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Ageing Research Reviews
4 (2005) 123–140

ageing
research
reviews

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Review

Aging, stress and the hippocampus

D.B. Miller *, J.P. O'Callaghan

Chronic Stress and Neurotoxicology Laboratories, TMBB-HELD, Mailstop L-3014, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health-CDC-NIOSH, 1095 Willowdale Road, Morgantown, WV 26505, USA

Received 4 March 2005; accepted 5 March 2005

Abstract

Functional loss often occurs in many body systems (e.g., endocrine, cognitive, motor) with the passage of years, but there is great individual variation in the degree of compromise shown. The current focus on brain aging will continue because demographic trends indicate that the average lifespan will show a continued increase. There is increasing emphasis on understanding how aging contributes to a decline in brain functions, cognition being a prime example. This is due in part to the fact that dementias and other losses in brain function that sometimes accompany aging cause an obvious decline in the quality of life and these deficits are of more concern as the number of elderly increase. Stress also is a ubiquitous aspect of life and there is now a greater interest in understanding the role of stress and the stress response in brain aging. The key role of the hippocampus and its related brain structures in cognition, as well as in the feedback control of the response to stress, have made this brain area a logical focus of investigation for those interested in the impact of stress on brain aging. Here, we describe how the hippocampus changes with age and we examine the idea that age-related changes in the secretion patterns of the hypothalamic-pituitary adrenal (HPA) axis can contribute to aging of this structure. We also examine the proposal that stress, perhaps due to compromised HPA axis function, can contribute to hippocampal aging through exposure to excessive levels of glucocorticoids. The aging hippocampus does not appear to suffer a generalized loss of cells or synapses, although atrophy of the structure may occur in humans. Thus, age-related cognitive impairments are likely related to other neurobiological alterations that could include changes in the signaling, information encoding, plasticity, electrophysiological or neurochemical properties of neurons or glia. Although excessive levels of glucocorticoids are able to interfere with cognition, as well as hippocampal neuronal integrity, and aging is sometimes accompanied by an increase in these steroids because of inadequate feedback control of the HPA axis, none of these are a foregone consequence of aging. The general preservation of cells and the plastic potential of the hippocampus

* Corresponding author. Tel.: +1 304 285 5732; fax: +1 304 285 6220.
E-mail address: dum6@cdc.gov (D.B. Miller).

1568-1637/$ – see front matter. Published by Elsevier Ireland Ltd.
doi:10.1016/j.arr.2005.03.002

provide a focus for the development of pharmacological, nutritive or lifestyle strategies to combat age-related declines in the hippocampus as well as other brain areas.
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Keywords: Hippocampus; Stress; Age; Plasticity

1. Introduction

Aging is inevitable and is most conveniently defined as the advance of chronological years, but the changes wrought by the passage of time vary greatly among individuals; for example, not all the elderly exhibit cognitive difficulties (Rowe and Hahn, 1987; Snowdon, 2003). Although some individuals may find the changes in motor function and reproductive capacity disturbing as they age, many more fear the loss of self and the decline in life quality caused by the dementias with their attendant loss of cognitive capabilities. The wide and non-uniform spectrum of cognitive capacity in the elderly has prompted general questions about how the brain ages; more specifically, this lack of uniform aging has focused interest on determining how brain structures crucial for cognition change with age and in determining if factors such as stress can contribute to these changes (Barnes, 1994; Blalock et al., 2003; Heuser and Lammers, 2003; Lee et al., 2000; Lupien et al., 1998; Miller and O'Callaghan, 2003; Polleri et al., 2002; Sapolsky, 1999; Smith, 2003). These concerns are becoming more prominent because the number of the oldest age segments of the population are growing and this likely will produce further increases in the dementias (Hebert et al., 2003).

2. The hippocampus and aging

Invariably, any description or characterization of brain aging includes a consideration of the hippocampus (Fig. 1). This structure of the medial temporal region of the brain is crucial for storage and retrieval of certain types of information and it often is identified as a key mediating structure in studies examining the pathophysiology of disordered memory (Panegyres, 2004). The CA1 area of hippocampus is one of the initial brain areas displaying pathology and neuronal loss in Alzheimer's disease—a disorder characterized by memory loss (West et al., 2004). In addition to its influential place in the study of memory, the hippocampus also is a focal point for researchers interested in understanding the physiology and the consequences of stress. Because the hippocampus is an important element of the feedback loop responsible for terminating the stress-induced release of glucocorticoids, there is great interest in knowing how chronic stress and potential excess in steroid levels impact the aging of the hippocampus (Miller and O'Callaghan, 2002, 2003). Although other hormones may play a role in brain aging (Azcoitia et al., 2005; Erickson et al., 2005; Mattson et al., 2004; Vallee et al., 2003), in this review we chose to examine the idea that the characteristics of aging displayed by this structure are at least partly caused by stress and glucocorticoids, a hypothesis that has come to dominate the contemporary neuroscience community.

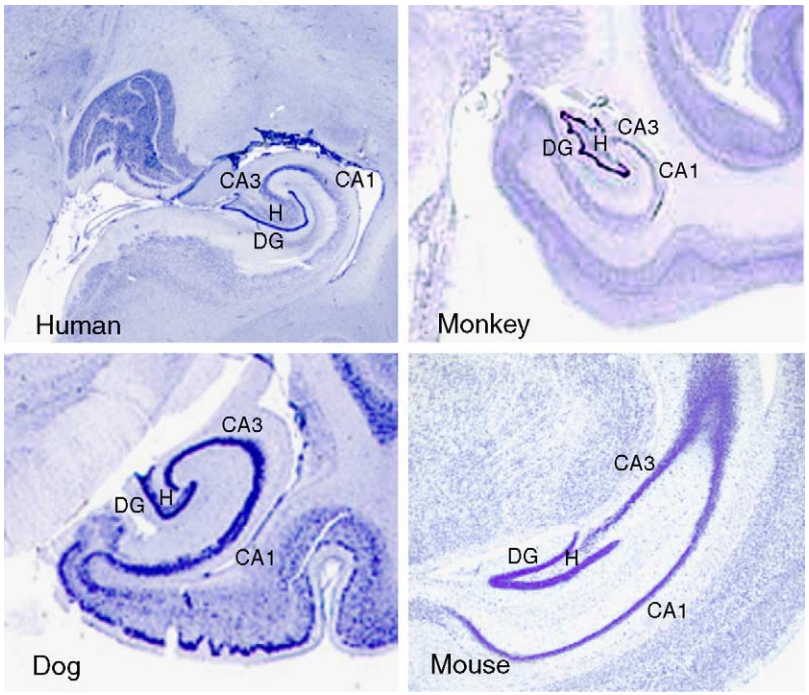

Fig. 1. The hippocampal formation in the human, monkey, dog and mouse; note the similarity in cytoarchitecture (photomicrographs graciously provided by Dr. Robert Switzer of NeuroScience Associates).

3. The structure and function of the hippocampus

The hippocampus, first labeled as such by Giulio Cesare Aranzi (Gross, 1998), is one of the phylogenetically oldest brain areas and it is located in the medial temporal region of the brain. It is a structure with a distinct shape and cytoarchitecture (Fig. 1) consisting of two major parts, the hippocampus proper (CA1–CA3 pyramidal cell layers) or Ammon's horn and the dentate gyrus. Although it is readily discerned across mammalian species (e.g., human, monkey, rodent) it occupies a smaller percentage of the total cortical area in the primate because of the dominance of the cerebral cortices in the higher species. This highly interconnected structure often is a focal point in discussions of cognitive function. For example, neuropsychological testing of subjects such as the profoundly amnesic H.M., who suffered memory loss after bilateral hippocampal resection as a palliative for his epilepsy (Scoville and Milner, 1957), as well as imaging of healthy humans, has revealed the hippocampus and its associated cortical areas to be pivotal for declarative memory. The recall of personal experiences and the acquisition of semantic or factual knowledge constitute important facets of declarative memory (Eichenbaum, 2004). Input to the hippocampus from the cortex is utilized in the formation of memories as well as in learning; the entorhinal cortex provides the major cortical input to the hippocampus. The entorhinal cortex receives information from all the senses, as well as multiple cortical

areas, and axons from this area project through the perforant path (PP) to the granule cells of the dentate gyrus.

There are multiple internal connections within the hippocampus that are critical in the transmission of information between the sub-regions of this structure and contribute to the operation of the hippocampus, especially the dentate gyrus in conjunction with the CA1, CA3 sub-regions, as a circuit. There is consensus that the hippocampus is crucial in the storage and retrieval of information but there is still debate about the exact role the hippocampus may play in processing the information concerned with pattern separation, association and completion as well as encoding, novelty detection, and the development of short- and intermediate-term memories (Kesner et al., 2004). However, recent evidence from a variety of avenues including lesion, behavioral, electrophysiological and gene activation studies suggest that, although the role of the hippocampus is most often evaluated as a singular entity, there are separable and distinct sub-region functions within this structure (Kesner et al., 2004). Thus, the dentate gyrus processes metric spatial representation and the CA3 subregion is responsible for spatial pattern association and completion, detection of novelty and short-term memory. Finally, the CA1 subregion mediates processes involved in temporal pattern association and completion as well as intermediate-term memory (Kesner et al., 2004; Miyashita, 2004). This notable subregion specialization in the hippocampus suggests that a thorough evaluation of the aging hippocampus should involve a closer examination of how age affects subregion function and anatomy; it should also be determined if age-related changes in these subregions are linked to specific patterns of memory deficits.

4. Characteristics of the aging hippocampus

The evaluations of the aging hippocampus have frequently centered on its anatomical and biochemical aspects with the objective of determining if age was associated with notable changes in hippocampal cell number, size or function. Early work often reported that in humans and many other species neuronal loss or a decrease in neuronal density inevitably accompanied aging. The decrease in neuronal density could be due to a loss of neurons or, in contrast, it could reflect shrinkage of neuronal elements such as dendrites, rather than actual cell loss. Importantly, the counting procedures used in these initial studies may have suffered from various types of biases, as they relied on assumptions about the orientation, shape, size and distribution of the neurons being evaluated. More precise methods are now available for counting cells as well as other elements of brain structure. The application of ''design-based'' stereology procedures does not require the use of the assumptions listed above and thus effectively eliminates these issues as sources of systematic error in the final calculation of neuron number (see Schmitz and Hof, 2005; West, 2002 for a discussion of relevant issues in stereology). Thus, recent investigations utilizing the newer quantitative unbiased stereology procedures, rather than traditional cell counting methods, have challenged the belief that aging of the hippocampus always involves neuron loss. Although a decrease in neuronal density does appear in many species to be a characteristic of the aging hippocampus, numerous studies now indicate neuron number remains quite stable across the lifespan (Calhoun et al., 1998; Landfield et al.,

1981; Long et al., 1999; Keuker et al., 2003; Rapp and Gallagher, 1996; Simic et al., 1997; West, 2002; Wickelgren, 1996). Further, when neuron loss occurs, it appears to be restricted to the CA1 area of the hippocampus, one of the regions first affected in AD and also a region displaying many other age-related changes (Haigler et al., 1986; Kerr et al., 1991; West and Gundersen, 1990; West, 2002). Even though some neuron loss is found in the CA1 area, it is very circumscribed and it is not a uniform loss throughout the entire subregion. Furthermore, not all studies examining CA1 in healthy or unhealthy aged hippocampus report a neuron loss (Rasmussen et al., 1996; West, 1993). The apparent stability of neuron number in the hippocampus throughout lifespan suggests that when neuron loss occurs it is due to frank disease and pathology, not age per se. As the subfields of the hippocampus differ on a cellular, molecular, and functional basis, more work is needed to determine the extent and subfield specificity of hippocampal cell loss in human aging when overt disease is not present (Kesner et al., 2004; Small et al., 2004).

The impact of aging on the size of the hippocampus also has been a focal point of research; its volume can easily be determined by the available noninvasive imaging techniques, because this structure can be precisely and clearly identified within the three orthogonal anatomic planes of the brain. High-resolution magnetic resonance imaging (MRI) of living individuals as well as that of post-mortem brains leaves little doubt that atrophy of the hippocampus may occur with certain diseases and disorders; these include major depression, dementias including Alzheimer's disease, untreated hypertension, coronary artery disease, Cushing's disease, posttraumatic stress disorder, obstructive sleep apnea, reduced glucose tolerance and diabetes (Bremner et al., 2005; Campbell et al., 2004; Convit et al., 2003; Den Heijer et al., 2003; Frodl et al., 2002; Gosche et al., 2001; Korf et al., 2004; Koschack and Irle, 2005; Macey et al., 2002; MacQueen et al., 2003; Van Petten, 2004; Villarreal et al., 2002). Although cell loss in the hippocampus is not a necessary concomitant of aging, hippocampal size varies widely across individuals; longitudinal as well as cross-sectional studies find size decreases with age and it occurs in those not suffering from neurological disease or insult; however, conventional neuroanatomical and MRI assessment of experimental animals finds little shrinkage of the hippocampus and not all studies of humans report atrophy (Cardenas et al., 2003; Eberline et al., 1997; Erickson et al., 2005; Gur et al., 2002; Jernigan et al., 2001; Lye et al., 2004; Raz et al., 2004, 2005; Sullivan et al., 2004; Van Petten, 2004; West, 2002). To add to the controversy of whether the hippocampus shrinks with age, when atrophy is found, it is not necessarily predictive of cognitive performance. Some studies report that the learning of complex spatial tasks increases the volume of the right hippocampus while others link shrinkage to memory impairment (Maquire et al., 2000; Lye et al., 2004; Mortimer et al., 2004; Tisserand et al., 2000; Wolf et al., 2004). Apparently, hippocampal shrinkage can begin in early adulthood and accelerate with age; losses of 0.3–2.1% per year are reported and women display less atrophy than men. However, the soundness of this conclusion is dependent on the reliability of the imaging techniques and questions have been raised due to methodological issues (Pruessner et al., 2001; Van Petten, 2004). An improvement of quantification methods in imaging studies, including the use of completely automated methods to monitor longitudinal change, should help to resolve the conflicting results concerning shrinkage of the hippocampus with age. Automation certainly will reduce the within and between rater errors that are prevalent in manual methods. Investigators also

may need a better awareness of the effects of statistical methodology. For example statistical normalization for head size, etc. may influence results by increasing variability (Cardenas et al., 2003; Van Petten, 2004).

Although frank neuronal loss is not likely responsible for the atrophy found in the aged hippocampus, the decreased volume could be accounted for by reductions in the size of neurons and their associated dendritic and synaptic fields (Long et al., 1999). Moreover, glia, the nonneuronal cellular elements of the hippocampus, markedly contribute to its volume due to the relative abundance of glia over neurons. Therefore, changes in the various types of glia (i.e., astrocytes, oligodendrocytes and microglia), may contribute to atrophy. Indeed, myelination, a function of oligodendrocytes, continues in the human hippocampus well into the 50s and 60s and aging can be associated with myelin deterioration and loss; white matter accounts for about 3% of the hippocampal formation (Bartzokis, 2004; Frodl et al., 2002).

The aging hippocampus of rat, mouse, rabbit, dog, monkey and human all show another type of change in glial morphology; a pronounced astrocyte hypertrophy, the hallmark of which is an increase in the amount of protein and mRNA for glial fibrillary acidic protein (GFAP) (Borras et al., 1999; David et al., 1997; Nichols et al., 2001; O'Callaghan and Miller, 1991; Sloane et al., 2000). Although astrocytosis generally occurs in response to neural damage or injury, interestingly, the increase found in aging brain occurs in apparently healthy individuals displaying no obvious cognitive impairment or disease. The importance of this age-related astrocytic hypertrophy is unknown, but it could contribute to atrophic changes, because astrocytes provide neurotrophic support that aids in the maintenance of neuronal integrity and function. To fully judge the respective roles of the various types of glial cells in aging of the hippocampus, as well as other areas of brain, will require a great deal more characterization and understanding of how glial cells interact with the neuropil and how these interactions change across the lifespan. In this regard, modern imaging studies have centered almost exclusively on neuronal populations and gray matter structures, there has been very little mapping of white matter (Jernigan and Fennema-Notestine, 2004). Many investigators, however, are now taking note of the importance of considering white matter changes as well as changes associated with other types of glia in determining the impact of disease and age on the brain (Bartzokis, 2004; Atwood et al., 2004; Courchesne et al., 2000; Lyons et al., 2004; Rajkowska, 2000; Rajkowska et al., 1999; Scott et al., 2004; Toussaint, 2003).

Healthy older individuals can display cognitive decline and deficits in memory functions without showing any other evidence of neurological decline. While the hippocampus is implicated in such impairments, hippocampal neuron loss is not likely to be responsible for the deficits because a frank loss of neurons is not a characteristic of aging in this brain area. A decrease in the size and density of hippocampal neurons is possible and there is some consensus that synapses are lost with age; all of these factors could account for the decline in cognitive function, but there is by no means consensus on this matter (Nichols et al., 2001; Morrison, 2001). The aging hippocampus is, however, characterized by marked and consistent changes in many neurochemical and neurophysiological aspects that could compromise function and account for the cognitive changes. For example, the pyramidal cells in aged rat hippocampus show a diminished response to acetylcholine, a neurotransmitter prominent in memory processes; the aged

monkey hippocampus also is characterized by a loss of microvascular integrity and glucose utilization (Eberline et al., 1997; Haigler et al., 1986; Keuker et al., 2000). Increased excitability is a characteristic of the principal neurons of the aged hippocampus. A loss of inhibitory processing within the intrinsic circuits contributes to the lack of ''silent'' cells (Stanley and Shetty, 2004). Action potentials can be elicited at lower thresholds in aged rats and the amplitude of the potential is lower; potassium currents are reduced as well (Haigler et al., 1986; Kerr et al., 1991). Cellular handling of calcium becomes dysregulated with age and this can involve improper influx, release, extrusion, buffering and storage of this important ion. Eventually, these disruptions result in the marked differences in the calcium-regulated signaling properties displayed by aged neurons, including those of the hippocampus. Such deficits have implications important for the function of both neurons and glia (Blalock et al., 2003; Toescu et al., 2004). Output neurons of the CA1 and CA3 regions of the aged hippocampus show marked and consistent increases in the calcium dependent afterpolarization (AHP) associated with increases in L-type voltage-gated Ca^{2+} channels. As slowing of the AHP promotes intrinsic neuronal excitability during hippocampal dependent learning, the abnormal functioning of the AHP in the aged hippocampus could account for the decline in cognitive ability observed with age. Inappropriate handling of calcium also may be responsible for the compromise in synaptic transmission as well as in the long-term and short-term forms of Ca^{2+}-dependent synaptic plasticity exhibited by aging hippocampus (Disterhoft et al., 2004; Papatheodoropoulos and Kostopoulos, 1996; Toescu et al., 2004). Long-term potentiation (LTP) and long-term depression (LTD), considered to be cellular models of learning and memory, are compromised in aged hippocampus; improvement of Ca^{2+} homeostasis impairments by caloric restriction may be how this manipulation retards the deficits in LTP normally observed in the aged hippocampus (Okada et al., 2003). Any of these neurochemical and neurophysiological changes in the aged hippocampus could account for the cognitive deficits often displayed by the elderly.

In summary, it appears that aging may cause a sub-region localized rather than a widespread neuronal loss in the hippocampus. Clearly, additional research will be needed to confirm this view, as well as to determine a role for changes in neuron number, because neuron number is an important although by no means the only determinant of functional capacity. Moreover, in terms of prevention and treatment, it is more likely that strategies can be developed to stave off or correct age-related hippocampal dysfunction if it is not due to neuronal loss, because it is unlikely that replacement of neurons will become a routine practice for many more years (Azcoitia et al., 2005; Landfield and Cadwallader-Neal, 1998; Okada et al., 2003; Verkhratsky et al., 2004).

5. Does stress cause or accelerate aging in the hippocampus?

The word stress is a convenient shorthand term used by everyone and, when we use it to describe internal states or feelings, it is at our own subjective interpretation of its meaning. However, the very ubiquity of this term presents problems in objectively determining how stress impacts the body. To counter this we, as well as many others, have chosen to define stress as any disruption of homeostasis and to refer to any of the myriad internal or external

challenges that produce this disruption as stressors (McEwen, 1998; Lupien et al., 2005; Miller and O'Callaghan, 2002; Smith, 2003).

Disturbing homeostasis initiates a series of events called the stress response or cascade (Fig. 2) and it is this well-choreographed response involving the hypothalamic pituitary adrenal (HPA) axis that restores homeostasis. The hippocampus, as well as the glucocorticoids synthesized and released from the adrenal glands, also is intimately involved in the response to homeostatic disturbance. With its abundance of glucocorticoid receptors, the hippocampus is a pivotal element in a classic negative feedback circuit in which the release of a species-specific glucocorticoid is responsible for terminating the signal initiating the cascade; failure or inefficient operation of this feedback loop can result in continuous high circulating levels of glucocorticoids. As the hippocampus is a target of glucocorticoids, there is concern that conditions resulting in a prolonged excess of glucocorticoids would harm this brain structure. Because the hippocampus can suffer deterioration with age, many investigators have speculated that the excess of glucocorticoids that sometimes occur with age may be at least a partial cause of this deterioration, either due to a primary action of these stress hormones or by enhancing

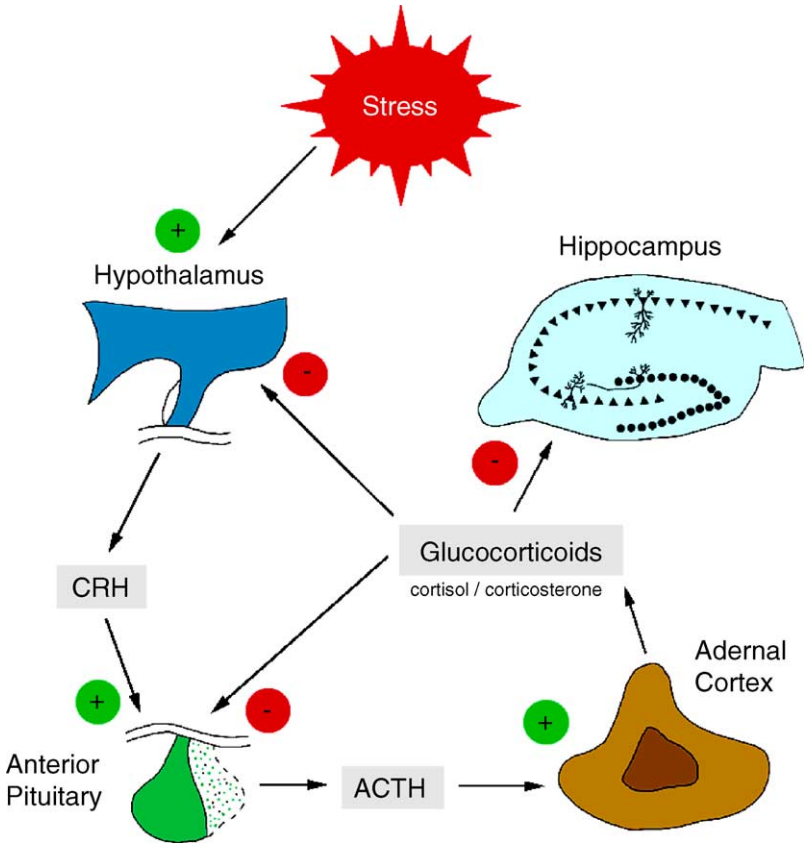

Fig. 2. Important components of the stress cascade (adapted from Miller and O'Callaghan, 2002).

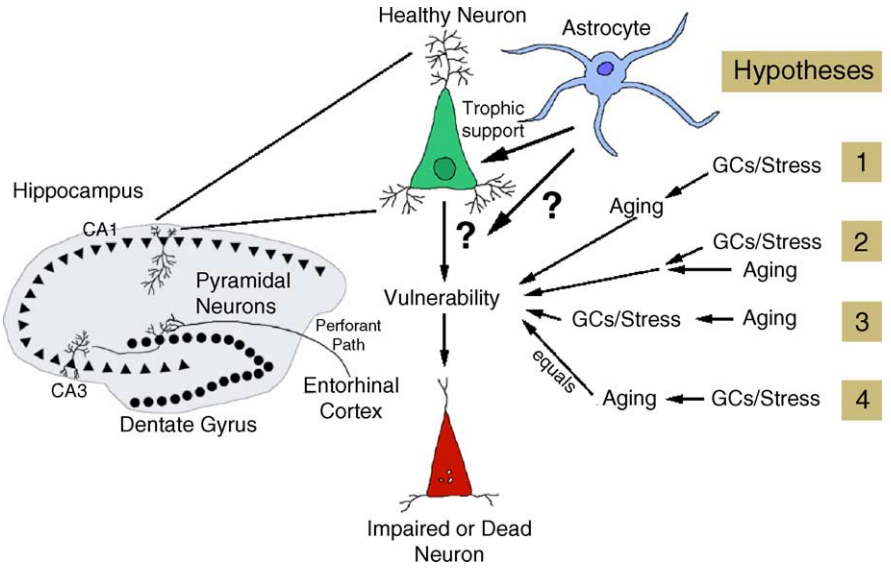

Fig. 3. Schematic illustrating the ways in which stress, glucocorticoids and aging may increase the vulnerability of the hippocampus (adapted from Miller and O'Callaghan, 2003; Porter and Landfield, 1998).

vulnerability to other insults (McEwen, 1999; Nichols et al., 2001; Porter and Landfield, 1998; Sapolsky et al., 1986). There are several ways (Fig. 3) in which the health of the hippocampus could be affected by interactions between stress and age: (1) stress/glucocorticoids accelerates or exacerbates aging (2) stress/glucocorticoids and aging act in parallel; (3) aging results in excessive stress/glucocorticoids and this enhances vulnerability; (4) all of the effects of aging are due to excessively high levels of stress/glucocorticoids, although this is likely the least probable of all the scenarios. Central to understanding how stress and glucocorticoids might foster the aging of the hippocampus is determining if and how the levels of glucocorticoids or the efficiency of the HPA axis change with age.

It is well known that glucocorticoids affect cognition and that cognitive deficits can accompany aging. These findings lead many to question whether excessive levels of glucocorticoids during aging could account for the deficits (Belanoff et al., 2001; McEwen, 1999). During the stress response, glucocorticoids have a coordinating role in promoting the processing of novel information related to the stressful event. Excessive levels of these steroids, whether due to hyper-secretion in response to a stressor, exogenous administration or as a concomitant of diseases like Cushing's syndrome, are known to produce cognitive impairment (Belanoff et al., 2001; Brown et al., 2004; De Kloet et al., 1999). Studies of the elderly are inconsistent regarding the effect of aging on the levels of glucocorticoids and/or the efficiency of the HPA axis. The daily secretion of glucocorticoids follows a distinct circadian pattern and, in humans, the basal levels are high at morning awakening and decline over the day. Some studies find elevated basal levels while others find protracted elevations following stress or after the administration of a steroid. All of these effects are

suggestive of impaired feedback, but in general, the many cross-sectional studies conducted have not found a relationship between advancing age and increases in glucocorticoid levels (Carvalhaes-Neto et al., 2003; Ferrari et al., 2001; Lupien et al., 2005; Nichols et al., 2001; Wilkenson et al., 2001). However, longitudinal studies have shown great individual differences with age and above normal cortisol levels predict deficits in declarative and working memory tasks mediated by the hippocampus. Inappropriate activation of the HPA axis does not appear to be a general characteristic of aging, but these longitudinal studies suggest, in any given population of the elderly, that individuals with above normal cortisol levels during the course of the evaluation are more likely to be those showing cognitive deficits. This suggests it is the cumulative exposure to excessive glucocorticoids that is detrimental (Lupien et al., 2005).

The protracted exposure of the hippocampus to excessive levels of glucocorticoids causes functional and structural changes; the exact nature of the structural change is still being debated. The early studies concluded that neuronal death could occur, with much of the work being stimulated by Sapolsky's intriguing ''glucocorticoid cascade'' hypothesis. These findings, documented in primates and rodents, showed an outright loss of neurons or a decrease in neuron density after exposure to protracted stress or excessive glucocorticoid levels. Other more recent work has produced conflicting data, suggesting that neuron death is not always a consequence of exposure to excessive glucocorticoids. Moreover, these studies suggest that other individual susceptibility factors, such as genetics, operate in the circumstances where such outright cell loss is observed (Angelucci, 2000; Landfield et al., 1978; Leverenz et al., 1999; Nichols et al., 2001; Sapolsky, 1996; Sapolsky et al., 1986; Sousa et al., 1998; Uno et al., 1989; Wickelgren, 1996).

Other aspects of hippocampal structure can be affected by glucocorticoid level. Brain imaging of individuals with Cushing's syndrome or patients receiving glucocorticoids in a therapeutic context indicate that the hippocampus can atrophy in response to high glucocorticoid levels (Brown et al., 2004; Wilner et al., 2002). Upon removal of the steroids, the atrophy is reversed, which suggests that the changes are not likely due to death of neurons.

The hippocampus displays remarkable structural plasticity and exposure to excessive levels of glucocorticoids compromises this plastic potential. In many species, including humans, neurogenesis is maintained throughout life and protracted stress or excessive glucocorticoid exposure inhibits the production of new neurons in the hippocampus. High levels also can cause atrophy of pyramidal cell dendrites and the loss of synapses. Exposure to glucocorticoids also inhibits repair responses, such as sprouting and formation of new synapses, responses that are part of neuronal compensation to injury. Glucocorticoids and stress also may indirectly impact hippocampal structure by interfering with the support provided by glia. The expression of GFAP, an astrocyte-localized intermediate filament protein, is suppressed by glucocorticoids and this suggests that hypertrophy of astrocytes in the aged hippocampus may represent a decreased responsiveness to steroids, perhaps through a decrease in receptor number rather than an injury response (Nichols et al., 2001; O'Callaghan et al., 1991). Age-related changes in astrocyte-neuron interactions may compromise neuronal function and perhaps account for the synaptic changes observed with age. How glucocorticoids contribute to this phenomena requires a greater understanding of glial-neuropil interactions (Cameron and McKay, 1999).

6. Is oxidative stress a major cause of brain aging?

While a role for oxidative stress and free radical generation serves as an attractive basis for ''stress'' and age-related neurodegeneration, this hypothesis may not be as unifying as it once seemed (Barja, 2004; Finch, 2003; Toussaint, 2003). As noted above, oxidative species do accumulate in the CNS with aging and anti-aging strategies that employ antioxidants can retard certain aspects of age-related neurodegeneration. Moreover, the ''free radical hypothesis'' of aging has gained attention because it serves as a common feature associated with protein misfolding/aggregate accumulation/excitotoxicity/inflammation, to name a few, i.e. processes linked with aging and neurodegenerative diseases (Anderson, 2004). These observations not withstanding, a causal role for oxidative stress in aging remains elusive. Indeed, the negative associations of reactive oxygen species with processes detrimental to key neural function, such as mitochondrial respiration and proteosome processing, recently has given way to the possibility of roles in physiological functions (Meffert and Baltimore, 2005). For example, up- and down-stream effectors in the cytokine, NF-κB, p-38 MAP kinase pathway can be implicated in oxidative stress mediated inflammatory processes including those occurring in the CNS. More recent evidence, however, serves to substantiate a key role of this pathway in CA-mediated synaptic signaling and the regenerative roles of neurons and glial following a variety of neural injuries. Thus, the same responses viewed as ''bad'' in the context of an inflammatory response, now appear to be physiological, or at the least, desired features of neural responses to injury.

A role for glia, astrocytes and microglia in particular, often is cited in the context of mediators of inflammatory responses and oxidative stress (Anderson, 2004). The oxidative ''burst'' associated with phagocytic activity of macrophages in the CNS, some of which share surface markers with microglia, may serve as one example of a useful function of cell-mediated localized ''cleanups'' with an oxidative stress component. The general connotation of glial activation as a detrimental inflammatory response (with or without an oxidative stress component), no longer should be considered accurate. Neurodegeneration can occur in the absence of inflammation and the induction of inflammatory mediators in the CNS due to activation of the immune system in the periphery does not result in neurodegeneration (Little et al., 2002). This suggests that astrocytic activation in response to injury and, perhaps the hypertrophy of astrocytes that occurs with aging, serves as the basis for a neurotrophic rather than a neurodegenerative role for this major cell type in the CNS. Also, recent work has shown a relationship between a reduction in GFAP and disease; in depression the packing density of astrocytes in prefrontal cortex is decreased with a concomitant reduction in GFAP levels an observation fueling speculation that depression may be a glial disorder (Miller and O'Callaghan, 2005; Si et al., 2004). Thus, appropriate astrocyte activation may serve to enhance neuronal plasticity, including increases in synaptic sprouting following injury. Likewise, microglial activation, a response that acts in concert with astrogliosis, and often precedes it in responding to injury, also serves a restorative rather than a regenerative role. Thus, when these cellular responses to injury and aging are associated with the production and elaboration of reactive oxygen species, such effects can just as well be viewed as beneficial rather than detrimental. Finally, the fact that glial activation has been highly conserved from an evolutionary

standpoint, argues strongly for a positive role of these cellular reactions and associated oxidative processes, both in response to injury and aging of the CNS (Faulkner et al., 2004).

7. Are there strategies to maintain the health of the hippocampus during aging?

Obviously, the preservation of neuron number in the hippocampus across the lifespan along with its remarkable molecular, cellular and system-level plasticity provide encouragement for those interested in developing preventive and intervention strategies that will slow the impact of aging on this important brain structure. Activity, both intellectual and physical, is protective against neurodegenerative disease and the cognitive decline that can accompany aging. The protective mechanism is not known but may involve the production or maintenance of neurotrophic factors, such as BDNF, that play a role in neural plasticity (Mattson et al., 2004). BDNF levels are increased in the hippocampal area of rats and mice with access to exercise wheels and trophic factor gene therapy can ameliorate hippocampal deficits in monkeys (Cotman and Berchtold, 2002; Smith et al., 1999).

Maintaining intellectual and physical activity across the lifespan is obviously important for successful brain aging, but dietary and nutritional manipulation also may prove useful in preserving the health of the hippocampus. Caloric restriction or manipulations leading to a decrease in total energy consumption without nutritional compromise has been found to increase vitality and longevity in species ranging from invertebrates to nonhuman primates (Mattson, 2003; Miller and O'Callaghan, 2003). In findings more specifically related to maintaining the health of the hippocampus, caloric restriction minimizes the age-related increases in GFAP, inflammation, the observed impairments in LTP, and the loss of neurotransmitter receptors (Chung et al., 2002; Finch, 2003; Morgan et al., 1999; Okada et al., 2003). Data from the Biosphere 2 project (albeit controversial) and various epidemiological reports, indicate caloric restriction likely will have the same benefits in humans, as it instigates physiological changes (e.g., lowered blood pressure, reduced homocysteine and cholesterol levels, etc.) that are linked to healthy aging (Mattson, 2003; Walford et al., 2002). Although obesity is clearly linked to excessive ingestion of calories, there also is some indication that even those able to maintain a lean phenotype when energy consumption is high may be at more risk for neurodegenerative disorders (Mattson, 2003). Although the amount of food is important, the type of food ingested also contributes to brain health. Certain dietary constituents appear to provide protection against the functional and degenerative assaults of age. This realization has generated interest in ''nutriceuticals'' and functional foods; the idea that food or naturally occurring substances (e.g., vitamins, amino acids, spices, herbal supplements) maybe a way to promote health and treat disease has become of interest to the scientific community as well as to the general public (Cooke, 1998; Joseph et al., 2003; Gertner, 2004; Takeda et al., 2004).

Components of foods with properties beneficial for brain health include certain types of fats and plant constituents (e.g., ω-3 polyunsaturated fatty acids, α-linolenic acid, folic acid, flavonoids, lutein, vitamin C, polyphenols) but there is little understanding of why these ''chemicals'' provide protection (Kalmijn et al., 1997; Youdim et al., 2002). Many of the age-retarding strategies examined to date (caloric restriction, ingestion of highly

pigmented fruits and vegetables, exercise) really appear to have their actions through the prevention or arrest of disease, possibly through anti-oxidant properties, although it is premature to ascribe their beneficial properties solely to this mode of action (Miller and O'Callaghan, 2003). The dietary or nutritional manipulation or control of insulin and cholesterol pathways also may be a viable strategy for maintaining brain health. Genetic analyses of lower organisms including *C. elegans* and *Drosophila* have identified mutations of components of the insulin/IGF-I pathway that increase longevity (Warner, 2005). In mice, targeted mutations that suppress signaling in insulin pathways increases their lifespan and ability to combat conditions of extreme oxidative stress (e.g., 80% oxygen) (Baba et al., 2005; Holzenberger et al., 2003). The age-related deficits in myelin integrity or function may be helped by strategies that increase myelination, such as greater production of or exposure to insulin-like growth factor-1. This growth factor is known to increase myelination and prevent apoptosis of oligodendrocytes as well as to control factors that can accelerate myelin deterioration such as hypercholesterolemia and hypertension. In healthy centenarians, genes that affect cholesterol characteristics such as HDL and LDL particle size have been linked to longevity (Perls, 2004).

Undoubtedly the interest in developing strategies for healthy aging will continue as longevity is expected to increase due to medical advances. The remarkable plasticity of the hippocampus coupled with the fact that this structure appears to suffer very little neuronal loss across the lifespan, presents unique opportunities for the development of treatments effective in combating its age-related deficits. It is likely that the use of pharmacological, life-style (stress reduction, exercise), and nutritive (''brain healthy'' diet) interventions will all contribute in the future to the assurance of healthy aging of the hippocampus.

Acknowledgements

The authors would like to thank Dr. Stanley Benkovic for his help in the development of the figures.

References

Angelucci, L., 2000. The glucocorticoid hormone: from pedestal to dust and back. Eur. J. Pharmacol. 405, 139–147.

Azcoitia, I., Perez-Martin, M., Salazar, V., Castillo, C., Ariznavarreta, C., Segura, L.M., Tresguerres, J.A.F., 2005. Growth hormone prevents neuronal loss in the aged rat hippocampus. Neurobiol. Aging 26, 697–703.

Anderson, J.K., 2004. Oxidative stress in neurodegeneration: cause or consequence? Nat. Rev. Neurosci. Suppl. Neurodegeneration S18–S25.

Atwood, L.D., Wolf, P.A., Heard-Costa, N.L., Massaro, J.M., Beiser, A., D'Agostino, R.B., DeCarli, C., 2004. Genetic variation in white matter hyperintensity volume in the Framingham Study. Stroke 35, 1609–1613.

Baba, T., Shimizu, T., Suzuki, Y., Ogawara, M., Isono, K., Koseki, H., Kurosawa, H., Shirasaw, T., 2005. Estrogen, insulin, and dietary signals cooperatively regulate longevity signals to enhance resistance to oxidative stress in mice, J. Biol. Chem. (EPub ahead of print).

Barja, G., 2004. Free radicals and aging. Trends Neurosci. 27, 595–600.

Barnes, C.A., 1994. Normal aging: regionally specific changes in hippocampal synaptic transmission. Trends Neurosci. 17, 13–18.

Bartzokis, G., 2004. Age-related myelin breakdown: a developmental model of cognitive decline and Alzheimer's disease. Neurobiol. Aging 25, 5–18.

Belanoff, J.K., Gross, K., Yager, A., Schatzberg, A.F., 2001. Corticosteroids and cognition. J. Psychiartr. Res. 35, 127–145.

Blalock, E.M., Chen, K-C., Sharrow, K., Herman, J.P., Porter, N.M., Foster, T.C., Lanfield, P.W., 2003. Gene microarrays in hippocampal aging: Statistical profiling identifies novel processes correlated with cognitive impairment. J. Neurosci. 23, 3807–3819.

Borras, D., Ferrer, I., Pumarola, M., 1999. Age-related changes in the brain of the dog. Vet. Pathol. 36, 202–211.

Bremner, J.D., Randall, P., Scott, T.M., Bronen, R.A., Seibyl, J.P., Southwick, S.M., Delaney, R.C., McCarthy, G., Charney, D.S., Innis, R.B., 2005. MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder. Am. J. Psychiatr. 152, 973–981.

Brown, E.S., Woolston, J.D., Frol, A., Bobadilla, L., Khan, D.A., Hanczyc, M., Rush, A.J., Fleckenstein, J., Babcock, E., Cullum, C.M., 2004. Hippocampal volume, spectroscopy, cognition, and mood in patients receiving corticosteroid therapy. Biol. Psychiatr. 55, 538–545.

Calhoun, M.E., Kurth, D., Phinney, A.L., Long, J.M., Hengemihle, J., Mouton, P.R., Ingram, D.K., Jucker, M., 1998. Hippocampal neuron and synaptophysin-positive bouton number in aging C57BL/6 mice. Neurobiol. Aging 19, 599–606.

Cameron, H.A., McKay, R.D.G., 1999. Restoring production of hippocampal neurons in old age. Nat. Neurosci. 2, 894–897.

Campbell, S., Marriott, M., Nahmias, MacQueen, G.M., 2004. Lower hippocampal volume in patients suffering from depression: a meta-analysis. Am. J. Psychiatr. 161, 598–607.

Cardenas, V.A., Du, A.T., Hardin, D., Ezekiel, F., Weber, P., Jagust, W.J., Chui, H.C., Schuff, N., Weiner, M.W., 2003. Comparison of methods for measuring longitudinal brain change in cognitive impairment and dementia. Neurobiol. Aging 24, 537–544.

Carvalhaes-Neto, N., Huayllas, M.K., Ramos, L.R., Cendoroglo, M.S., Kater, C.E., 2003. Cortisol, DHEAS and aging: resistance to cortisol suppression in frail institutionalized elderly. J. Endocrinol. Invest. 26, 17–22.

Chung, H.Y., Kim, H.J., Kim, K.W., Choi, J.S., Yu, B.P., 2002. Molecular inflammation hypothesis of aging based on the anti-aging mechanism of calorie restriction. Microsc. Res. Tech. 59, 264–272.

Convit, A., Wolf, O.T., Tarshish, C., de Leon, M.J., 2003. Reduced glucose tolerance is associated with poor memory performance and hippocampal atrophy among normal elderly. Proc. Natl. Acad. Sci. 100, 2019–2022.

Cooke, J.P., 1998. Nutriceuticals for cardiovascular health. Am. J. Cardiol. 82 (Suppl.2), 43S–46S.

Cotman, C.W., Berchtold, N.C., 2002. Exercise: a behavioral intervention to enhance brain health and plasticity. Trends Neurosci. 25, 295–301.

Courchesne, E., Chisum, H.J., Townsend, J., Cowles, A., Cobington, J., Egaas, B., Harwood, M., Hinds, S., Press, G.A., 2000. Normal brain development and aging: quantitative analysis at in vivo MR imaging in healthy volunteers. Radiology 216, 672–682.

David, J.-P., Ghozali, F., Fallet-Bianco, C., Wattez, A., Delaine, S., Boniface, B., Di Menza, C., Delacourte, A., 1997. Glial reaction in the hippocampal formation is highly correlated with aging in human brain. Neurosci. Lett. 235, 53–56.

De Kloet, E.R., Oitzl, M.S., Joels, M., 1999. Stress and cognition: are corticosteroids good or bad guys? Trends Neurosci. 22, 422–426.

Den Heijer, T., Vermeer, S.E., van Dijk, E.J., Prins, N.D., Koudstaal, P.J., Hofman, A., Breteler, M.M., 2003. Type 2 diabetes and atrophy of medial temporal lobe structures on brain MRI. Diabetologia 46, 1604–1610.

Disterhoft, J.F., Wu, W.W., Ohno, M., 2004. Biophysical alterations of hippocampal pyramidal neurons in learning, ageing and Alzheimer's disease. Ageing Res. Rev. 3, 383–406.

Eberline, J.L., Roberts, J.A., Rapp, P.R., Tuszynski, M.H., Jagust, W.J., 1997. Cerebral glucose metabolism and memory in aged rhesus macaques. Neurobiol. Aging 18, 437–443.

Eichenbaum, H., 2004. Hippocampus: cognitive processes and neural representations that underlie declarative memory. Neuron 44, 109–120.

Erickson, K.I., Colcombe, S.J., Raz, N., Korol, D.L., Scalf, P., Webb, A., Cohen, N.J., McAuley, E., Kramer, A.F., 2005. Selective sparing of brain tissue in postmenopausal women receiving hormone replacement therapy. Neurobiol. Aging (EPub ahead of print).

Faulkner, J.R., Herrmann, J.E., Woo, M.J., Tansey, K.E., Doan, N.B., Sofroniew, M.V., 2004. Reactive astrocytes protect tissue and preserve function after spinal cord injury. J. Neurosci. 24, 2143–2155.

Ferrari, E., Casarotti, D., Muzzoni, B., Albertelli, N., Cravello, L., Fikoravanti, M., Solerte, S.B., Magri, F., 2001. Age-related changes of the adrenal secretory pattern: possible role in pathological brain aging. Brain Res. Rev. 37, 294–300.

Frodl, T., Meisenzahl, E.M., Zetzsche, T., Born, C., Groll, C., Jager, M., Leinsinger, G., Bottlender, R., Hahn, K., Moller, H.-J., 2002. Hippocampal changes in patients with a first episode of major depression. Am. J. Psychiatr. 159, 1112–1118.

Finch, C.E., 2003. Neurons, glia, and plasticity in normal brain aging. Neurobiol. Aging 24, S123–S127.

Gertner, J., 2004. Eat Chocolate, Live Longer? The New York Times Magazine, October 10.

Gosche, K.M., Mortimer, J.A., Smith, C.D., Markesbery, W.R., Snowdon, D.A., 2001. An automated technique for measuring hippocampal volumes from MR imaging studies. Am. J. Neuroradiol. 22, 1686–1689.

Gross, C.G., 1998. Brain, Vision, Memory. Tales in the History of Neuroscience. MIT Press, Cambridge.

Gur, R.C., Gunning-Dixon, F., Bilker, W.B., Gur, R.E., 2002. Sex differences in temporo-limbic and frontal brain volumes of healthy adults. Cereb. Cortex 12, 998–1003.

Haigler, H.J., Cahill, L., Crager, M., Charles, E., 1986. Acetylcholine, aging and anatomy: differential effects in the hippocampus. Brain Res. 362, 157–160.

Hebert, L.E., Scherr, P.A., Bienias, J.L., Bennett, D.A., Evans, D.A., 2003. Alzheimer disease in the US population: prevalence estimates using the 2000 census. Arch. Neurol. 60, 1119–1122.

Heuser, I., Lammers, C-H., 2003. Stress and the brain. Neurobiol. Aging 24, S69–S76.

Holzenberger, M., Dupont, J., Ducos, B., Leneuve, P., Geloen, A., Even, P.C., Cervera, P., Le Bouc, Y., 2003. IGF-1 receptor regulates lifespan and resistance to oxidative stress in mice. Nature 421, 182–187.

Jernigan, T.L., Archibald, S.L., Fennema-Notestine, C.F., Gamst, A.C., Stout, J.C., Bonner, J., Hesselink, J.R., 2001. Effects of age on tissues and regions of the cerebrum and cerebellum. Neurobiol. Aging 22, 581–584.

Jernigan, T.L., Fennema-Notestine, C., 2004. White matter mapping is needed. Neurobiol. Aging 25, 37–39.

Joseph, J.A., Denisova, N.A., Arendash, G.M., Gordon, M., Diamond, D., Shukitt-Hale, B., Morgan, D., 2003. Blueberry supplementation enhances signaling and prevents behavioral deficits in an Alzheimer disease model. Nutr. Neurosci. 6, 153–162.

Kalmijn, S., Launer, L.J., Ott, A., et al., 1997. Dietary fat intake and the risk of incident dementia in the Rotterdam study. Ann. Neurol. 42, 776–782.

Kerr, D.S., Campbell, L.W., Applegate, M.D., Bodish, A., Landfield, P.W., 1991. Chronic stress-induced acceleration of electrophysiologic and morphometric biomarkers of hippocampal aging. J. Neurosci. 11, 1316–1328.

Kesner, R.P., Lee, I., Gilbert, P., 2004. A behavioral assessment of hippocampal function based on a subregional analysis. Rev. Neurosci. 15, 333–351.

Keuker, J.I., Luiten, P.G., Fuchs, E., 2000. Capillary changes in hippocampal CA1 and CA3 areas of the aging rhesus monkey. Acta Neuropathol. 100, 665–672.

Keuker, J.I.H., Luiten, P.G.M., Fuchs, E., 2003. Preservation of hippocampal neuron numbers in aged rhesus monkeys. Neurobiol. Aging 24, 157–165.

Korf, E.S.C., White, L.R., Scheltens, P., Launer, L.J., 2004. Midlife blood pressure and the risk of hippocampal atrophy: the Honolulu Asia Aging Study. Hypertension 44, 9–34.

Koschack, J., Irle, E., 2005. Small hippocampal size in cognitively normal subjects with coronary artery disease. Neuobiol. Aging 25, 865–871.

Landfield, P.W., Cadwallader-Neal, L., 1998. Long-term treatment with calcitriol (1,25(OH)2 vit D3) retards a biomarker of hippocampal aging in rats. Neurobiol. Aging 19, 469–477.

Landfield, P.W., Baskin, R.K., Pitler, T.A., 1981. Brain aging correlates: retardation by hormonal-pharmacological treatments. Science 214, 581–584.

Landfield, P.W., Waymire, J.C., Lynch, G., 1978. Hippocampal aging and adrenocorticoids: quantitative correlations. Science 202, 1098–1102.

Lee, C.K., Weindruch, R., Prolla, T.A., 2000. Gene-expression profile of the aging brain in mice. Nat. Genet. 25, 294–297.

Leverenz, J.B., Wilkinson, C.W., Wamble, M., Corbin, S., Grabber, J.E., Raskind, M.A., Peskind, E.R., 1999. Effect of chronic high-dose exogenous cortisol on hippocampal neuronal number in aged nonhuman primates. J. Neurosci. 19, 2356–2361.

Little, A.R., Benkovic, S.A., Miller, D.B., O'Callaghan, J.P., 2002. Chemically induced neuronal damage and gliosis: enhanced expression of the proinflammatory chemokine, monocyte chemoattractant protein (MCP)-1, without a corresponding increase in proinflammatory cytokines. Neuroscience 115, 307–320.

Long, J.M., Mouton, P.R., Jucker, M., Ingram, D.K., 1999. What counts in brain aging? Design-based stereological analysis of cell number. J. Gerontol. 54A, B407–B417.

Lupien, S.J., Fiocco, A., Wan, N., Maheu, F., Lord, C., Schramek, T., Tu, M.T., 2005. Stress hormones and human memory function across the lifespan. Psychoneuroendocrinology 30, 225–242.

Lupien, S.J., de Leon, M., de Santi, S., Convit, A., Tarshish, C., Nair, N.P., McEwen, B.S., Hauger, R.I., Meaney, M.J., 1998. Cortisol levels during human aging predict hippocampal atrophy and memory deficits. Nat. Neurosci. 1, 69–73.

Lye, T.C., Piguet, O., Grayson, D.A., Creasey, H., Ridley, L.J., Bennett, H.P., Broe, G.A., 2004. Hippocampal size and memory function in the ninth and tenth decades of life: the Sydney older persons study. J. Neurol. Neurosurg. Psychiatr. 75, 548–554.

Lyons, D.M., Yang, C., Eliez, S., Reiss, A.L., Schatzberg, A.F., 2004. Cognitive correlates of white matter growth and stress hormones in female squirrel monkey adults. J. Neurosci. 24, 3655–3662.

Macey, P.M., Henderson, L.A., Macey, K.E., Alger, J.R., Frysinger, R.C., Woo, M.A., Harper, R.K., Yan-Go, F.L., Harper, R.M., 2002. Brain morphology associated with obstructive sleep apnea. Am. J. Respir. Crit. Care Med. 166, 1382–1387.

MacQueen, G.M., Campbell, S., McEwen, B.S., Macdonald, K., Amano, S., Joffe, R.T., Nahmias, C., Young, L.T., 2003. Course of illness, hippocampal function, and hippocampal volume in major depression. Proc. Natl. Acad. Sci. 100, 1387–1392.

Maquire, E.A., Gadian, D.G., Johnsrude, I.S., Good, C.D., Ashburner, J., Frackowiak, R.S., Frith, D.D., 2000. Navigation-related structural change in the hippocampi of taxi drivers. Proc. Natl. Acad. Sci. 97, 4398–4403.

Mattson, M.P., 2003. Will caloric restriction and folate protect against AD and PD? Neurology 60, 690–695.

Mattson, M.P., Maudsley, S., Martin, B., 2004. A neural signaling triumvirate that influences ageing and age-related disease: insulin/IGF-1, BDNF and serotonin. Ageing Res. Rev. 3, 445–464.

McEwen, B.S., 1998. Protective and damaging effects of stress mediators. New Engl. J. Med. 338, 171–179.

McEwen, B.S., 1999. Stress and the aging hippocampus. Frontiers Neuroendocrinol. 20, 49–70.

Meffert, M.K., Baltimore, D., 2005. Physiological functions for brain NF-kB. Trends Neurosci. 28, 37–43.

Miller, D.B., O'Callaghan, J.P., 2002. Neuroendocrine aspects of the response to stress. Metabolism 51 (Suppl. 1), 5–10.

Miller, D.B., O'Callaghan, J.P., 2003. Effects of aging and stress on hippocampal structure and function. Metabolism 52 (Suppl. 2), 17–21.

Miller, D.B., O'Callaghan, J.P., 2005. Depression, cytokines and glial function. Metabolism (EPub ahead of publication).

Miyashita, Y., 2004. Cognitive memory: cellular and network machineries and their top-down control. Science 306, 435–440.

Morgan, T.E., Xie, Z., Goldsmith, S., Yoshida, T., Lanzrein, A.S., Stone, D., Rozovsky, I., Perry, G., Smith, M.A., Finch, K.E., 1999. The mosaic of brain glial hyperactivity during normal ageing and its attenuation by food restriction. Neuroscience 89, 687–699.

Morrison, J.H., 2001. Which synapses are affected in aging and what is the nature of their vulnerability? A commentary on ''life span and synapses: will there be a primary senile dementia?''. Neurobiol. Aging 22, 349–350.

Mortimer, J.A., Gosche, K.M., Riley, K.P., Markesbery, W.R., Snowdon, D.A., 2004. Neurology 62, 428–432.

Nichols, N.R., Zieba, M., Bye, N., 2001. Do glucocorticoids contribute to brain aging? Brain Res. Rev. 37, 273–286.

O'Callaghan, J.P., Miller, D.B., 1991. The concentration of glial fibrillary acidic protein increases with age in the mouse and rat brain. Neurobiol. Aging 12, 171–174.

O'Callaghan, J.P., Brinton, R.E., McEwen, B.S., 1991. Glucocorticoids regulate the synthesis of glial fibrillary acidic protein in intact and adrenalectomized rats but do not affect its expression following brain injury. J. Neurochem. 57, 860–869.

Okada, M., Nakanishi, H., Amamoto, T., Urae, R., Ando, Susumu, Yazawa, K., Fujiwara, M., 2003. How does prolong caloric restriction ameliorate age-related impairment of long-term potentiation in the hippocampus? Mol. Brain Res. 111, 175–181.

Panegyres, P.K., 2004. The contribution of the study of neurodegenerative disorders to the understanding of human memory. Q. J. Med. 97, 555–567.

Papatheodoropoulos, C., Kostopoulos, G., 1996. Age-related changes in excitability and recurrent inhibition in the rat CA1 hippocampal region. Eur. J. Neurosci. 8, 510–520.

Perls, T., 2004. Centenarians who avoid dementia. Trends Neurosci. 27, 633–636.

Polleri, A., Gianelli, M.V., Murialdo, G., 2002. Dementia: a neuroendocrine perspective. J. Endocrinol. Invest. 25, 73–83.

Porter, N.M., Landfield, P.W., 1998. Stress hormones and brain aging: adding injury to insult? Nat. Neurosci. 1, 3–4.

Pruessner, J.C., Collins, D.L., Pruessner, M., Evans, A.C., 2001. Age and gender predict volume decline in the anterior and posterior hippocampus in early adulthood. J. Neurosci. 21, 194–200.

Rajkowska, G., 2000. Postmortex studies in mood disorders indicate altered numbers of neurons and glial cells. Biol. Psychiatr. 48, 766–777.

Rajkowska, G., Miguel-Hidalgo, J.J., Wei, J., Dilley, G., Pittman, S.D., Meltzer, H.Y., Overholser, J.C., Roth, B.L., Stockmeier, D.A., 1999. Morphometric evidence for neuronal and glial prefrontal cell pathology in major depression. Biol. Psychiatr. 45, 1085–1098.

Rapp, P.R., Gallagher, M., 1996. Preserved neuron number in the hippocampus of aged rats with spatial learning deficits. Proc. Natl. Acad. Sci. 93, 9926–9930.

Rasmussen, T., Schliemann, T., Sorensen, J.C., Zimmer, J., West, M.J., 1996. Memory impaired aged rats; no loss of principal hippocampal and subicular neurons. Neurobiol. Aging 17, 143–147.

Raz, N., Gunning-Dixon, F., Head, D., Rodrigue, K.M., Williamson, A., Acker, J.D., 2004. Aging, sexual dimorphism, and hemispheric symmetry of the cerebral cortex: replicability of regional differences in volume. Neurobiol. Aging 25, 377–396.

Raz, N., Lindenberger, U., Rodrigue, K.M., Kennedy, K.M., Head, D., Williamson, A., Dahle, C., Gerstorf, D., Acker, J.D., 2005. Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. Cereb. Cortex (EPub ahead of print).

Rowe, J.W., Hahn, R.L., 1987. Human aging: usual and successful. Science 237, 143–149.

Sapolsky, R.M., 1999. Glucocorticoids, stress, and their adverse neurological effects: relevance to aging. Exp. Gerontol. 34, 721–732.

Sapolsky, R.M., 1996. Stress, glucocorticoids, and damage to the nervous system: the current state of confusion. Stress 1, 1–19.

Sapolsky, R.M., Krey, L.C., McEwen, B.S., 1986. The neuroendocrinology of stress and aging: the glucocorticoid cascade hypothesis. Endocr. Rev. 7, 284–301.

Schmitz, C., Hof, P.R., 2005. Design-based sterology in neuroscience. Neuroscience 130, 813–831.

Scott, T.M., Tucker, K.L., Bhadelia, A., Benjamin, B., Patz, S., Bhadelia, R., Liebson, E., Price, L.L., Griffith, J., Rosenberg, I., Folstein, M.F., 2004. Homocysteine and B vitamins relate to brain volume and white-matter changes in geriatric patients with psychiatric disorders. Am. J. Geriatr. Psychiatr. 12, 631–638.

Scoville, W.B., Milner, B., 1957. Loss of recent memory after bilateral hippocampal lesions. J. Neurol. Neurosurg. Psychiatr. 20, 11–12.

Si, S., Miguel-Hidalgo, J.J., O'Dwyer, G., Stockmeier, C.A., Rajkowska, G., 2004. Age-dependent reductions in the level of glial fibrillary acidic protein in the prefrontal cortex in major depression. Neuropsychopharmacology 29, 2088–2096.

Simic, G., Kostovic, I., Winblad, B., et al., 1997. Volume and number of neurons of the human hippocampal formation in normal aging and Alzheimer's disease. J. Comp. Neurol. 379, 482–494.

Sloane, J.A., Hollander, W., Rosene, D.L., Moss, M.B., Kemper, T., Abraham, C.R., 2000. Astrocytic hypertrophy and altered GFAP degradation with age in subcortical white matter of the rhesus monkey. Brain Res. 862, 1–10.

Small, S.A., Chawla, M.K.I., Buonocore, M., Rapp, P.R., Barnes, C.A., 2004. Imaging correlates of brain function in monkeys and rats isolates a hippocampal subregion differentially vulnerable to aging. Proc. Natl. Acad. Sci. 101, 7181–7186.

Smith, J., 2003. Stress and aging: theoretical and empirical challenges for interdisciplinary research. Neurobiol. Aging 24, S77–S80.

Smith, D.E., Roberts, J., Gage, F.H., Tuszynski, M.H., 1999. Age-associated neuronal atrophy occurs in the primate brain and is reversible by growth factor gene therapy. Proc. Natl. Acad. Sci. 96, 10893–10898.

Snowdon, D.A., 2003. Healthy aging and dementia: findings from the nun study. Ann. Intern. Med. 139, 450–454.

Sousa, N., Almeida, O.F., Holsboer, F., Paula-Barbosa, M.M., Madeira, M.D., 1998. Maintenance of hippocampal cell numbers in young and aged rats submitted to chronic unpredictable stress. Comparison with the effects of corticosterone treatment. Stress 2, 237–249.

Stanley, D.P., Shetty, A.K., 2004. Aging in the rat hippocampus is associated with widespread reductions in the number of glutamate decarboxylase-67 positive interneurons but not interneuron degeneration. J. Neurochem. 89, 204–216.

Sullivan, E.V., Marsh, L., Pfefferbaum, A., 2004. Preservation of hippocampal volume throughout adulthood in healthy men and women. Neurobiol. Aging 26, 1093–1098.

Takeda, E., Terao, J., Nakaya, Y., Miyamoto, K., Baba, Y., Chuman, H., Kaji, R., Ohmori, T., Rokutan, K., 2004. Stress control and human nutrition. J. Med. Invest. 51, 139–204.

Tisserand, D.J., Visser, P.J., van Boxtel, M.P.J., Jolles, J., 2000. The relation between global and limbic brain volumes on MRI and cognitive performance in healthy individuals across the age range. Neurobiol. Aging 21, 569–576.

Toescu, E.M., Verkhratsky, A., Landfield, P.W., 2004. Ca^{2+} regulation and gene expression in normal brain aging. Trends Neurosci. 27, 614–620.

Toussaint, O., 2003. Normal brain aging: a commentary. Neurobiol. Aging 24, 129–S130.

Uno, H., Tarara, R., Else, J.G., Suleman, M.A., Sapolsky, R.M., 1989. Hippocampal damage associated with prolonged and fatal stress in primates. J. Neurosci. 9, 1705–1711.

Vallee, M., Purdy, R.H., Mayo, W., Koob, G.F., LeMoal, M., 2003. Neuroactive steroids: new biomarkers of cognitive aging. J. Steroid Biochem. Mol. Biol. 85, 329–335.

Van Petten, C., 2004. Relationship between hippocampal volume and memory ability in healthy individuals across the lifespan: review and meta-analysis. Neuropsychologia 42, 1394–1413.

Verkhratsky, A., Mattson, M.P., Toescu, E.C., 2004. Aging in the mind. Trends Neurosci. 27, 577–578.

Villarreal, G., Hamilton, D.A., Petropoulos, H., Driscoll, I., Rowland, L.M., Griego, J.A., Kodituwakku, P.W., Hart, B.L., Escalona, R., Brooks, W.M., 2002. Reduced hippocampal volume and total white matter volume in posttraumatic stress disorder. Biol. Psychiatr. 15, 119–125.

Walford, R.I., Mock, D., Verdery, R., MacCallum, T., 2002. Calorie restriction in biosphere 2: alterations in physiologic, hematologic, hormonal, and biochemical parameters in humans restricted fro a 2-year period. J. Gerontol. A Biol. Sci. Med. Sci. 57, B211–B224.

Warner, H.R., 2005. Longevity genes: from primitive organisms to humans. Mech. Ageing Dev. 126, 235–242.

West, M.J., 1993. Regionally specific loss of neurons in the aging human hippocampus. Neurobiol. Aging 14, 287–293.

West, M.J., 2002. Design-based stereological methods for counting neurons. Prog. Brain Res. 135, 43–51.

West, M.J., Gundersen, H.J.G., 1990. Unbiased stereological estimation of the number of neurons in the human hippocampus. J. Comp. Neurol. 296, 1–22.

Wilkenson, C.W., Petrie, C.C., Murray, S.R., Colasurdo, E.A., Raskind, M.A., Peskind, E.R., 2001. Human glucocorticoid feedback inhibition is reduced in older individuals: evening study. J. Clin. Endocrinol. Metab. 86, 545–550.

Wilner, A.P., de Varennes, B., Gregoire, P.A., Lupien, S., Pruessner, J.C., 2002. Glucocorticoids and hippocampal atrophy after heart transplantation. Ann. Thorac. Surg. 73, 1965–1967.

West, M.J., Kawas, C.H., Stewart, W.F., Rudow, G.L., Troncoso, J.C., 2004. Hippocampal neurons in pre-clinical Alzheimer's disease. Neurobiol. Aging 25, 1205–1212.

Wickelgren, I., 1996. Is hippocampal cell death a myth? Science 271, 1229–1230.

Wolf, H., Hensel, A., Krugggel, F., Riedel-Heller, S.G., Arendt, T., Wahlund, L.-O., Gertz, H.-J., 2004. Structural correlates of mild cognitive impairment. Neurobiol. Aging 25, 913–924.

Youdim, K.A., Spencer, J.P.E., Schroeter, H., et al., 2002. Dietary flavinoids as potential neuroprotectants. Biol. Chem. 383, 503–519.