# Modifiable factors that alter the size of the hippocampus with ageing

*Majid Fotuhi, David Do and Clifford Jack*

**Abstract** | The hippocampus is particularly vulnerable to the neurotoxic effects of obesity, diabetes mellitus, hypertension, hypoxic brain injury, obstructive sleep apnoea, bipolar disorder, clinical depression and head trauma. Patients with these conditions often have smaller hippocampi and experience a greater degree of cognitive decline than individuals without these comorbidities. Moreover, hippocampal atrophy is an established indicator for conversion from the normal ageing process to developing mild cognitive impairment and dementia. As such, an important aim is to ascertain which modifiable factors can have a positive effect on the size of the hippocampus throughout life. Observational studies and preliminary clinical trials have raised the possibility that physical exercise, cognitive stimulation and treatment of general medical conditions can reverse age-related atrophy in the hippocampus, or even expand its size. An emerging concept—the dynamic polygon hypothesis—suggests that treatment of modifiable risk factors can increase the volume or prevent atrophy of the hippocampus. According to this hypothesis, a multidisciplinary approach, which involves strategies to both reduce neurotoxicity and increase neurogenesis, is likely to be successful in delaying the onset of cognitive impairment with ageing. Further research on the constellation of interventions that could be most effective is needed before recommendations can be made for implementing preventive and therapeutic strategies.

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## Introduction

Large hippocampal size is closely linked with good memory and cognitive function;[1] conversely, atrophy of the hippocampus is associated with the development of dementia.[2–5] In patients with mild cognitive impairment (MCI), a high rate of decline in hippocampal size strongly heralds conversion to Alzheimer disease (AD).[6,7] Accelerated progression of atrophy is also associated with rapid cognitive decline in both MCI and AD.[8–10] Given these associations, determination of the exact size of the hippocampus on brain MRI is becoming increasingly important in the prediction and diagnosis of AD.[4]

Traditionally, hippocampal atrophy was attributed to neurodegeneration caused by AD or, to a lesser degree, by frontotemporal lobar degeneration.[11–18] A small hippocampus has also been reported in patients with various neurological conditions, including multiple sclerosis and epilepsy-related hippocampal sclerosis.[19–21] Notably, studies from the past 2–3 years suggest that hippocampal atrophy can be modulated by processes other than neurodegeneration. For example, elderly individuals with a large hippocampus can remain free of dementia, even in the presence of substantial AD pathology.[22] Elucidation of the factors that have an effect on hippocampal size is, therefore, critical.

This Review focuses on modifiable factors that can reduce or increase the size of the hippocampus throughout life. We first examine evidence for a link between various medical conditions and hippocampal atrophy, and the potential underlying mechanisms that might account for this association. We then review studies that demonstrate the effects of several interventions that can result in a significant increase in hippocampal volume over a period of weeks to months.

## Measuring the hippocampus

Hippocampal size can be assessed in a number of different ways. The most common and straightforward approach is simple visual inspection of MRI scans. This approach has proved to be effective in evaluating conditions such as AD.[23,24] However, visual assessment of hippocampal size is not as accurate as formal measurement for detecting subtle variations in size. Another limitation of visual ranking is the considerable subjective inter-rater variability. Formal measurement of hippocampal size on MRI scans, using computer-aided software tools, enables manual tracing of the entire three-dimensional boundary of the hippocampus. These tools were introduced in the late 1980s to assess seizure lateralization in patients with epilepsy who would be undergoing surgery.[25,26] Manual tracing has been useful for research in many diseases (such as epilepsy and dementia); however, the technique is time-consuming, requires trained operators, and results in tracer-to-tracer variability.[27,28] Consequently, when conducting large-scale studies, in which sample sizes might comprise thousands of patients, or when using hippocampal volume measures for clinical purposes, the manual tracing

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Neurology Institute for Brain Health and Fitness, 1205 York Road, Suite 18, Lutherville, MD 21093, USA (**M. Fotuhi**). Johns Hopkins University School of Medicine, 733 North Broadway, Suite 137, Baltimore, MD 21205, USA (**D. Do**). Department of Radiology, Mayo Clinic, 200 1st Street SW, Rochester, MN 55905, USA (**C. Jack**).

Correspondence to:
M. Fotuhi
mfotuhi@jhu.edu



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**Key points**

- Atrophy in the hippocampus is a key factor in the process of age-related memory loss and dementia, and might not be solely attributable to Alzheimer disease pathology
- Automated MRI measurements of brain size assist in detecting reductions or expansions in hippocampal volume, which can occur with ageing, some medical conditions or neurodegeneration
- Vascular risk factors, such as obesity, diabetes mellitus and obstructive sleep apnoea, are associated with a reduction in hippocampal size and early development of cognitive impairment
- Elevated levels of inflammatory markers and cortisol, and dynamic changes in the levels of several enzymes and transcription factors, have been implicated in hippocampal atrophy
- Cognitive stimulation, physical exercise and treatment of vascular risk factors seem to result in measurable increases in hippocampal volume, in addition to improvements in memory
- Improved understanding of the modifiable factors that cause changes in hippocampal volume throughout life will assist in the development of clinical trials aimed at preventing age-related cognitive impairment

**Box 1** | Factors associated with hippocampal atrophy

- Cardiovascular disease
- Cardiac arrest
- Atrial fibrillation
- Diabetes
- Hypertension
- Obesity
- Obstructive sleep apnoea
- Vitamin $B_{12}$ deficiency
- Mood disorders
- Post-traumatic stress disorder
- Head trauma
- *APOE ε4* genotype

approach is not practical. Fortunately, fully automated software tools that provide rapid and reproducible results are now available.[29–31]

When conducting routine measurements of the hippocampus in clinical trials, factors other than computer software also need to be considered. The hippocampal volume of any individual is the product of several features; for example, the presence and severity of medical conditions (such as diabetes mellitus), or therapeutic interventions aimed at improving fitness, can change the size of the hippocampus. In addition, the size of the hippocampus, like that of the whole brain, is related to the height of the individual—the intracranial structures are scaled to the size of the cranial cavity, which in turn is approximately scaled to the height of the individual. Methods to correct calculations of hippocampal volume to account for individual differences in the size of the cranial cavity are needed.[26,32] In the meantime, a recommended approach for measuring the volume of the hippocampus to assist with the detection of disease in patients is to scale the hippocampal volume for an individual relative to a normative database.[33]

The advent of automated measurements of hippocampal size should facilitate the generation of definitive data that are based on double-blind, placebo-controlled studies. As such, effective strategies for increasing the size of the hippocampus or slowing its rate of atrophy, as well as reducing comorbidities that might be working together with neurodegenerative processes in the brain, can be determined.

## Risk factors for hippocampal atrophy

A diverse range of medical conditions seem to influence the size of the hippocampus with increasing age. Cardiovascular disease (CVD) and vascular risk factors, as well as other common conditions such as clinical depression, anxiety and traumatic brain injury (TBI), have all been linked with a small hippocampus (Box 1).

### CVD and vascular risk factors

CVD in midlife increases the risk of late-life dementia.[34] CVD has been linked to varying degrees of atrophy in the hippocampus (Figure 1).[35–39] The marked cognitive decline that occurs in patients following cardiac arrest, or as a result of atrial fibrillation, diabetes mellitus, hypertension, obesity or obstructive sleep apnoea, is partly attributable to hippocampal atrophy.[40] Commonly, more than one vascular risk factor is present in an individual, and these factors can have synergistic effects on the processes involved in normal ageing of the brain.[40] However, a single risk factor can also affect cognitive function through a reduction in the size of the whole brain, and the hippocampus in particular. For example, children with heart failure have a marked reduction in hippocampal volume in the absence of obesity, hypertension and other vascular comorbidities.[41]

#### *Obesity*

Obesity is associated with a below-average hippocampal size, and with an increased risk of cognitive impairment in late life.[42–46] Furthermore, a high BMI in midlife is associated with an increased rate of hippocampal atrophy in late life.[46–49] One study that controlled for confounding variables (age, sex and ethnic group) found that elderly individuals with a BMI >30 and normal cognition had smaller hippocampi compared with those who had a BMI <30.[48] Low total brain volumes are also reported in overweight individuals and in those who have a normal BMI but a large abdominal diameter. Central obesity (waist-to-hip ratio >0.9) seems to be particularly damaging to the brain—a 1 SD increase in the waist-to-hip ratio is associated with a 0.2 SD decrease in hippocampal volume.[46]

#### *Diabetes mellitus*

The hippocampus seems to be particularly vulnerable to the neurotoxic effects of diabetes mellitus (Box 2). Patients of all ages with diabetes mellitus who have elevated levels of haemoglobin $A_{1c}$ are at high risk of developing cognitive deficits and exhibiting considerable atrophy of the hippocampus.[50,51] Results from the cohort of individuals involved in the Honolulu–Asia Aging Study showed that elderly people with diabetes mellitus have smaller hippocampi than those without diabetes mellitus.[52] In another study, in which the relative decline in cognitive performance (measured using the Mini-Mental State Examination [MMSE]) of elderly



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patients with diabetes mellitus was compared with that in an age-matched control group without diabetes mellitus, those with diabetes mellitus had increased atrophy of the hippocampus and the whole brain.[53] The MMSE scores in the group with diabetes mellitus were negatively correlated with the amount of hippocampal atrophy, but not with whole-brain atrophy.[53] A cross-sectional study found a similar correlation among obese adolescents:[54] obese teenagers with type 2 diabetes mellitus had smaller hippocampi than did those without diabetes mellitus.

*Hypertension*

The association between chronic, untreated hypertension and hippocampal atrophy in late life is complex.[55,56] In the Honolulu–Asia Aging Study, patients with hypertension who had never received treatment with antihypertensive agents had significantly smaller hippocampi than those who had received such treatment.[56] However, low diastolic blood pressure in patients treated with antihypertensive agents has also been associated with hippocampal atrophy.[55] In elderly patients with hypertension, a small whole-brain volume and a nonsignificant trend towards reduced hippocampal size has been observed.[57] Further studies are underway to elucidate the effects of high systolic versus high diastolic blood pressures, well-controlled hypertension versus treatment-resistant hypertension, and different antihypertensive medications (such as calcium channel blockers and β-blockers) on the brain during the process of ageing.

*Hypoperfusion injury*

The hippocampus is particularly vulnerable to acute cerebral hypoperfusion. MRI scans of children with a history of mild hypoxic brain injury—who experience minimal cognitive deficits consisting largely of episodic memory loss—exhibit signs of atrophy in the hippocampus alone.[58] Acute cerebral hypoperfusion in patients following cardiac arrest also seems to damage the hippocampus, more so than any other brain region.[59–61] Investigators from one study reported that the hippocampus was 28% smaller in patients 8–21 days after cardiac arrest than in healthy controls matched for age, sex and body size distribution, and that most cell loss occurred in the CA1 subdivision of the hippocampus.[59] In fact, the hippocampus is the only region of the brain that consistently undergoes atrophy in all patients with anoxia.[62] A recent study suggests that specific segments of the hippocampus might be particularly sensitive to hypoxia:[63] volume reductions were most evident in posterior areas of the hippocampus in a cohort of patients following successful resuscitation after cardiac arrest.

*Elevated homocysteine levels*

Patients with vitamin $B_{12}$ deficiency have elevated levels of homocysteine, which are associated with a 2.9-fold increased risk of AD and a 5.5-fold increased risk of stroke.[64] In a study of 1,077 individuals without dementia aged from 60–90 years, elevated plasma levels of homocysteine were associated with hippocampal atrophy.[65]

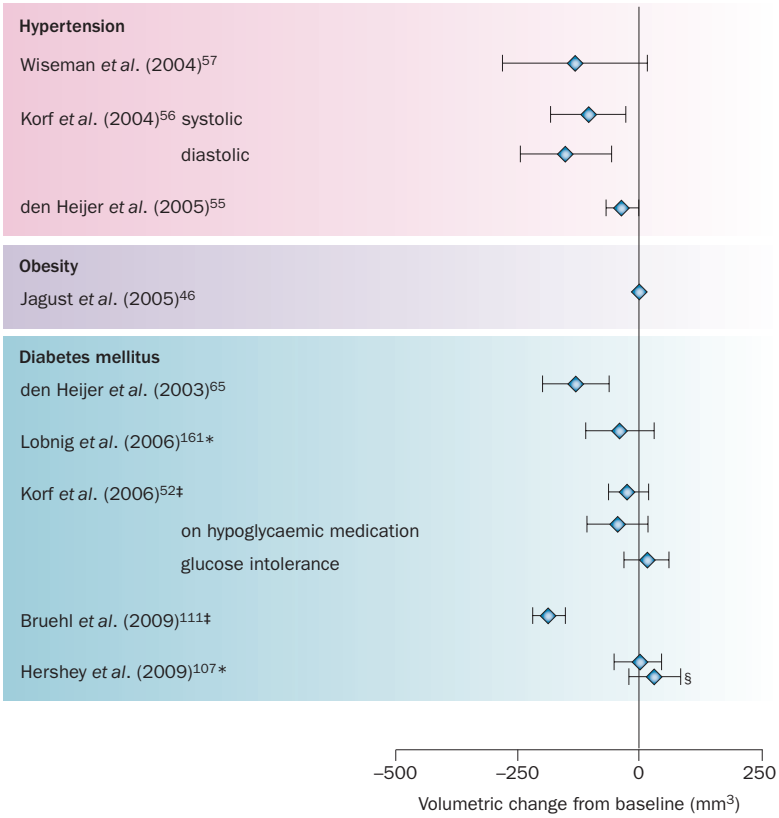



**Figure 1** | Comparison of studies of hippocampal volume in patients with cardiovascular disease. These studies were conducted to investigate the effects of diabetes mellitus type 1 and type 2, obesity and hypertension on hippocampal size, and most have shown a reduction in volume. Unless otherwise stated, the researchers measured the volume of the left hippocampus only or the average of the combined volumes of the left and right hippocampi. *Patients with type 1 diabetes mellitus. ‡Patients with type 2 diabetes mellitus. §Volume of the right hippocampus.

**Box 2** | Hippocampal atrophy in diabetes mellitus

The following mechanisms are thought to contribute to hippocampal atrophy in type 2 diabetes mellitus:

- Vascular ischaemic damage
- Neural pathology (amyloid-β plaques and neurofibrillary tangles)
- Hyperinsulinaemia
- Elevated cortisol levels
- Abnormal glycosylation of proteins
- Oxidative stress
- Inflammation

The most important mechanisms are thought to be microvascular ischaemia and elevated cortisol levels.

High homocysteine levels seem to correlate closely with both low baseline hippocampal size and a high rate of hippocampal atrophy over a 2-year period.[66]

## Psychiatric disorders

The relationship between psychiatric disorders and the hippocampus has frequently been investigated, in view of the functional importance of the hippocampus in neural circuits related to mood and cognition. Many studies have examined the effects of clinical depression,



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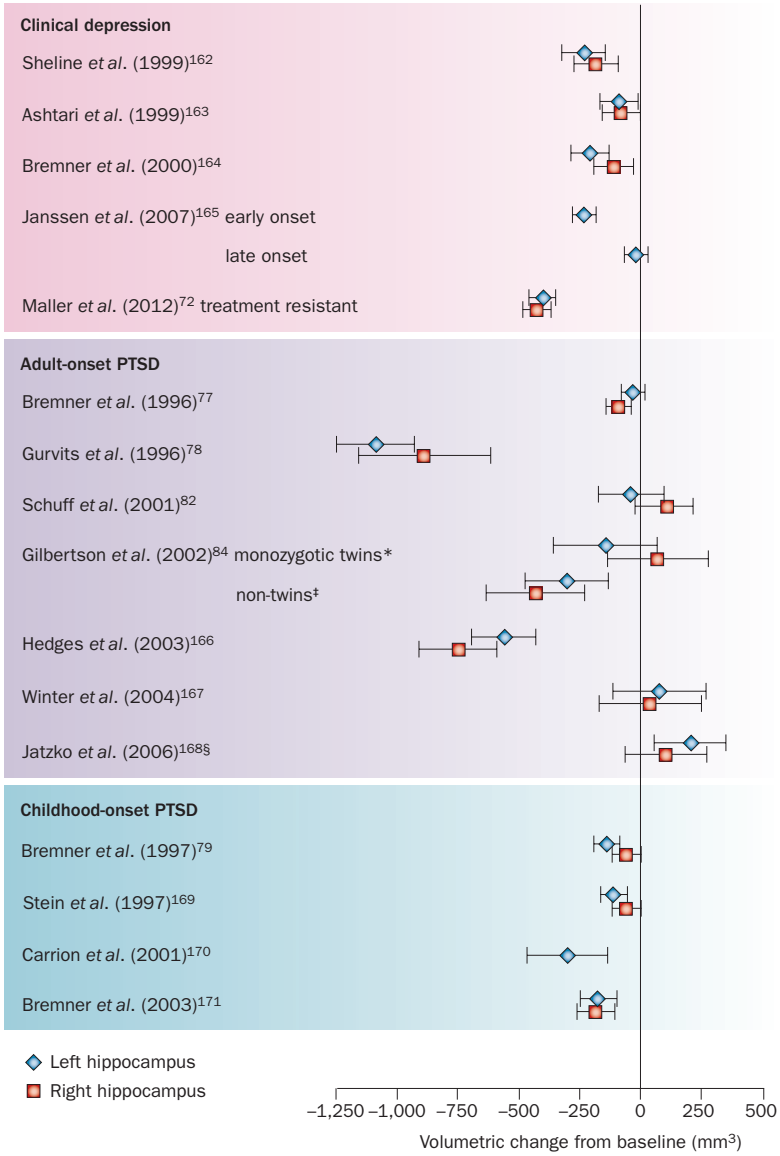



**Figure 2** | Comparison of studies of hippocampal volume in clinical depression and PTSD. Studies conducted from 1995–2012 established a link between small hippocampal size (right and left hippocampi) and clinical depression. The association between hippocampal atrophy and PTSD is more pronounced in childhood-onset PTSD than in adult-onset PTSD. *Comparing hippocampal volume in study participants with war-related PTSD and their non-military twins. ‡Comparing hippocampal volume in combat-exposed veterans who developed war-related PTSD and combat-exposed veterans who did not develop PTSD. §Study participants with chronic PTSD had no history of drug or alcohol abuse. Abbreviation: PTSD, post-traumatic stress disorder.

bipolar affective disorder and post-traumatic stress disorder (PTSD) on the hippocampus, with variable results (Figure 2).[67,68]

### *Clinical depression*

The severity and duration of clinical depression, and the response of this condition to medical treatment, have all been linked to the size of the hippocampus.[67,69–72] In five of 12 small cross-sectional studies included in a meta-analysis, significant differences were observed in hippocampal size between patients with clinical depression and a healthy control group.[67] The aggregated data from all 12 studies, which included 351 patients with clinical depression, showed smaller hippocampi in patients than in controls (approximately 8% smaller left hippocampus and 10% smaller right hippocampus).[67]

Whether clinical depression causes hippocampal atrophy or whether reduced hippocampal tissue volume results in a predisposition to clinical depression is unclear. Although the results of some studies provide evidence for a causative relationship, other studies, by correlating lifelong duration of illness with the amount of atrophy in different patient populations,[73] support the predisposition hypothesis. For example, a brain MRI study of children with a family history of clinical depression showed evidence of hippocampal atrophy predating any signs of the illness.[74] Two studies of hippocampal volume in patients with a first episode of clinical depression produced conflicting results on whether atrophic changes were present at baseline.[75,76] On the basis of the available data, the association between clinical depression and hippocampal atrophy is most likely to be a bidirectional process.

### *Post-traumatic stress disorder*

Overall, the evidence for hippocampal atrophy in patients with PTSD is equivocal. The results from several studies, including one in a population of Vietnam combat veterans, have demonstrated significant hippocampal atrophy in patients with PTSD.[77–79] However, after accounting for potential confounding variables (alcoholism, sleep disorders and clinical depression), the association between PTSD and the volume of the hippocampus often loses significance.[80–83] By contrast, a robust connection between childhood-onset PTSD and hippocampal size has been identified. Children exposed to emotional, physical and sexual abuse have below-average hippocampal sizes compared with their peers, and this difference persists into adulthood.[83]

As with clinical depression, whether this association represents a causal relationship is unclear. PTSD tends to occur in individuals with a family history of the disorder, and is triggered after acute stress, but this predisposition for PTSD might be associated with a small hippocampal size. One study found, on average, 10% smaller hippocampi in veterans with PTSD than in those without PTSD. The veterans in this study were each part of a set of monozygotic twins. The non-military twins of veterans with PTSD also had equally small hippocampi.[84] The results of this study suggest a weak association, in which small hippocampal size renders a person more vulnerable to traumatic events.

### *Chronic alcohol abuse*

Studies of clinical depression and PTSD are often confounded by the effects of chronic alcohol abuse. Hippocampal volume is, on average, 8% smaller in individuals with chronic alcohol abuse than in the general population, and increased atrophy is seen with a longer duration of abuse.[81,85] Adolescents seem to be affected more severely by alcohol abuse than are adults.[86]



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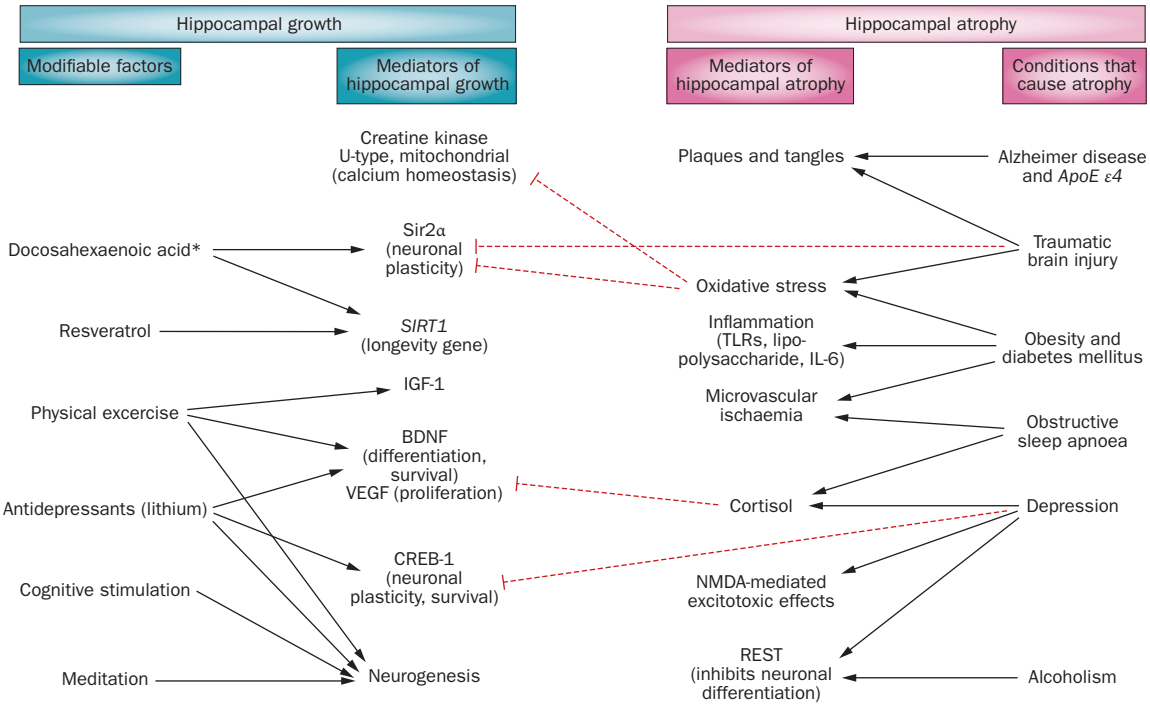



**Figure 3** | Pathways leading to hippocampal growth or atrophy. Modifiable factors, such as meditation, cognitive stimulation, exercise and antidepressant treatment, increase neurogenesis, whereas conditions such as traumatic brain injury, obesity, clinical depression and alcoholism both inhibit neurogenesis and cause atrophy. These conditions and therapies mediate hippocampal atrophy or growth, respectively, via a number of common signalling pathways. *An omega-3 fatty acid. Abbreviations: *APOE ε4*, apolipoprotein E, allele ε4; BDNF, brain-derived neurotrophic factor; CREB-1, cAMP-responsive element-binding protein 1; IGF, insulin-like growth factor; NMDA, *N*-methyl-D-aspartate; REST, RE1-silencing transcription factor, TLRs, Toll-like receptors; VEGF, vascular endothelial growth factor.

### Head trauma

Physical trauma to the head—either repeated minor injuries or a single major injury—can reduce the size of the hippocampus.[87–96] The selective vulnerability of the hippocampus to head trauma seems to be one of the main reasons for the high prevalence of cognitive impairment and dementia among war veterans and American football players.[97]

#### *Chronic traumatic brain injury*

Repeated head trauma of low (often subclinical) magnitude in sports such as boxing, American football, rugby and hockey leads to neurodegenerative changes termed chronic traumatic encephalopathy.[87–96] A study of 100 individuals who were either professional boxers or martial artists who had competed for an average of 5 years found that 59% had hippocampal atrophy.[87] Chronic traumatic encephalopathy has been associated with development of clinical depression, dementia and alcoholism.[98]

#### *Acute traumatic brain injury*

Patients with a history of a single TBI tend to develop dementia earlier than the general population.[99] Atrophic changes generally start to develop between 3 and 7 months after the injury. The changes are persistent, and are associated with cognitive decline, including memory loss.[94,95] In an experimental model of head trauma, quantitative MRI measurements showed that an acute decrease in the size of the ipsilateral hippocampus at 3 h to 3 days after the event predicted long-term deficits in memory and spatial learning.[87] Neurofibrillary tangles and amyloid-β plaques are seen years after the injury in 28% of cases.[100]

## Mechanisms of hippocampal atrophy

### CVD and vascular risk factors

The mechanisms through which different vascular risk factors affect the hippocampus, both directly and indirectly, remain an active area of intense research, and most probably involve a combination of the following: microvascular ischaemia; inflammation; abnormal glycosylation of proteins in the brain; alterations to glucose transportation in the brain; impaired amyloid clearance; and high levels of cortisol, insulin, leptin and ghrelin (Box 2 and Figure 3).[40,43,101] The neurochemical consequences of obstructive sleep apnoea and clinical depression, which are common comorbid conditions in patients with obesity and diabetes mellitus, might also be important mediators of hippocampal atrophy.[102–105]

Metabolic syndrome and type 2 diabetes mellitus have both been linked with substantial brain injury over time.[43] The microvascular ischaemia and inflammation associated with both conditions cause damage (both directly and indirectly, via hypertension) to axons throughout the brain and contribute to diffuse white matter disease that, in turn, can lead to hippocampal atrophy.[40,50] Although type 1 diabetes mellitus has not



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**Box 3** | Factors associated with hippocampal growth

**Therapies that increase hippocampal size**
- Cognitive stimulation
- Physical exercise (such as walking)
- Meditation

**Interventions that might reverse hippocampal atrophy**
- Treatment of risk factors for cardiovascular disease
- Treatment of clinical depression and obstructive sleep apnoea

been associated with atrophy of the hippocampus,[106,107] patients with a long history of this condition are at high risk of developing coronary heart disease, renal impairment and stroke, and are, therefore, also at risk of brain atrophy.[108] Interestingly, a prospective study published in 2011 demonstrated that over a period of 2 years, young people (mean age 12.5 years) with type 1 diabetes mellitus who had frequent episodes of hyperglycaemia had a significantly greater decrease in whole-brain grey matter compared with those with good glycaemic control.[109]

In addition to vascular injury and inflammation in both the heart and the brain, diabetes mellitus impairs the feedback mechanism for suppression of the hypothalamic–pituitary–adrenal (HPA) axis.[110,111] The resulting high levels of cortisol can directly impair glucose transport in hippocampal neurons and lead to *N*-methyl-D-aspartate (NMDA)-mediated excitotoxic effects.[111,112] Corticosteroids bind to intracellular and extracellular glucocorticoid and mineralocorticoid receptors in the hippocampus, and chronic elevation of corticosteroid levels induces changes in transcription of genes encoding corticotropin-releasing hormone receptors, manifesting as neurotoxicity, suppression of dendritic arborization, and inhibition of neurogenesis.[113] These effects might occur as a result of downregulation of brain-derived neurotrophic factor (BDNF), which is believed to be an important mediator in the association between exercise, hippocampal growth and improved memory in both animals and humans.[114–116]

The selective vulnerability of the hippocampus to hypoxia in patients after cardiac arrest might be related, in part, to the high density of NMDA receptor subtypes in this region of the brain.[117] Another mechanism that could result in selective vulnerability of the hippocampus is apoptotic cascades triggered by glucocorticoid receptors: the hippocampus has a large concentration of neurons with glucocorticoid and mineralocorticoid receptors that seem to be particularly sensitive to hypoxia.[118]

Inflammation seems to be a factor in many processes that cause atrophy in the hippocampus and throughout the brain, including neurotoxicity in diabetes mellitus, as well as obesity, clinical depression, systemic lupus erythematosus and epilepsy.[40,119,120] Inflammation can also accelerate the neurodegenerative processes leading to dementia.[121]

Alcohol-mediated hippocampal atrophy is incompletely understood, but much attention is focused on its inhibition of neurogenesis by modulation of cAMP-responsive element-binding protein 1 (CREB-1) and RE1-silencing transcription factor (REST, also known as neural-restrictive silencer factor, or NRSF) signalling pathways.[122] Other possible mechanisms include induction of oxidative stress and neuroinflammation.[86]

### Psychiatric disorders

PTSD and clinical depression might cause hippocampal injury and atrophy via the mechanisms described for vascular risk factors. In fact, the widely accepted explanation for a small-sized hippocampus in patients with PTSD and clinical depression involves dysregulation of the HPA axis and subsequent elevation of cortisol and corticotropin-releasing hormone.[123] The downstream effect of HPA axis dysregulation involves downregulation of CREB-1, leading to decreased levels of BDNF,[122] and activation of REST, which inhibits neuronal differentiation. Predictably, patients with Cushing syndrome (which is associated with high baseline cortisol levels) also have small hippocampi; however, this feature is reversible with treatment for the primary condition.[124] Results from a 2-year study of patients with AD showed that the elevation in baseline cortisol levels predicted the extent of hippocampal atrophy, suggesting that glucocorticoids are critical mediators of hippocampal atrophy and cognitive decline, even in patients with classic AD pathology.[125] A host of other stress-related molecules modulate the hippocampal circuitry; however, limited evidence is available for their involvement in hippocampal atrophy. The levels of these molecules—which include vasopressin, dopamine, noradrenaline, orexin, ghrelin and dynorphin—depend on the magnitude and duration of the stressful stimuli.[113]

### Head trauma

Neurons in the hippocampus are more prone to degeneration after TBI than are those in any other cortical or subcortical area.[88] This acute injury could be mediated by a contusion, axonal damage, vascular damage leading to microhaemorrhage, or increased intracranial pressure due to brain swelling.[88] In addition, brain injury (even from a single event) can cause the formation of neurofibrillary tangles and amyloid-β plaques, as observed in neurodegenerative diseases;[100] the role and pathogenesis of these neurohistological findings is unclear. Beyond the immediate damage, TBI leads to a state of oxidative stress in the brain, causing reductions in levels of the proteins Sir2α, creatine kinase U-type, mitochondrial, and other mitochondrial kinases, which in turn can cause cell death and reduced neurogenesis.[126] Sir2α enhances DNA repair and conveys longevity in yeast, and this protein is also thought to mediate homeostasis under challenging conditions.[126]

## Counteracting hippocampal atrophy

In the past 2–3 years, automated high-resolution brain imaging techniques have aided the evaluation of interventions that can potentially increase the size of the hippocampus and reverse the atrophy caused by degenerative, traumatic or cardiovascular aetiologies. The hippocampus possesses a particular capacity for neuroplasticity



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**Table 1** | Effects of cognitive stimulation and music on hippocampal volume

| Study design and inclusion criteria | Outcome measures and results | Further comments |
|---|---|---|
| ***Maguire et al. (2000)***[133] | | |
| Cross-sectional study; 16 right-handed, male, licensed London taxi drivers with >1.5 years' experience in the profession (mean 14.3 years), mean age 44 years (range 32–62 years); 50 age-matched controls who did not drive taxis | MRI–VBM<br>No significant difference in total hippocampal volume between taxi drivers and control group<br>Taxi drivers had larger posterior hippocampi ($P$<0.05) and smaller anterior hippocampi ($P$<0.05) than controls | Number of years of taxi-driving experience correlated with higher posterior hippocampal volume ($P$<0.06) and lower anterior hippocampal volume ($P$<0.05) |
| ***Draganski et al. (2006)***[131] | | |
| 6-month prospective cohort study; 38 medical students studying for their national medical examination, mean age 24 years; 12 physical therapy students (matched controls) | MRI–VBM at –3 months, 0 months, and +3 months relative to the examination<br>Medical students demonstrated an increase in hippocampal grey matter that became significant toward the third time point ($P$<0.05 for left and right hippocampi) | Bilateral increase in parietal cortex grey matter volume in medical students ($P$<0.001) |
| ***Fortin et al. (2008)***[132] | | |
| Cross-sectional study; 12 participants with early-onset blindness (age of onset <5 years), mean age 33.8 years; 7 participants with late-onset blindness (age of onset ≥14 years), mean age 39.9 years; 19 sighted, blindfolded, matched controls, mean age 36.0 years | Performance in a maze task and MRI–VBM<br>Participants with either early or late-onset blindness had on average 8.5% larger hippocampi than the control group (hippocampal volume 4,237 $mm^3$ [blind] versus 3,906 $mm^3$ [sighted], $P$<0.01)<br>No difference in hippocampal grey matter volume and route-learning performance between groups with early-onset and late-onset blindness | Blind individuals made fewer errors on the complex route-learning task than did sighted individuals ($P$<0.01) |
| ***Groussard et al. (2010)***[172] | | |
| Cross-sectional study; 20 right-handed musicians from a music conservatory (average 15.3 years of experience), mean age 22.85 years; 20 controls who were not musicians, mean age 24.55 years | MRI–VBM<br>Musicians had higher grey matter density in the left hippocampal head (no statistical data available) | None |
| ***Woollett et al. (2011)***[134] | | |
| 4-year prospective cohort study; 59 male participants training to become licensed taxi drivers in London (39 eventually qualified, 20 failed), mean age 38 years; 31 controls who were not training to become taxi drivers | MRI–VBM<br>Trainees who qualified: bilaterally increased grey matter in the posterior hippocampi ($P$<0.05, corrected for multiple comparisons across the whole brain) compared with baseline measurements<br>No significant change in hippocampal size in trainees who did not qualify | Baseline hippocampal volume not statistically different between participants who succeeded and those who failed to qualify |

Abbreviation: VBM, voxel-based morphometry.

and, therefore, some interventions could conceivably slow down the rate of atrophy with ageing. Results from initial studies investigating these interventions have been promising (Box 3 and Tables 1–4).[115,127]

## Cognitive stimulation

Brain stimulation with various cognitive interventions has been associated with a reduced risk of developing dementia (Table 1). Individuals without dementia who participate in cognitively engaging leisure activities (such as reading, writing, and crossword puzzles) have reduced rates of both decline in memory and development of AD later in life.[128] Neuroplastic changes with cognitive stimulation are not limited to the hippocampus. In fact, engaging in training sessions to perform juggling or mirror-reading can lead to an increase in cortical grey matter volume in the frontal, parietal and temporal lobes of the brain.[129,130]

Another study examined the correlation between intense cognitive stimulation and size of the temporal lobe and hippocampus in medical students.[131] Comparison of the MRI scans showed that the size of the parietal lobe increased during 3 months of intensive studying for National Board examinations, and this structural change was maintained during the 3 months after the examination. Surprisingly, the posterior hippocampi, which grew substantially during the 3 months of intensive studying and memorization, continued to grow at the same rate during the subsequent 3 months of light mental work. One possible explanation for this unexpected result is that during the period of intensive studying, increased neurogenesis might have occurred in the hippocampus compared with other regions of the brain, leading to an increased density of neuropil as new neurons formed interconnections both inside and outside the hippocampus.[131]

Researchers investigating hippocampal volumes in blind people found that these individuals had significantly larger hippocampi (on average, 8.5% larger) than did age-matched, sighted controls.[132] Blind people also made significantly fewer errors on a complex route learning task compared with the control group. The increased effort associated with learning orientation and navigation skills without the aid of vision might have stimulated hippocampal growth in these individuals.

A cross-sectional study involving taxi drivers reported that individuals with extensive experience of navigating through the streets of London had proportionally



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**Table 2** | Effects of exercise and fitness on hippocampal volume

| Study design and inclusion criteria | Outcome measures | Results | Further comments |
|---|---|---|---|
| ***Erickson et al. (2009)[127]*** | | | |
| Cross-sectional study in 165 participants; mean age 66.6 years; normal cognition | Correlation between cardiorespiratory fitness (measured by maximal $O_2$ consumption) and hippocampal volume (measured using MRI) | Individuals with high fitness levels had, on average, larger hippocampi than those with low fitness levels; linear correlation ($P$<0.001 for left and right hippocampi) | Fitness measures explained 7.8% and 12.2% of variance in right and left hippocampal volumes, respectively, after age, sex and years of education were taken into account |
| ***Erickson et al. (2010)[144]*** | | | |
| 9-year prospective cohort study; 299 participants; mean age 78 years; normal cognition and no history of neurological disease | Brain volume (measured using MRI and voxel-based morphometry) and self-reported physical activity level (measured by number of city blocks walked per week) | Hippocampal volume 8–13% larger for participants in highest quartile of physical activity (70–300 blocks per week) compared with participants in all other quartiles (<70 blocks per week), $P$<0.05<br>No significant differences in hippocampal volume between lowest three quartiles | Large hippocampal volume associated with reduced risk of developing cognitive impairment ($P$<0.009)<br>High levels of physical activity also predicted large volumes of frontal, occipital and entorhinal regions |
| ***Pajonk et al. (2010)[145]*** | | | |
| 3-month randomized controlled trial of aerobic exercise (30 min three times per week); 16 patients with schizophrenia (eight assigned to exercise and eight undertaking no exercise), 8 age-matched healthy controls; mean age 35.0 years<br>Patients with chronic schizophrenia, mean duration of illness 10.4 years (SD 6.8 years) | Hippocampal cross-sectional area measured using MRI | With exercise, patients and healthy individuals had an increase in hippocampal volume (of 12% and 16%, respectively, mean 14%, $P$<0.001)<br>Nonexercising patients had hippocampal volume loss of 1% | Increase in hippocampal volume with exercise correlated with improvement in aerobic fitness, as measured by maximum $O_2$ consumption ($P$=0.003)<br>Increase in hippocampal volume for combined exercising and nonexercising patients correlated with improvement in short-term memory test scores ($P$<0.05) |
| ***Erickson et al. (2011)[115]*** | | | |
| 1-year, single-blind randomized controlled trial of aerobic exercise (walking for 40 min 3 days per week) versus stretching exercises (control); 120 participants, aged 55.0–80.0 years (mean 66.5 years)<br>Normal cognition and no history of neurological disease | Hippocampal volume (measured using manual segmentation of MRI scans) | Intervention group: increased volume of left and right hippocampi (2.12% and 1.97% respectively) over 1 year<br>Control group: volume loss in left and right hippocampi (1.40% and 1.43%, respectively, over the same interval, $P$<0.001) | Volume change most notable in anterior hippocampus<br>No significant difference in volume in posterior hippocampus<br>Volume changes correlated with higher serum levels of brain-derived neurotrophic factor ($P$<0.01) |

larger posterior hippocampi than those who did not drive taxis.[133] A recent longitudinal study examined the changes in hippocampal size in adults who were preparing to take the qualifying examination to become a taxi driver in London. No increase in hippocampal size was observed either in individuals who failed to qualify or control participants who were not preparing for the examination; however, after 4 years of training, 30 of 59 individuals who passed the examination demonstrated a significant bilateral increase from baseline in the volume of grey matter in the posterior hippocampus.[134]

Patients with bilateral impairment of the vestibular system often have difficulties with spatial memory and navigation, and exhibit a loss of up to 16.9% of their hippocampal volume compared with age-matched healthy control groups.[135,136] Activation of the vestibular system enhances memory in humans,[137] although no studies have yet demonstrated that it increases the size of the hippocampus.

Neuroplasticity and an increase in the volume of grey matter are not unique to the hippocampus. Indeed, challenging activities that require intense training and practice can also cause an increase in the volume of cortical areas engaged in performing the specific task.[138] For example, a prospective study showed that healthy volunteers who learned how to juggle showed a bilateral increase in the size of their cortex in the midtemporal areas.[129] Other studies have documented changes in the cerebellar vermis in basketball players; in the parietal lobe in mathematicians; in Broca's area in symphony orchestra musicians; and in the sensorimotor cortex in ballet dancers.[139] A prospective study showed that novice golfers had an increase in sensorimotor cortical areas after 40 h of training.[140] The structural changes in the brain could be the result of axonal remodelling, synaptogenesis, gliogenesis, neurogenesis, an increase in neural cell size, or an increase in interstitial fluid or blood flow within the organ.[139]

Cognitive and leisure activities that stimulate different areas of the cortex and hippocampus seem to have the potential to modulate and improve the function of the areas affected by the activity. Further studies are needed to confirm these emerging findings, and to establish a therapeutic regimen involving activities that might be protective against cognitive impairment with ageing.

### Physical fitness

Exercise in midlife is associated with a reduced risk of MCI or dementia in late life.[141,142] In a population-based



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**Table 3** | Effects of meditation on hippocampal volume

| Study design and inclusion criteria | Outcome measures and results | Further comments |
|---|---|---|
| ***Holzel et al. (2008)*[146]** | | |
| Cross-sectional study; 20 mindfulness (Vipassana) meditators (mean practice 8.6 years, 2 h daily), mean age 34 years; 20 nonmeditating controls matched for sex, age, education and handedness | MRI–VBM<br>Meditators: higher grey matter concentration in right hippocampus compared with controls ($P$=0.027)<br>No correlation between grey matter concentration and duration of meditation | Mean grey matter concentration in left inferior temporal gyrus could be estimated from amount of meditation training |
| ***Luders et al. (2009)*[147]** | | |
| Cross-sectional study; 22 meditation practitioners (mean practice 24.18 years), mean age 53 years: 22 nonmeditating controls matched for sex and age | MRI–VBM<br>Right hippocampus larger in meditators than in controls (volume 3.73 ml vs 3.53 ml, $P$=0.01) | Meditators had increased grey matter in right orbitofrontal cortex, left inferior temporal cortex and right thalamus |
| ***Holzel et al. (2011)*[148]** | | |
| 8-week controlled, longitudinal study; 16 healthy, meditation-naive participants who underwent a mindfulness-based stress-reduction training programme (average 27 min daily), mean age 37.89 years; 17 individuals on waiting list for training programme (control group), mean age 39.00 years | MRI–VBM<br>Increase in grey matter concentration in left hippocampus in intervention group compared with controls ($P$=0.014) | Intervention group also had increased grey matter concentration in posterior cingulate cortex ($P$=0.004), cerebellum ($P$=0.018) and temporoparietal junction ($P$=0.036) |

Abbreviation: VBM, voxel-based morphometry.

study of 1,324 individuals without dementia at baseline, moderate exercise in midlife was associated with a 32% reduction in the odds ratio for developing MCI.[143] In other research, a linear correlation was evident between improved fitness and large hippocampi in elderly individuals (Table 2).[127] An observational study found that walking more than 1 mile daily was associated with increased hippocampal size and a reduced risk of developing AD.[144]

A randomized controlled trial confirmed that moderate-intensity aerobic exercise (brisk walking) could significantly increase the size of the hippocampus, improve memory, and reduce cognitive impairment, compared with gentle activity (stretching or mild yoga).[115] A significant increase in mean hippocampal size, of 2.12% and 1.97% in the left and right hippocampus, respectively, was seen in participants in the intervention group. These individuals also had higher serum levels of BDNF and performed better on memory tests than the control group.[115] A significant increase in hippocampal volume with exercise has also been demonstrated in both young patients with schizophrenia and age-matched healthy controls.[145]

Exercise increases the incorporation of new neurons into functional circuitry of the dentate gyrus in the hippocampus, as seen in animal studies.[116] Animals that exercised had more-extensive dendrites and axons within the hippocampal circuitry than did the control group.

### Meditation

Stress, clinical depression and PTSD have notable negative effects on the size of the hippocampus. Conversely, meditation seems to have a protective effect and can increase hippocampal size (Table 3). Studies have indicated that individuals who participate in mindfulness relaxation techniques can demonstrate an increase in the size of their hippocampus in as little as 8 weeks.[146–148] Increased volume has also been noted in the posterior cingulate gyrus, parahippocampal gyrus and temporoparietal junction in individuals who use these techniques.[148]

## Therapeutic and lifestyle implications

### The effects of intervention

Given the growing number of studies that demonstrate a reduction in hippocampal size associated with CVD and psychiatric disorders, researchers are increasingly focusing on examining the effects of treatment on reversal or slowing of cerebral atrophy (Table 4). Cholesterol-lowering treatment in patients with atrial fibrillation reduces medial and temporal lobe atrophy bilaterally and improves short-term and long-term memory performance.[149] In addition, treatment of obstructive sleep apnoea is associated with a significant bilateral increase in the size of the hippocampus.[150] These preliminary studies involving small groups of patients show promising results that remain to be confirmed with larger clinical trials.

In patients with clinical depression, treatment with antidepressants and electroconvulsive therapy has been shown to increase hippocampal volume.[114,151–153] In patients with clinical depression that was refractory to pharmacological treatment, electroconvulsive therapy resulted in significant (4–5%) increases in left and right hippocampal volume 2 weeks after initiation of treatment.[151] Findings from animal studies suggest that the mechanism of action of these therapies depends on hippocampal neurogenesis.[122,154,155] Antidepressants raise synaptic levels of serotonin and noradrenaline, which activate pathways involving the second messengers cAMP and CREB-1.[154] This action of antidepressant agents suggests that these treatments might increase neuronal plasticity, proliferation and survival.[154] Levels of BDNF and vascular endothelial growth factor are also increased with antidepressant use, and these proteins promote survival and proliferation of both neural and



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**Table 4** | Effects of treating medical conditions that cause hippocampal atrophy

| Study design and inclusion criteria | Outcome measures and results | Further comments |
|---|---|---|
| ***Yucel et al. (2007)***[156] | | |
| 4-year longitudinal study of lithium therapy; 12 patients with bipolar affective disorder with no prior pharmacological therapy, mean age 28.8 years; 40 age-matched controls with no history of psychiatric illness | Hippocampal volumetry using manual segmentation of MRI scans<br>After 4 years of treatment, hippocampal volume increased by 4–5% ($P$<0.001), with most growth occurring in first 9–12 months | Improved performance in verbal memory with treatment<br>Association between improvement in memory (number of items recalled in a memory task) and increase in size of left and right hippocampi ($P$<0.01) |
| ***Yucel et al. (2008)***[157] | | |
| 8-week prospective, controlled study of lithium therapy; 21 patients with bipolar affective disorder who had no prior pharmacological therapy and no history of substance abuse (12 patients treated with lithium, mean age 25.7 years; 9 patients not receiving treatment, mean age 24.4 years); 30 controls without bipolar affective disorder, mean age 25.3 years | Hippocampal volumetry using manual segmentation of MRI scans<br>Bilateral increases in hippocampal volume after 1–8 weeks of treatment compared with patients not receiving medication (left hippocampus, $P$=0.03; right hippocampus, $P$=0.02) | Head of hippocampus was most affected; structural changes apparent even after a short course of lithium treatment |
| ***Gazdzinski et al. (2008)***[158] | | |
| 1-month prospective study; 24 men with alcohol dependency* who underwent a period of abstinence from alcohol (intervention group: 13 smokers, mean age 50.7 years, and 11 nonsmokers, mean age 50.2 years); 14 age-matched, nonsmoking controls who were light drinkers (mean age 47.3 years) | Hippocampal volumetry using three-dimensional atlas-based segmentation of MRI scans<br>No significant differences observed at baseline between hippocampal volumes of nonsmoking participants intervention group and those of control group, but smokers with alcohol dependency had 6.9% smaller hippocampal volumes than controls ($P$=0.08)<br>1 month after alcohol cessation, intervention group (smokers and nonsmokers) demonstrated increased hippocampal size ($P$<0.01) | Spectroscopic analysis of NAA levels supports the idea that alcohol-related hippocampal volume deficits are mostly glial losses, as demonstrated by histological analysis: 10.4% lower concentration of NAA in alcohol-dependent smokers than controls, $P$=0.02; 12.8% lower concentration of NAA in alcohol-dependent nonsmokers compared with controls, $P$=0.008 |
| ***Canessa et al. (2011)***[150] | | |
| 3-month prospective study of treatment for obstructive sleep apnoea; 17 patients who had received no prior treatment for the condition, mean age 44.00 years; 15 controls without obstructive sleep apnoea, mean age 42.15 years | MRI and voxel-based morphometry<br>Treated group had increased left and right hippocampal volume after 3 months ($P$<0.05 for left and right hippocampi) | Improvements in memory, attention, and executive functioning also noted in treatment group |
| ***Nordanskog et al. (2010)***[151] | | |
| 2-week prospective study of ECT in 12 patients with clinical depression refractory to pharmacological treatment; mean age 40 years, range 19–67 years | Hippocampal volumetry using manual segmentation of MRI scans<br>1 week after ECT, patients had bilateral 4–5% increase in hippocampal volume (left hippocampus, $P$<0.001; right hippocampus, $P$<0.01) | None |
| ***Tendolkar et al. (2012)***[149] | | |
| 1-year, randomized controlled trial of cholesterol-lowering therapy (including statins); 34 elderly patients with atrial fibrillation but no history of stroke and normal cognition, mean age 74.5 years, randomly assigned to treatment (atorvastatin and ezetimibe) or placebo | Hippocampal volumetry using manual segmentation of MRI scans<br>Bilateral hippocampal volume declined in both groups; however, patients on treatment had less atrophy of right hippocampus than did controls ($P$=0.068). | Improvement in cognitive speed (assessed using digit symbol substitution test, $P$<0.010) and short-term and long-term memory ($P$<0.030) with treatment |

*Alcohol dependence defined as more than 150 drinks per month for at least 8 years. Abbreviations: ECT, electroconvulsive therapy; NAA, *N*-acetylasparate.

endothelial cells. Lithium treatment in patients with bipolar affective disorder can also produce a significant increase in hippocampal volume bilaterally and a significant improvement in memory after 9–12 months of therapy.[156,157] In a follow-up study, significant bilateral hippocampal growth was already present after only 1–8 weeks of lithium therapy.[157]

Treatment of alcoholism is effective in reversing, to some extent, the hippocampal atrophy seen in patients with clinical depression. Enlargement of the hippocampus was found in individuals with a history of chronic alcohol abuse, after abstaining from alcohol for 1 month.[158] Furthermore, individuals in this study who smoked cigarettes (in addition to alcohol abuse) demonstrated a slower recovery of metabolic activity in the medial temporal lobe than did nonsmokers. These findings suggest that providing advice and/or treatment for smoking cessation is just as important as treating alcoholism.

To our knowledge, no studies have investigated the prevention of hippocampal atrophy after TBI in humans. However, animal studies have shown that both resveratrol[159] and docosahexaenoic acid (an omega-3 fatty acid that is abundant in fish)[126] confer neuroprotection after TBI. Sir2α—a mediator of cellular stability—is present in fish oil, although it seems to have no beneficial effect on hippocampal size in the absence of TBI. Other



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evidence suggests that vitamin E, a potent antioxidant, confers neuroprotection after TBI.[160]

### Integrating positive and negative factors

Various conditions and processes, individually or in combination, contribute to a reduction in the size of the hippocampus. These include hypertension, diabetes mellitus, obesity, obstructive sleep apnoea, PTSD, head trauma, and neurodegenerative processes that cause excessive aggregation of toxic proteins in the brain (Box 1). Conversely, several interventions, including improved fitness, cognitive stimulation, and meditation, can, individually or in combination, increase the size of the hippocampus (Box 3). The net balance of these negative and positive factors ultimately seems to determine the size and health of the hippocampus and, in turn, the extent to which cognitive acuity is preserved with ageing or dementia.

An attempt to integrate the positive and negative factors (and their associated biochemical processes) that have an effect on the hippocampus has led to the formulation of a new model that encompasses the effects of these factors in late-life dementia. In this model, which is called the dynamic polygon hypothesis, the specific constellation of genetic and environmental risk factors (including apolipoprotein E genotype, obesity, diabetes mellitus, hypertension, head trauma, systemic illnesses, and obstructive sleep apnoea) that is present in a given individual is considered to contribute to the development of late-life brain atrophy and dementia.[40] Essentially, this model considers the interaction of genes with environmental exposures that are known to modulate the size and integrity of the neocortex and hippocampus. The model also emphasizes the dynamic nature of the mechanisms involved in determining the baseline size of the hippocampus and, ultimately, the individual's baseline cognitive function.[40] Understanding the details of processes that have an effect on the hippocampus is important when designing interventions that could reduce memory loss and cognitive impairment in ageing individuals, but long-term clinical trials are needed to determine whether such interventions might prevent or delay the onset of dementia.

## Conclusions

Late-life dementia is a process that involves atrophy in both the hippocampus and the cortex. However, the hippocampus is unique in that it has not only heightened vulnerability to a variety of mechanisms of injury to the brain (such as hypoxia, obesity and concussion), but also an enhanced capacity for neuroplasticity, which provides neuroprotection. With the ageing process, the hippocampus has a greater propensity to atrophy than other regions of the brain. The rate of hippocampal atrophy accelerates with a number of conditions, including diabetes mellitus, white matter disease, cardiac arrest, clinical depression, head trauma, and obstructive sleep apnoea. Reversal of this process can be achieved by improving physical fitness and by engaging in cognitively stimulating endeavours. Consistent observations by researchers that elderly individuals with large hippocampi can withstand high brain concentrations of amyloid-β plaques and neurofibrillary tangles without exhibiting signs of dementia, combined with results from studies that demonstrate the slowing of hippocampal atrophy in individuals with AD who join fitness programmes, emphasizes that the hippocampus is a dynamic structure with the potential to change in size throughout life. Given the large number of medical conditions that have a role in hippocampal atrophy the development of a single drug to prevent late-life dementia is highly unlikely. A more realistic approach would be to combine the strategies that improve brain health, such as improved cardiovascular fitness and diet, and to minimize stress-inducing factors.

### Review criteria

MEDLINE was searched for articles in English published from January 1980 to December 2011. The search terms used were "hippocampus size", "MRI", "brain size", "brain volume", "atrophy", "memory", "cognition", "dementia", "aging", "neuroplasticity", "neurogenesis", "voxel-based morphometry", "vascular risk factors", "concussion", "inflammation" and "measurements". The reference sections of relevant articles were checked for additional important publications.


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**Author contributions**

All authors contributed to discussions of the article content, writing the article and to review and/or editing of the manuscript before submission. In addition, M. Fotuhi and D. Do researched the data for the article.



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