis in dentate gyrus of adult rats. *Int J Vitam Nutr Res* 2002;**72**:170–6.
149 Stewart J, Mitchell J, Kalant N. The effects of life-long food restriction on spatial memory in young and aged Fischer 344 rats measured in the eight-arm radial and the Morris water mazes. *Neurobiol Aging* 1989;**10**:669–75.
150 Ingram DK, Weindruch R, Spangler EL *et al*. Dietary restriction benefits learning and motor performance of aged mice. *J Gerontol* 1987;**42**:78–81.
151 Fontan-Lozano A, Saez-Cassanelli JL, Inda MC *et al*. Caloric restriction increases learning consolidation and facilitates synaptic plasticity through mechanisms dependent on NR2B subunits of the NMDA receptor. *J Neurosci* 2007;**27**:10185–95.
152 Rich NJ, Van Landingham JW, Figueiroa S *et al*. Chronic caloric restriction reduces tissue damage and improves spatial memory in a rat model of traumatic brain injury. *J Neurosci Res* 2010;**88**:2933–9.
153 Lutter M, Krishnan V, Russo SJ *et al*. Orexin signaling mediates the antidepressant-like effect of calorie restriction. *J Neurosci* 2008;**28**:3071–5.
154 Stoll AL, Severus WE, Freeman MP *et al*. Omega 3 fatty acids in bipolar disorder: a preliminary double-blind, placebo-controlled trial. *Arch Gen Psychiatry* 1999;**56**:407–12.
155 Osher Y, Bersudsky Y, Belmaker RH. Omega-3 eicosapentaenoic acid in bipolar depression: report of a small open-label study. *J Clin Psychiatry* 2005;**66**:726–9.
156 Keck PE Jr, Mintz J, McElroy SL *et al*. Double-blind, randomized, placebo-controlled trials of ethyl-eicosapentanoate in the treatment of bipolar depression and rapid cycling bipolar disorder. *Biol Psychiatry* 2006;**60**:1020–2.
157 Hooijmans CR, Van der Zee CEEM, Dederen PJ *et al*. DHA and cholesterol containing diets influence Alzheimer-like pathology, cognition and cerebral vasculature in APPswe/PS1dE9 mice. *Neurobiol Dis* 2009;**33**:482–98.
158 Petursdottir AL, Farr SA, Morley JE *et al*. Effect of dietary n-3 polyunsaturated fatty acids on brain lipid fatty acid composition, learning ability, and memory of senescence-accelerated mouse. *J Gerontol Ser A Biol Sci Med Sci* 2008;**63**:1153–60.
159 Yang RH, Wang F, Hou XH *et al*. Dietary Omega-3 polyunsaturated fatty acids improves learning performance of diabetic rats by regulating the neuron excitability. *Neuroscience* 2012;**212**:93–103.
160 Antypa N, Smelt AH, Strengholt A *et al*. Effects of omega-3 fatty acid supplementation on mood and emotional information processing in recovered depressed individuals. *J Psychopharmacol* 2011;**26**:738–43.
161 Spencer JP. Flavonoids and brain health: multiple effects underpinned by common mechanisms. *Genes Nutr* 2009;**4**:243–50.
162 Spencer JP. The impact of fruit flavonoids on memory and cognition. *Br J Nutr* 2010;**104**(Suppl. 3):S40–7.
163 Rendeiro C, Guerreiro JD, Williams CM *et al*. Flavonoids as modulators of memory and learning: molecular interactions resulting in behavioural effects. *Proc Nutr Soc* 2012;**71**:246–62.
164 Rendeiro C, Spencer JP, Vauzour D *et al*. The impact of flavonoids on spatial memory in rodents: from behaviour to underlying hippocampal mechanisms. *Genes Nutr* 2009;**4**:251–70.
165 Zhang PH, Tang HQ, Zheng MZ *et al*. Effect of total flavonoids from *Chrysanthemun morifolium* on learning and memory in aging mice. *Zhongguo Ying Yong Sheng Li Xue Za Zhi* 2011;**27**:368–71.
166 Wang W, Wang F, Yang YJ *et al*. The flavonoid baicalein promotes NMDA receptor-dependent long-term potentiation and enhances memory. *Br J Pharmacol* 2011;**162**:1364–79.
167 Ding BJ, Ma WW, He LL *et al*. Soybean isoflavone alleviates beta-amyloid 1–42 induced inflammatory response to improve learning and memory ability by down regulation of Toll-like receptor 4 expression and nuclear factor-kappaB activity in rats. *Int J Dev Neurosci* 2011;**29**:537–42.

168 Baluchnejadmojarad T, Roghani M. Chronic epigallocatechin-3-gallate ameliorates learning and memory deficits in diabetic rats via modulation of nitric oxide and oxidative stress. *Behav Brain Res* 2011;**224**:305–10.

169 Li F, Gong QH, Wu Q *et al*. Icariin isolated from Epimedium brevicornum Maxim attenuates learning and memory deficits induced by d-galactose in rats. *Pharmacol Biochem Behav* 2010;**96**:301–5.

170 Krikorian R, Shidler MD, Nash TA *et al*. Blueberry supplementation improves memory in older adults. *J Agric Food Chem* 2010;**58**:3996–4000.

171 Papandreou MA, Dimakopoulou A, Linardaki ZI *et al*. Effect of a polyphenol-rich wild blueberry extract on cognitive performance of mice, brain antioxidant markers and acetylcholinesterase activity. *Behav Brain Res* 2009;**198**:352–8.

172 Reeta KH, Mehla J, Gupta YK. Curcumin ameliorates cognitive dysfunction and oxidative damage in phenobarbitone and carbamazepine administered rats. *Eur J Pharmacol* 2010;**644**:106–12.

173 Tang H, Lu D, Pan R *et al*. Curcumin improves spatial memory impairment induced by human immunodeficiency virus type 1 glycoprotein 120 V3 loop peptide in rats. *Life Sci* 2009;**85**:1–10.

174 Dong J, Lu DX, Pan R *et al*. Effect and mechanism of curcumin on learning and memory dysfunction induced by gp120 in rats. *Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi* 2008;**24**:328–31.

175 Sun CY, Qi SS, Sun SH. Effect of curcumin on the learning, memory and hippocampal Ca^{+}/CaMK II level in senescence-accelerated mice. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 2011;**31**:376–80.

176 Pan R, Qiu S, Lu DX *et al*. Curcumin improves learning and memory ability and its neuroprotective mechanism in mice. *Chin Med J (Engl)* 2008;**121**:832–9.

177 Ahmed T, Enam SA, Gilani AH. Curcuminoids enhance memory in an amyloid-infused rat model of Alzheimer's disease. *Neuroscience* 2010;**169**:1296–306.

178 Huang Z, Zhong XM, Li ZY *et al*. Curcumin reverses corticosterone-induced depressive-like behavior and decrease in brain BDNF levels in rats. *Neurosci Lett* 2011;**493**:145–8.

179 Xu Y, Ku B, Tie L *et al*. Curcumin reverses the effects of chronic stress on behavior, the HPA axis, BDNF expression and phosphorylation of CREB. *Brain Res* 2006;**1122**:56–64.

180 Xu Y, Ku BS, Yao HY *et al*. Antidepressant effects of curcumin in the forced swim test and olfactory bulbectomy models of depression in rats. *Pharmacol Biochem Behav* 2005;**82**:200–6.

181 Xu Y, Ku BS, Yao HY *et al*. The effects of curcumin on depressive-like behaviors in mice. *Eur J Pharmacol* 2005;**518**:40–6.

182 Cocco S, Diaz G, Stancampiano R *et al*. Vitamin A deficiency produces spatial learning and memory impairment in rats. *Neuroscience* 2002;**115**:475–82.

183 Etchamendy N, Enderlin V, Marighetto A *et al*. Vitamin A deficiency and relational memory deficit in adult mice: relationships with changes in brain retinoid signalling. *Behav Brain Res* 2003;**145**:37–49.

184 Winocur G, Greenwood CE. Studies of the effects of high fat diets on cognitive function in a rat model. *Neurobiol Aging* 2005;**26**(Suppl. 1):46–9.

185 Valladolid-Acebes I, Stucchi P, Cano V *et al*. High-fat diets impair spatial learning in the radial-arm maze in mice. *Neurobiol Learn Mem* 2011;**95**:80–5.

186 Abildgaard A, Solskov L, Volke V *et al*. A high-fat diet exacerbates depressive-like behavior in the Flinders Sensitive Line (FSL) rat, a genetic model of depression. *Psychoneuroendocrinology* 2011;**36**:623–33.

187 Alzoubi KH, Abdul-Razzak KK, Khabour OF *et al*. Adverse effect of combination of chronic psychosocial stress and high fat diet on hippocampus-dependent memory in rats. *Behav Brain Res* 2009;**204**:117–23.

188 Goldbart AD, Row BW, Kheirandish-Gozal L *et al*. High fat/refined carbohydrate diet enhances the susceptibility to spatial learning deficits in rats exposed to intermittent hypoxia. *Brain Res* 2006;**1090**:190–6.

189 Granholm AC, Bimonte-Nelson HA, Moore AB *et al*. Effects of a saturated fat and high cholesterol diet on memory and hippocampal morphology in the middle-aged rat. *J Alzheimers Dis* 2008;**14**:133–45.

190 Stranahan AM, Norman ED, Lee K *et al*. Diet-induced insulin resistance impairs hippocampal synaptic plasticity and cognition in middle-aged rats. *Hippocampus* 2008;**18**:1085–8.

191 Ross AP, Bartness TJ, Mielke JG *et al*. A high fructose diet impairs spatial memory in male rats. *Neurobiol Learn Mem* 2009;**92**:410–6.

192 Kanoski SE, Zhang Y, Zheng W *et al*. The effects of a high-energy diet on hippocampal function and blood–brain barrier integrity in the rat. *J Alzheimers Dis* 2010;**21**:207–19.

193 Gold PE. Glucose and age-related changes in memory. *Neurobiol Aging* 2005;**26**:60–4.

194 Kubo KY, Ichihashi Y, Kurata C *et al*. Masticatory function and cognitive function. *Okajimas Folia Anat Jpn* 2010;**87**:135–40.

195 de Almeida MN, Mendes FC, Felicio AP *et al*. Spatial memory decline after masticatory deprivation and aging is associated with altered laminar distribution of CA1 astrocytes. *BMC Neurosci* 2012;**13**:23.

196 Costa MS, Botton PH, Mioranzza S *et al*. Caffeine improves adult mice performance in the object recognition task and increases BDNF and TrkB independent on phospho-CREB immunocontent in the hippocampus. *Neurochem Int* 2008;**53**:89–94.

197 Smith AP. Caffeine, cognitive failures and health in a non-working community sample. *Hum Psychopharmacol* 2009;**24**:29–34.

198 Lucas M, Mirzaei F, Pan A *et al*. Coffee, caffeine, and risk of depression among women. *Arch Intern Med* 2011;**171**:1571–8.

199 Abreu RV, Silva-Oliveira EM, Moraes MF *et al*. Chronic coffee and caffeine ingestion effects on the cognitive function and antioxidant system of rat brains. *Pharmacol Biochem Behav* 2011;**99**:659–64.

200 Robles N, Sabria J. Effects of moderate chronic ethanol consumption on hippocampal nicotinic receptors and associative learning. *Neurobiol Learn Mem* 2008;**89**:497–503.

201 Parsons OA. Neurocognitive deficits in alcoholics and social drinkers: a continuum? *Alcohol Clin Exp Res* 1998;**22**:954–61.

202 Hauser SR, Getachew B, Taylor RE *et al*. Alcohol induced depressive-like behavior is associated with a reduction in hippocampal BDNF. *Pharmacol Biochem Behav* 2011;**100**:253–8.

203 Delwing D, Bavaresco CS, Monteiro SC *et al*. alpha-Tocopherol and ascorbic acid prevent memory deficits provoked by chronic hyperprolinemia in rats. *Behav Brain Res* 2006;**168**:185–9.

204 Lockrow J, Prakasam A, Huang P *et al*. Cholinergic degeneration and memory loss delayed by vitamin E in a Down syndrome mouse model. *Exp Neurol* 2009;**216**:278–89.

205 Monteiro SC, Matte C, Bavaresco CS *et al*. Vitamins E and C pretreatment prevents ovariectomy-induced memory deficits in water maze. *Neurobiol Learn Mem* 2005;**84**:192–9.

206 Mills JD, Hadley K, Bailes JE. Dietary supplementation with the omega-3 fatty acid docosahexaenoic acid in traumatic brain injury. *Neurosurgery* 2011;**68**:474–81; discussion 481.