ELSEVIER

Neurobiology of Aging 23 (2002) 941–955

NEUROBIOLOGY OF AGING

www.elsevier.com/locate/neuaging

Exercise, experience and the aging brain☆

James D. Churchill[a,b,c], Roberto Galvez[a,b], Stanley Colcombe[a,c], Rodney A. Swain[e], Arthur F. Kramer[a,c], William T. Greenough[a,b,c,d,*]

[a] *Beckman Institute, University of Illinois at Urbana-Champaign, 405 N. Mathews, Urbana, IL 61801, USA*
[b] *Neuroscience Program, University of Illinois at Urbana-Champaign, Urbana, IL 61801, USA*
[c] *Department of Psychology, University of Illinois at Urbana-Champaign, Urbana, IL 61801, USA*
[d] *Departments of Psychiatry and Cell and Structural Biology, University of Illinois at Urbana-Champaign, Urbana, IL 61801, USA*
[e] *Department of Psychology, University of Wisconsin at Milwaukee, Milwaukee, WI, USA*

Received 31 October 2001; received in revised form 14 February 2002; accepted 19 February 2002

Abstract

While limited research is available, evidence indicates that physical and mental activity influence the aging process. Human data show that executive functions of the type associated with frontal lobe and hippocampal regions of the brain may be selectively maintained or enhanced in humans with higher levels of fitness. Similarly enhanced performance is observed in aged animals exposed to elevated physical and mental demand and it appears that the vascular component of the brain response may be driven by physical activity whereas the neuronal component may reflect learning. Recent results have implicated neurogenesis, at least in the hippocampus, as a component of the brain response to exercise, with learning enhancing survival of these neurons. Non-neuronal tissues also respond to experience in the mature brain, indicating that the brain reflects both its recent and its longer history of experience. Preliminary measures of brain function hold promise of increased interaction between human and animal researchers and a better understanding of the substrates of experience effects on behavioral performance in aging.

Keywords: Memory; Cognitive; Activity dependent; Neuron; Glia; Angiogenesis; Neurogenesis; Hippocampus; Executive function; Frontal cortex

1. Introduction

For the most part, investigations of aging on plasticity of brain and cognition have been functionally dichotomized. Brain plasticity typically has been examined using animal models while studies of cognitive plasticity have been performed predominantly in humans. Recent advances in neuroimaging techniques and a convergence of behavioral intervention strategies have begun to narrow the gulf between animal brain plasticity and human cognitive studies of aging. In the following discussion, we will review the unique contributions of animal and human studies to our understanding of plasticity during aging, highlight those areas of overlap, and speculate on promising avenues for further research.

2. Human cognitive decline: fitness and aging

Much of the current research on human cognition and aging has focused on characterizing the qualitative and quantitative changes that take place in human cognition from young adulthood to old age. Indeed, the great majority of this research suggests that both general as well as process specific declines occur in a variety of perceptual, cognitive and action-related processes during the course of normal aging. Older adults typically perform more poorly than young adults in terms of both response latency and accuracy on tasks as diverse as perceptual speed, working memory, tracking, decision making, explicit memory and multiple task processing [21,113,149]. Indeed, a recent large cross-sectional study of 350 individuals from their 20s through their 80s indicated a consistent decline in the quality of performance across a wide variety of tasks over the lifespan [134].

Despite such declines in a multitude of perceptual, cognitive and motor processes during the course of aging, recent findings suggest that a variety of interventions can be used to impede or minimize selective aspects of cognitive

☆ The first three authors contributed equally to this publication.
* Corresponding author. Tel.: +1-217-333-4472; fax: +1-217-244-5180.
E-mail address: wgreenou@s.psych.uiuc.edu (W.T. Greenough).

0197-4580/02/$ – see front matter © 2002 Elsevier Science Inc. All rights reserved.
PII: S0197-4580(02)00028-3

decline. For example, age-related deficits in the ability to concurrently perform multiple tasks or rapidly switch between two different tasks can be reduced through training [111,112]. Indeed, not only can age-related deficits in multiple task performance be reduced on a set of trained tasks but performance improvements can be retained for several months ([112], see also [17]). Furthermore, older adults who learned to rapidly shift their priorities between concurrently performed tasks were able to apply this processing strategy to an untrained set of tasks, thereby dramatically reducing age-related deficits in dual-task performance as compared to a control group of young and older adults who were trained with a more traditional multiple task method. Other studies have demonstrated the effectiveness of a variety of different intellectual training programs for the improvement and maintenance of memory [169], visual search and attention [14], fluid intelligence [174], and spatial orientation and inductive reasoning skills [175].

Another intervention strategy that has been shown to reduce selective aspects of cognitive decline is fitness training. Consistent with the research on the behavioral effects of exercise in aging animals reviewed below, there is now a substantial body of literature that suggests that a lifetime of exercise can result in enhancements in a number of aspects of cognition. Much of this literature has focused on aerobic exercise such as walking, running, bicycling and swimming.

With few exceptions, cross-sectional studies have reported benefits of aerobic exercise on both peripheral and central components of reaction time [19,27,43,86,130,159]. That is, individuals who had engaged in exercise for a lengthy period of their lives were faster in responding to the presentation of auditory or visual stimuli, discriminating between multiple stimuli, and making ballistic movements. Additionally, exercisers have been shown to outperform non-exercisers on tasks such as reasoning, working memory, Stroop, Trails-B, Symbol digit, vigilance monitoring, and fluid intelligence tests [1,33,44,48,52–54,56,137,152,159]. However, differences in performance on seemingly similar tasks between lifetime exercisers and non-exercisers have not always been found. For example, there were no reported beneficial effects of exercise level on the performance of simple and choice reaction time tasks, short-term memory and digit span tasks, and for measures of somatosensory thresholds [1,45,54,166,167].

In general, the effects of exercise on cognitive processes of older adults appear to be beneficial, yet the cross-sectional nature of these studies complicates their interpretation. The presumably positive effects of exercise may, in fact, reflect self-selection of individuals who are fast and accurate responders to participate in exercise. Of course, to the extent that lifestyle differences (e.g. diet, smoking, nutrition) co-vary with exercise, these factors may also account for all or part of the relationship between fitness and cognition.

Clearly, converging evidence regarding the efficacy of exercise and fitness for the maintenance of cognitive function of older adults is necessary. One source of converging evidence has been epidemiological studies in which longitudinal data is examined to predict cognitive change some years later. The goal of one such study [3], with over a thousand participants, was to predict cognitive change, as indexed by a composite cognitive measure that included language, verbal and non-verbal memory, conceptualization, and visuospatial tests, over a 2.5 years period in adults between the ages of 70 and 79. As previously observed, education and income were strong predictors of cognitive vitality at the original assessment as well as 2.5 years later [60]. Interestingly, a number of measures of cardiorespiratory fitness and general physical activity level also served as strong predictors of cognitive vitality for this population. In a more recent study, the relationship between cognition (measured via the mini-mental state examination) and physical activity (assessed via self-report measures of walking and total kilocalories expended per week) of 5925 community dwelling older women over a period of 6–8 years was examined [176]. Even after adjusting for a variety of covariates (e.g. education level, co-morbid conditions, and smoking) they found that women with greater physical activity levels at baseline assessment were less likely to experience cognitive declines at follow-up sessions (see also [116]).

The results of cross-sectional, prospective and retrospective epidemiological studies suggest a link between the cognitive vitality of older adults and fitness level. An important question, however, is whether randomized clinical trials also support this link. Indeed, a number of intervention studies have found improvements in cognitive function with fitness training. For example, in a now classic study, Dustman et al. observed performance improvements in a number of tasks including, critical flicker fusion, digit symbol and Stroop following a 4-month exercise program [55]. These improvements were specific to an aerobic exercise group exhibiting a significant improvement in cardiovascular function (27% improvement in VO_2 max). In contrast, subjects that participated in a strength and flexibility program and those in a non-exercise control group did not show performance improvements across test administrations. Similarly, it was reported that a 3-year aerobic fitness program served to eliminate declines in choice reaction time performance that were observed for a non-exercise control group [141]. Interestingly, fitness-related performance sparing was not reported for a simple reaction time task. Finally, 124 sedentary but healthy older adults (age range 60–75) were trained for a period of 6 months with either an aerobic (walking) or anaerobic (toning and stretching) exercise program [110]. Each of the subjects was tested in a variety of attention and memory tasks, selected because components of a subset of these tasks have been shown, either through human lesion, neuroimaging, or animal studies, to entail executive control processes and to be supported, in part, by frontal or pre-frontal cortical regions of the brain. These regions of the brain and the processes they support have been shown to exhibit large and disproportionate age-related declines

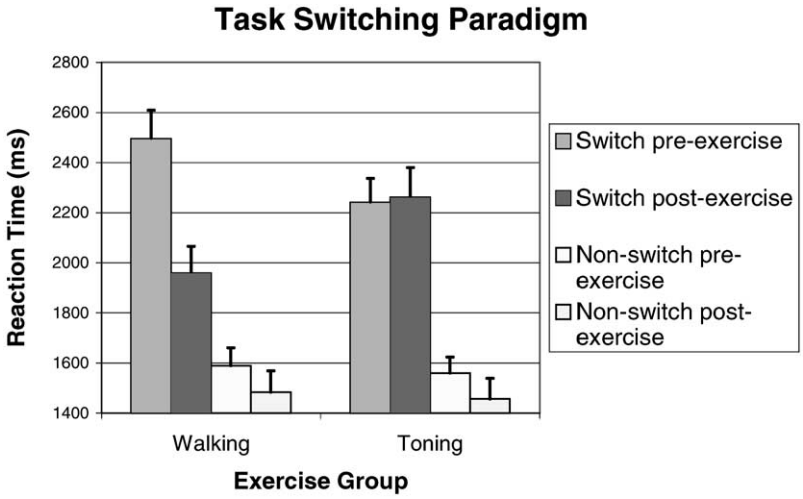

Fig. 1. Illustration of how different forms of exercise can differentially influence specific types of cognitive processes. Following a 6-month training period, reaction time was significantly quicker in the aerobically trained subjects (walkers) on the switch trials, while reaction time for subjects involved in a toning program was not affected. This switch task demands executive control, which has been suggested to be heavily dependent upon activation of pre-frontal and/or frontal cortical areas. In contrast, tasks that did not require recruitment of frontal cortex were not differentially influenced by either form of exercise. These observations suggest that the effects of exercise are not ubiquitously expressed throughout the brain, rather exercise has a more dramatic influence on specific aspects of cognition.

[172]. The primary question addressed was whether performance on tasks that had components of executive control processes would be improved over the course of the exercise program for the walkers but not for the stretching group, while non-executive control processes would show equivalent performance trends for both exercise groups. Largely, this was the pattern of results observed in the study. The aerobic training group improved to a significantly greater extent than the anaerobic group in their ability to ignore irrelevant visual information, abort a pre-programmed action, and coordinate multiple tasks, all skills that involve aspects of executive control and are supported, at least in part, by regions of frontal and prefrontal cortex. An example of such an improvement is shown in Fig. 1. As can be seen in the figure, the aerobically trained subjects (walkers) displayed faster reaction time performance after the 6-month intervention on the switch trials. In contrast, the anaerobic group (toning) failed to show similar improvements on the switch trials. Previous studies have suggested that switching between tasks taps a number of aspects of executive control [4,143]. Interestingly, both the walkers and toning group showed small and equivalent improvements in reaction time on the non-switch trials. These tasks do not involve executive control processes. Taken together, the results of these longitudinal studies (see also [41,57,87,125,173]) are supportive of selective improvements in a number of cognitive processes with relatively short-term programs of aerobic exercise.

While the effects of aerobic exercise on cognition and performance appear to be encouraging, other longitudinal studies have failed to observe improvements in cognitive function in response to increased levels of aerobic fitness. For example, both aerobic and anaerobic exercise groups improved performance on a memory search task across test administrations that spanned 12 weeks [26]. A later study reexamined the effects of aerobic exercise on memory search performance in older (60–83 years) and less fit subjects performing a memory search task both separately and in conjunction with a secondary auditory discrimination task [117]. The secondary task was included in an effort to determine whether more attentional demanding tasks would benefit from short-term programs of exercise. There was no significant difference in the pre/post-memory performance exhibited by members of an aerobic exercise group or control group (for other failures to find cognitive benefits associated with improvements in fitness, see [91,129,133]).

To summarize, the literature suggests that although a lifetime of aerobic exercise may help preserve a subset of cognitive capabilities in older adults, the benefits of short-term programs of exercise are more equivocal. A possible confound in making direct comparison in the literature concerns the nature of the cognitive processes that have been examined as well as the exercise programs. A comparison of the fitness levels reported for the post-exercise groups in the longitudinal studies and those reported for the lifetime exercisers clearly suggests that high levels of fitness are achieved after years, rather than months of training. Therefore, it might be unreasonable to expect that brief periods of exercise could have beneficial effects on a wide array of cognitive processes. Instead, it is conceivable that short-term exercise benefits might be restricted to a subset of cognitive processes that have shown the most substantial age-related decrements.

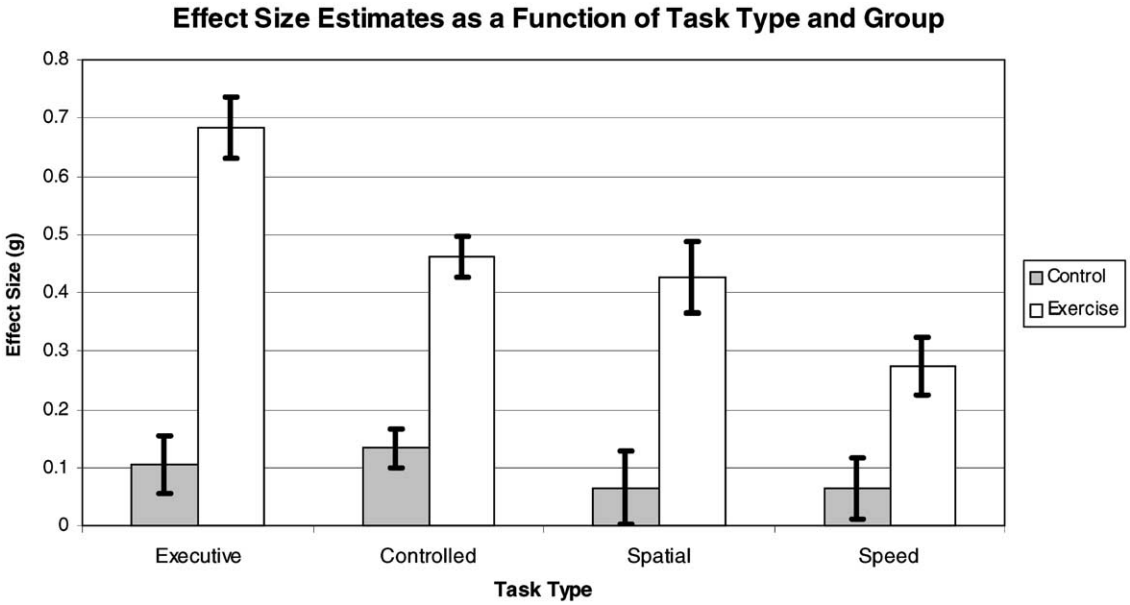

Fig. 2. Exhibition of the differential influence of exercise on specific types of tasks. Fitness effect sizes were substantially larger for tasks and task components that included executive control processes (i.e. processes including planning, scheduling, coordination, inhibition, working memory) than tasks that involved minimal executive control processing. These findings suggest that while exercise may have a global effect on the brain, the effects of exercise also appear to be selectively enhanced in specific brain regions (as is evident by the differential improvements on specific types of tasks).

In order to further test this selective cognitive improvement hypothesis as well as to examine other potential moderating influences on the relationship between fitness training and cognition, Colcombe and Kramer [46] recently performed a meta-analysis on all of the randomized fitness trials with control groups from 1966 until the present conducted with adults over the age of 55. Consistent with our selective improvement hypothesis, fitness effect sizes were substantially larger for tasks and task components that included executive control processes (i.e. processes including planning, scheduling, coordination, inhibition, working memory) than tasks that involved minimal executive control processing (see Fig. 2). Fitness also had larger positive effects on cognition when training sessions exceeded 30 min for older adults (>65 years of age), and when the subject samples comprised greater than 50% females. Thus, the results of the meta-analysis begin to establish the boundary conditions on the relationship between fitness and cognition as well as to suggest potentially fruitful lines of future research. One important area of research that is lacking is the examination of the relationship among fitness, cognition and brain function in human studies. To date such information is not readily available. To examine such relationships, animal models are of great utility.

3. Behavioral effects of exercise in aging animals

There is a small but consistent body of literature on the effects of exercise on behavioral learning tasks in animals. One aspect of this work that parallels observations from human studies involves hippocampal-dependent tasks that parallel those requiring executive function in humans. For example, it has been demonstrated that physical activity enhanced performance on a spatial learning task in rodents [65,67]. In addition to increasing performance, exercise has also been shown to increase the acquisition rate of a spatial learning task [11]. Interestingly, light (non-aerobic) exercise, forced walking in an alley, had virtually no discernible effect on tests of skilled motor performance, whereas motor skill training generalized very well to novel motor tasks (see Fig. 3 and also [107]).

4. Brain plasticity in aging animals

The responsiveness of human cognition to interventions such as exercise is paralleled by animal studies of brain responsiveness to experience. Origins of this work date to Hebb [88,89], who was among the first to show that the conditions under which animals were housed affected their behavioral abilities. Subsequently, Rosenzweig et al. [144] demonstrated that the volume of the cerebral cortex could be altered by rearing animals in what they termed “enriched” versus “impoverished” environments. It has since become clear that this cortical volume change involves modification in both neurons and non-neuronal tissue. Furthermore, work using a similar paradigm (now referred to as a complex environment) has demonstrated that this type of conditioning can also mitigate age-related declines in neural structure (e.g.

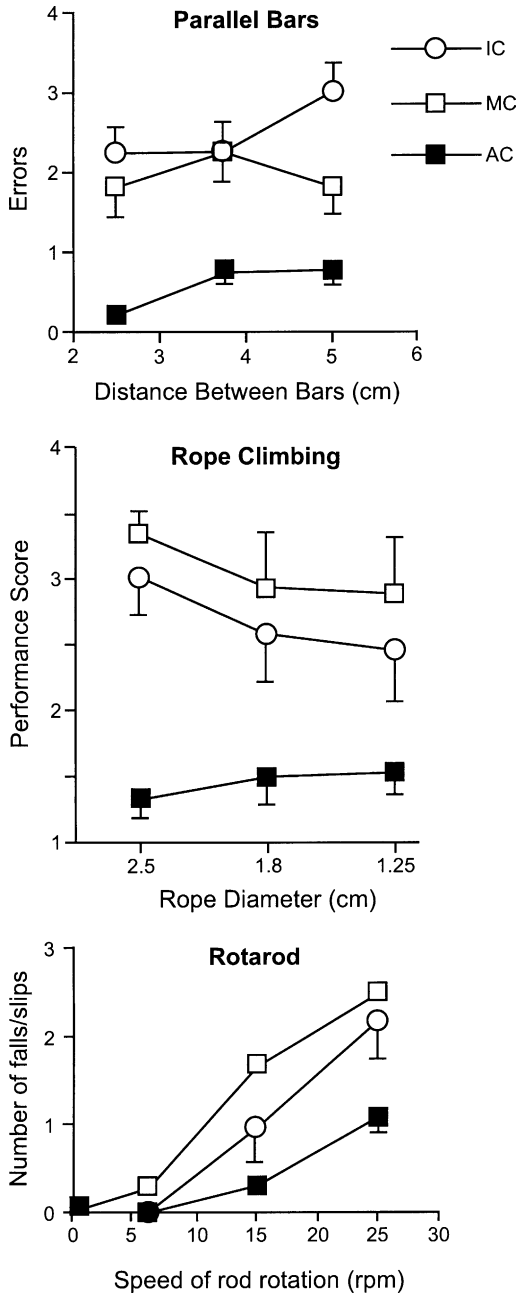

Fig. 3. Depiction of the performance of rats on three measures of motor skill (parallel bars, rope climbing, and rotarod) after training on an obstacle course (AC) or walking in a closed alley (MC). While motor skill training (AC) enhanced performance on a number of subsequent behavioral tasks, motor activity (MC) alone had little effect on performance, compared to inactive (IC, daily handling only) rats (from [107]).

[80]) as well as increase neuron proliferation and survival in the hippocampus [101,168].

5. Synaptogenesis

Early studies of brain morphology indicated that regions of cerebral cortex were heavier and thicker in rats exposed to a complex environment [20]. These observations could be accounted for by one of two primary neural mechanisms: (1) that neurogenesis was occurring at a rate that greatly exceeded that of apoptotic cell death; or (2) that existing cells were expanding the number of contacts made with surrounding neurons. The former explanation was not met with overwhelming enthusiasm as mitosis within the central nervous system was considered to be, at best, a very limited and restricted phenomenon and seemed even less likely as a mechanism in mature or senescent animals (addressed below). Without the (apparent) possibility of new cell addition, the most parsimonious explanation was that the existing neuropil was simply augmented in some manner.

In studies employing the complex environment paradigm, typically rodents are reared in a complex environment condition (EC; this abbreviation is maintained from [144]). For this type of conditioning, rodents live in large cages that are filled with a variety of objects that are replaced, or repositioned each day to maximize learning. While this EC experience is still “deprived” in comparison to rodents in their natural environment, this condition is considerably more stimulating than standard laboratory housing conditions in which animals are housed in individual cages (ICs) or social cages (SCs), containing only food, water and bedding material. In general, the results of studies comparing cerebral cortex suggest that the level of neuropil expansion positively correlates with the degree of environmental complexity [72,96,171].

While the cerebral cortex is frequently the focal point of studies attempting to study the “memory” of an event, certain forms of learning emphasize other brain areas. For example, there is strong evidence that the cerebellum is capable of responding to experience in a manner much like cerebral cortex. Pysh and Weiss [138] reared mice in object-filled cages and forced them to swim, climb wires and poles, and perform other tasks involving exercise and presumably motor learning. They reported that these experiences resulted in a thickening of specific cerebellar lobules and that dendritic branching was more extensive on Purkinje cells in these animals. Similarly, Floeter and Greenough [64] studied monkeys (infant, juvenile and adult) reared in a colony environment with a variety of objects that allowed for both gross and fine motor activity. They reported that cerebellar Purkinje cell dendrites were larger in the colony animals, relative to controls that had been cage-reared either socially in pairs or individually in closed environments that did not permit sight or sound of other monkeys. Similarly, Purkinje cell somata size in some cerebellar areas was greater in the colony animals, compared to controls. In contrast to the Purkinje cell measures, granule cell dendritic fields showed no significant effects of the rearing conditions. These data suggest that experience-driven plasticity may be restricted to specific synapses. That is, the parallel fiber axons of the granule cells (and the climbing fiber synapses from the inferior olive; [9]) exhibit synaptic number plasticity on both Purkinje neurons and inhibitory stellate neurons in cerebellar cortex, while

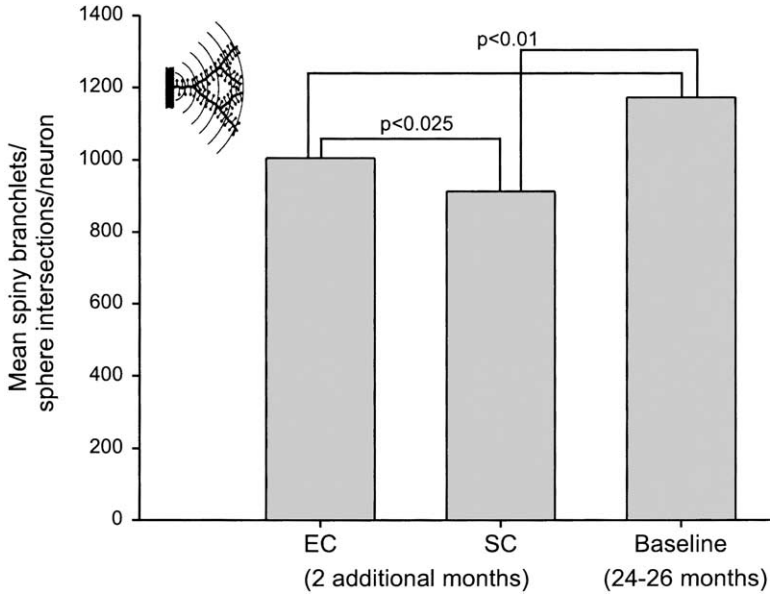

Fig. 4. Illustration of the influence of rearing conditions on dendritic morphology. The inset diagram is a caricature of a dendritic branch and spines with a series of concentric rings super-imposed. The frequency of events such as sphere intersections at constant intervals from the cell body are determined using these rings (from Sholl [154]). Sphere intersections are a measure of the amount of Purkinje cell dendrite receiving parallel fiber input. In this figure, the baseline rats were sacrificed at the outset of the experiment. The two remaining groups were housed for an additional 2 months in either a complex environment (EC) or in a social environment that was devoid of further stimulation (SC). EC housing mitigated some of the spiny branchlet degeneration normally seen at this age, as is reflected in the data from the SC condition.

the target of Purkinje cell output, the lateral deep nucleus, did not exhibit synaptic number plasticity [22,103–106].

While the EC paradigm has proven to be vital in studying the mechanisms of synaptogenesis, such studies have, by in large, focused on developing or young–adult subjects. Yet the capacity for synaptogenesis is not restricted to these periods as similar dendritic growth occurs in the cortex of young (3–4-month-old) and mature (15-month-old) rats [78,93,165]. Likewise, in studies assessing the effects of experience and aging on synaptic loss in the cerebellum, it was reported that sectors of the dendritic arbor of Purkinje cells from rats housed in EC conditions beginning at 24–26 months of age were more extensive when compared to controls (see Fig. 4, [80]).

While the aforementioned experiments provided valuable insight regarding the relationship between experience and neural morphology, it was not clear whether any neural activity or only learning-associated neural activity was the basis of the morphological differences between treatment conditions. In an attempt to resolve this issue, we assessed the effects of these two potential sources independently [22]. To maximize the opportunity for learning, a group of mature adult female rats was trained on an acrobat course (AC), a challenging series of elevated planks, rope, wire cloth, chain and dowels. The latency to navigate the task and the number of errors made decreased dramatically across training sessions. Additional groups of animals served as controls for the physical and associated neural activity experienced by the AC rats. One group was prompted to exercise on a moving treadmill (FX), a second group exercised voluntary on a running wheel attached to their home cage (VX), and a final group remained undisturbed in their cages except for daily handling to simulate the treatment of the other groups (IC). The results showed that cerebellar cortical synapse density was elevated in the AC group but unaffected by exercise. Likewise, Kleim et al. [102] compared AC, MC (a modification of the exercise group in which animals are yoked to paired AC subjects and prompted to traverse a flat alleyway) and IC rats after several days of training. They reported that the number of synapses did not differ in motor cortex across groups after 1 or 2 days of training, but increased in the AC group across days 5, 10 and 20. By contrast, the mean size of synapses in the AC rats, as reflected in cross-sectional length of the post-synaptic density, peaked at day 2 relative to controls, before synapse number changes were detectable, then decreased to control levels at day 5, when most of new synapses came into place, and gradually rose again across days 10 and 20. Furthermore, the number of perforated synapses (which increase in response to both experience [81] and following induction of LTP [71]) followed a pattern essentially identical to that of synapse size. Taken together, these observations indicate that routine activity of cells need not trigger synaptogenesis; that some aspect of the activity that is related to skill acquisition or other forms of learning is an essential feature necessary to induce synaptic modification; and that synaptogenesis is likely a phenomenon that occurs throughout the brain. These general observations are currently being extended to both developing

and senescent animals in an attempt to determine how experience might influence neuronal morphology across the lifespan and whether such experiences might have rehabilitative effects.

While it appears that the underlying neuronal architecture is amendable to differential experiences across the lifespan, surely functional correlates of such synaptic modifications must be present as well. To address this question, we have begun to examine the physiological correlates of AC, MC, and IC training [42]. Using electrodes that span cortical layers, it is possible to elicit evoked responses that exhibit a characteristic early latency component (associated with multiunit discharge) and a later component (likely representing the monosynaptic EPSP, for review see [38]). One day of training was without effect on baseline responses, however, after only 5 days of training, the amplitude of the later component was increased in both the AC and MC groups and the early component was elevated in the AC animals. In contrast, only the IC animals showed a significant propensity for LTP induction at these early time points, indicating that capacity for plasticity in the trained animals may have been "used up" with training. Following 10 days of training, basal evoked response amplitudes in AC, MC, and IC animals did not differ and all animals displayed a capacity for LTP, suggesting that the circuits involved in processing this information may have been "reset" in the AC and MC groups, thereby making LTP expression once again possible.

This research indicates that structural and functional changes are not only correlated, but are also modifiable by differential experience across the lifespan. Such morphological (e.g. [58,121]) and physiological plasticity (e.g. [132,142]) can occur very rapidly. While physiologically defined modifications are somewhat easier to detect, a significant amount of dendritic change must occur before it can be readily discerned. In aged animals, the rate at which learning (behaviorally defined) and synapse addition (morphologically defined) occur could simply be delayed. That is, senescent animals may be as capable of plastic responses (defined both morphologically and behaviorally), but the rate at which these animals achieve optimal performance is delayed. The extent of change is not stable across the lifespan, as declines in the magnitude of experience-induced brain plasticity in older animals have been reported (e.g. [23,78]). Moreover, aged animals may readily learn novel tasks, but may attempt to use alternative learning strategies (some of which are not always the most efficient strategies or readily available) to accomplish similar goals, as has been previously suggested [16]. Such alternative strategies could be interpreted as compensatory in nature [34] as there are undoubtedly functional and structural declines associated with advanced age that could underlie learning and memory deficits. These observations hold promise that behavioral "therapy" may be a useful strategy in mitigating age-related neuronal deterioration throughout the brain.

6. Neurogenesis

In addition to maintaining the ability to modify specific neuronal properties outlined above, it has become clear that at least some regions of the adult brain can also respond to environmental stimuli by adding new neurons. Though this form of brain plasticity still evokes some controversy, postnatal neurogenesis is now gaining general acceptance. The first report of adult neurogenesis dates back to 1962 in a study assessing the response of the brain to injury. Using ^{6}H-thymidine incorporation into mitotic cells, Altman [5] reported that not only were new glial cells found in response to the insult, but there were also several labeled cells that appeared to have a neuronal morphology. Subsequently, cell division was characterized in the subventricular zone, olfactory bulb [6], hippocampus and neocortex [7]. Unfortunately, Altman used light microscopy and a general cytological stain to assess cell lineage, a method that made it difficult to positively identify that labeled cells were indeed of neural, and not glial origin. For this reason, Kaplan and co-workers combined this method with electron microscopy in a subsequent attempt to determine cellular morphology and demonstrate neurogenesis in the rodent hippocampus [97] and visual cortex [98]. Kaplan followed these observations with a report of mitosis in the subventricular zone of the adult monkey, demonstrating that cell division occurs in not only rodents and cats, but in the adult primate as well [99]. Even with these reports, the notion that new neurons were generated in adulthood was not well accepted. It was not until new techniques and detection methods were developed that the study of adult neurogenesis was re-instigated. Using these new methods, neurogenesis has subsequently been reported in the adult rodent hippocampus [114], olfactory bulb, and cerebral cortex and in other species such as non-human primates [76,77,109] and humans [59].

Accepting that neurogenesis occurs in adulthood, the focus in the study of this phenomenon has been directed at characterizing the occurrence of neurogenesis and determining what stimuli can modulate the proliferation and/or survival rate of these newly formed neurons. Recently, it was demonstrated that exercise on a running wheel increased the rate of neuron proliferation in the rodent dentate gyrus when compared to both learning and inactive controls [168]. How exercise might specifically increase cell proliferation is unknown; however, several biochemical candidates exist. For example, serotonin, a neurotransmitter known to be increased in response to exercise [25] and chronic antidepressant administration, has been shown to increase neuron proliferation [29,120]. In contrast, serotonin depletion decreased neuron proliferation [28]. Serotonin is not the only compound in the brain known to be modulated by exercise and to influence adult neurogenesis. For example, brain-derived neurotrophic factor (BDNF) mRNA is up-regulated in response to exercise [146] and has been shown to induce neurogenesis in regions of the brain that do not commonly undergo neuron proliferation [136].

Moreover, administration of BDNF has been shown to promote survival and/or neuronal differentiation of progenitor cells in vitro [153]. In contrast, increased stress levels, which are known to elicit multiple hormonal as well as neuronal responses, including decreasing BDNF mRNA levels [146], have been reported to decrease neuronal proliferation in the dentate gyrus [75]. Furthermore, reduction of corticosteroid levels, which are elevated in response to stress, have been shown to increase cell proliferation in aged rats to levels comparable with young adults [37]. Further study of these types of behavioral and chemical interventions will hopefully provide a better understanding of the molecular mechanism(s) controlling neuronal proliferation throughout the brain and how age influences these effects.

Several recent studies have focused on the viability of these newly formed neurons and what factors might influence this process. For example, olfactory occlusion has been shown to not only decrease proliferation rates, but to also decrease survival rates of newly formed neurons in the olfactory bulb [49]. In contrast, exposure to a complex environment has been reported to elevate neuron survival in the dentate gyrus [101]. While the rate of neurogenesis in the dentate gyrus may decrease with age, exposure to a complex environment has been reported to increase not only the survival rate of newly formed neurons in aged mice (20-month-old), but also the likelihood that a progenitor cell would differentiate into a neuron and not a glial cell [100]. These observations suggest that both experience and exercise can influence survival rate of new neurons and selectively direct proliferating cells to a neuronal fate.

7. Glial plasticity

Less well known than these effects of neuron addition and plasticity of established neurons are the extensive effects of experience upon non-neuronal elements of the brain. For example, astrocyte process surface density is approximately 20% greater per neuron in the visual cortex of EC rats, compared to IC rats [157]. An issue of interest, already addressed above, is the specific relationship of these changes to the types of functional demands. Specifically, there are at least two aspects of living in a complex environment that could influence brain function: (1) learning, which clearly occurs based upon demonstrations that EC animals exposed after weaning or in adulthood differ behaviorally from SC or IC reared animals (e.g. [68,69,79,82,89,94]), and (2) neuronal activity, driven by peripheral stimulation. Using 10-month-old rats exposed to either motor learning (AC), exercise (VX), or inactive conditions (IC), it was shown that the volume of astrocyte processes in the cerebellar cortex of AC rats was highly correlated with synapse number per neuron and, surprisingly, not correlated with measures of vasculature [10]. These astrocyte measures reflected changes induced in adult animals, indicating that astrocytic plasticity is not limited to development. Oligodendrocytes, reflected in measures of myelin, exhibit similar plastic responses to experience. Early work by Szeligo and Leblond [164] and subsequent work by Juraska and Kopcik [95] indicated that complex environment exposure subsequent to weaning affected myelination of subcortical and callosal white matter axons. Again, this form of plasticity is not limited to development as corpus callosum myelination was increased in adult EC rats, compared to IC rats [30]. It is fascinating to consider what roles are played by dramatically increasing the conduction velocity in a specific callosal pathway in an adult animal (or human).

Together these data suggest an orchestrated response of numerous cell types in the brain to experience. The plasticity of neurons occurs in the context of changes of tissues we view as supporting neuronal function. There is ample evidence that plasticity of astrocytes could modify neuronal interactions (e.g. [18,124,126]), and the myelination consequences of experience must certainly modify function as well. The impression generated is that all (or most) elements of brain (1) have the capacity for plastic change in response to demand, and (2) reflect in their structural and functional organization the history of experience.

8. Vascular plasticity

As is evident above, investigations of pathological modifications of the brain associated with the aging process have focused almost exclusively on neuronal morphology; however, significant deterioration of the brain's vasculature also occurs [50,51,61,62]. This decline may include loss of vessels, changes in vessel wall characteristics, deposition of collagen and other material, and declines in blood flow, oxygen extraction and glucose transport [156]. The precise role that these degenerative changes may play in cognitive impairments observed with aging is still unclear. In fact, whether these changes precede pathological changes in the neuron or are a product of altered neuron function is still a matter of extensive debate.

It is clear, however, that increasing evidence supports the observation that manipulating blood flow to the brain alters behavioral performance on a variety of tasks [123,135]. For example, administration of erythropoietin (a glycoprotein that stimulates red blood cell production) has been shown to enhance cognitive performance in rodents [90,148] and humans [2,122,128]. Similar effects were obtained using the cholinergic agonists citicoline [8] and milmaline [151] as well as the alpha-2A adrenergic agonist, guanficine [13] all of which have been reported to increase blood flow. A significant body of work has also linked estrogen with increased blood flow and enhanced cognitive performance (for review, see [119]).

Behavioral strategies may also be capable of increasing blood flow and enhancing cognition. Numerous animal studies have documented transient increases in cerebral blood flow [70,83,158], oxygen extraction, and glucose utilization

[170] during the execution of motor tasks as well as for a brief period following the cessation of physical activity. It is likely that prolonged exercise and the concomitant neural activity associated with it have significant long-term consequences for behavioral and neural plasticity. For example, several studies have reported that neurotrophins such as BDNF, VEGF, and FGF are elevated following prolonged periods of exercise [73,74,127,146]. Though the consequences of growth factor up-regulation are presently unclear, several studies have reported that animals exposed to prolonged exercise regimens exhibit significantly better performance on a variety of spatial learning tasks that cannot be attributed simply to enhanced muscle strength or endurance [11,65–67,139]. Further studies will be necessary to determine whether growth factor interactions with neurons, capillaries, or glial cells underlie this phenomenon.

Perhaps the most striking effect of exercise on plasticity of the brain's vascular system is that of angiogenesis, the growth of new capillaries from preexisting vessels. Initially angiogenesis, much like that for neurons, was believed to be limited to periods of development [15,36,84,145] or in response to pathological insults [12,85,108,131]. It has since been reported that angiogenesis is a natural consequence of heightened physical activity and the concomitant increase in neural activity, and can be induced by exposure to a complex environment [24] and exercise [22,92]. Thus, this growth is not restricted to developmental periods but extends, albeit less robustly, into maturity and beyond [23].

Recently, the etiology of angiogenesis in the rat cerebellum has been characterized. Using an antibody against the CD61 integrin expressed only on developing capillaries [39,40] in the cerebellum of adult animals that exercised for a variety of periods of time, it has been reported that angiogenesis begins quickly (within 3 days) after the onset of a voluntary exercise program and that this growth temporally coincides with elevated levels of exercise performance [161,163].

While it is clear that angiogenesis persists across the lifespan, the precise signals and mechanisms for capillary addition are unknown. Cellular hypoxia and glucose deficits, both likely products of intense exercise, as well as exercise itself, have all been reported to increase the production of VEGF [115,150,155] which is believed to be the primary growth factor associated with capillary formation in the developing brain [47,63]. Recently, expression of at least one target for VEGF, the tyrosine kinase receptor flk-1, has been observed to increase prior to the onset of both cerebellar and cortical angiogenesis, suggesting that activation of this receptor may be critical for the induction of vessel growth [31,32].

Angiogenesis in the brain is not restricted to the cerebellum. This phenomenon has also been demonstrated in visual cortex of rats exposed to complex environments [24] and more recently in primary motor cortex of rats permitted to exercise voluntarily [160,162]. We hypothesized that angiogenesis is likely to occur in any area of the adult brain that is activated and lacks sufficient vascularization to support chronic levels of elevated neuronal activity. It is important to emphasize that while the angiogenesis we have described reflects a chronic change in the capillary innervation of the brain, it may also substantially alter the dynamics of the blood-vascular response on a moment-to-moment basis. For example, when adult rats were permitted to exercise, blood volume within the motor cortex was approximately 19% greater than control animals ([160,162]; see Fig. 5). Flow alternating inversion recovery (FAIR) images, which are sensitive to flow rate, obtained from animals breathing air with a normal level of CO_2 indicated that blood flow rate within this increased capillary volume did not differ from that of inactive controls. However, when exposed to elevated CO_2 levels, the exercise group displayed enhanced flow rates. Finally, immunolabeling of actively growing vessels indicated that motor cortex is capable of substantial increases in vessel density across 30 days of training. In other words, structure, perfusion, and response rate of the vascular system were altered by exercise.

Taken as a whole, the literature indicates that the brain vascular system is highly plastic and remains so across the lifespan. The vascular system is capable of responding to environmental demands in both a phasic and tonic manner. Any manipulation that increases brain vascularization, and hence blood flow, might prove to be an effective strategy to minimize or delay the cognitive declines associated with aging. Finally, the data provide additional insight into how the vascular system might be altered in the aging human and how the progress of these changes might be non-invasively monitored via functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) imaging.

9. Brain imaging and humans

The rapidly developing field of human neuroimaging provides a means for establishing the relationship between fitness, cognition and brain function. Indeed, in recent years, there has been a growing body of literature examining age-related differences in patterns of brain activation, through the use of PET and fMRI, in a variety of cognitive operations including attention, multi-task processing and task switching, linguistic processing, and aspects of working and long-term memory. Although it is beyond the scope of the present paper to provide a detailed discussion of this research, there are several important observations that are noteworthy. A substantial number of studies investigating aging, cognition, and brain function have found evidence for dedifferentiation, that is, the observation that older adults show less specificity than young adults in the regions of brain that are recruited to carry our a variety of cognitive tasks [35,134]. For example, using PET to study age differences in verbal and spatial working memory, it was reported that while younger adults showed a lateralized

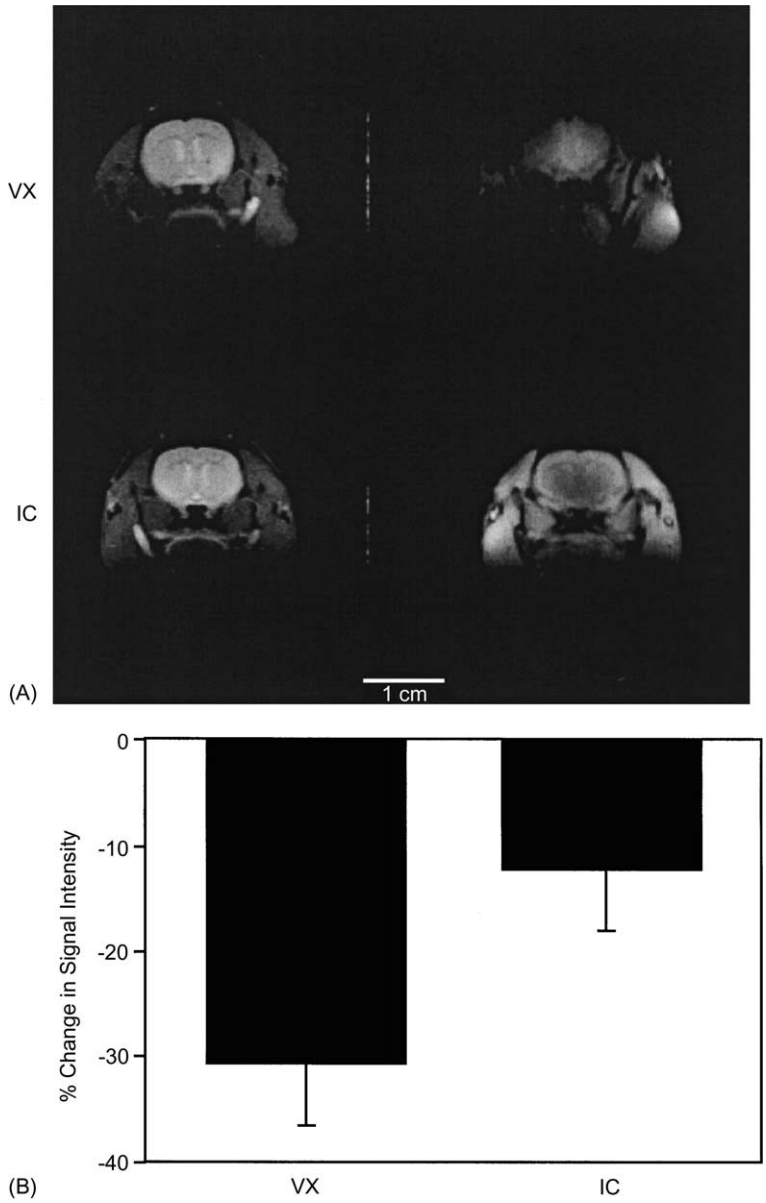

Fig. 5. This figure portrays the effects of exercise on blood flow in the brain of rats. Panel A depicts structural (left) and functional (right) magnetic resonance images from an exercise animal (VX, top) and control animal (IC, bottom) which illustrate the marked changes in signal intensity that accompany exercise. Deoxygenated hemoglobin in the blood subtracts from the image, such that greater blood utilization darken the images on the right. The loss of signal is greater in the exercising animal in the upper right. Panel B provides a graphical representation of this effect for all animals.

pattern of frontal activity in these tasks, older adults showed a pattern of bilateral frontal activation in both memory tasks [140]. Similarly, right frontal activation has been observed in young adults during retrieval of verbal material, whereas older adults displayed bilateral frontal activation in the same task [118] (see also [34]). It is possible that similar events could be occurring in animals solving laboratory tasks using strategies that change with age, as proposed by Barnes et al. [16].

Thus far, it is uncertain whether dedifferentiation in brain activity during aging serves as a compensatory function or instead represents a marker of decline. With regard to the compensatory hypothesis, it is conceivable that older adults may counteract, in part, cognitive deficits by recruiting additional cortical regions. For example, using event-related fMRI it was shown that higher levels of activation of dorsolateral prefrontal cortex were associated with faster working memory retrieval in older adults [147]. Furthermore, using PET, it was reported that activation levels in the left parahippocampal and right middle frontal gyri were significant predictors of reaction time in older adults during encoding of verbal material [118]. These studies suggest that older adults use a selective compensatory mechanism when processing information.

10. Summary and conclusions

The overall goal of this special section of *Neurobiology of Aging* is to ask whether there are interventions that can mitigate the brain aging process. As our review of some of the data regarding the effects of experience, and particularly of physical exercise, makes clear, studies of the aging brain and behavioral response to experience have revealed parallel patterns across animal and human research, despite the rather disparate measures that have been applied to the issues. In the human literature, we focused upon physical exercise. While there appears to be considerable divergence in reports of positive exercise effects on behavioral performance, a closer look at the data suggests that physical exercise may selectively affect particular cognitive functions. A meta-analysis of the data indicates that exercise specifically affects tasks that involve executive control, processes such as planning, scheduling, coordination, inhibition, and working memory [46]. Many behavioral studies in animals support this result, finding that exercise improves performance of animals on hippocampus-dependent tasks [11]. Moreover, while aged animals frequently can learn complex tasks to an extent as proficient as younger animals, the strategies, and subsequently the brain areas, used by older animals may be significantly different than those of younger subjects [16]. Studies of brain plasticity in animals permits dissection of the effects of experience into discrete categories such as those effects associated with learning and those effects associated with exercise. Of particular interest is that the adult and aging brain continues to generate new neurons in response to exercise and that learning selectively enhances synaptogenesis into adulthood. A second effect of exercise that is likely to be very important is its enhancement of non-neural components of brain, such as vasculature. In the one case in which the effects of added vasculature on physiological function have been evaluated, there appears to be a greater capacity to respond to demand in animals that have exercised. These discrete biological responses have yet to be fully understood, yet the notion that various forms of activity can differentially influence specific tissue types suggests that these changes occur to enable the organism to more efficiently respond to environmental challenges. A direction in which the animal and human work may come together involves fMRI measures of brain blood flow "under load." While this is likely not the only mechanism whereby physical exercise and mental activity affect brain function in aging, it is likely to be an important one.

Acknowledgments

Supported in part by grants NIA/AG10154 (WTG), NIA/AG14966 (AFK), MH35321 (WTG), Institute for the Study of Aging (AFK).

References

[1] Abourezk T, Toole T. Effect of task complexity on the relationship between physical fitness and reaction time in older women. J Aging Phy Act 1995;3:251–60.
[2] Ajmani RS, Metter EJ, Jaykumar R, Ingram DK, Spangler EL, Abugo OO, et al. Hemodynamic changes during aging associated with cerebral blood flow and impaired cognitive function. Neurobiol Aging 2000;21(2):257–69.
[3] Albert MS, Jones K, Savage CR, Berkman L, Seeman T, Blazer D, et al. Predictors of cognitive change in older persons: MacArthur studies of successful aging. Psychol Aging 1995;10:578–89.
[4] Allport A, Wylie G. Task switching, stimulus-response bindings, and negative priming. In: Monsell S, Driver J, editors. Attention and performance, vol. XVIII. Cambridge, MA: MIT Press, 2000. p. 35–70.
[5] Altman J. Are new neurons formed in the brains of adult mammals? Science 1962;135:1127–8.
[6] Altman J. Autoradiographic, with special reference to persisting neurogenesis in the olfactory bulb. J Comp Neurol 1969;137:433–58.
[7] Altman J. Autoradiographic investigation of cell proliferation in the brains of rats, with implications for a morphological theory of memory. Anat Rec 1963;145:573–91.
[8] Alvarez XA, Mouzo R, Pichel V, Perez P, Laredo M, Fernandez-Novoa L, et al. Double-blind placebo-controlled study with citicoline in APOE genotyped Alzheimer's disease patients: effects on cognitive performance. Meth Find Exp Clin Pharmacol 1999;21(9):633–44.
[9] Anderson BJ, Alcantara AA, Greenough WT. Motor skill learning: changes in synaptic organization of the rat cerebellar cortex. Neurobiol Learn Mem 1996;66:221–9.
[10] Anderson BJ, Li X, Alcantara AA, Isaacs KR, Black JE, Greenough WT. Glial hypertrophy is associated with synaptogenesis following motor-skill learning, but not with angiogenesis following exercise. Glia 1994;11:73–80.
[11] Anderson BJ, Rapp DN, Baek DH, McCloskey DP, Coburn-Litvak PS, Robinson JK. Exercise influences spatial learning in the radial arm maze. Physiol Behav 2000;70(5):425–9.
[12] Ausprunk DH, Folkman J. Migration and proliferation of endothelial cells in preformed and newly formed blood vessels during tumour angiogenesis. Microvasc Res 1977;14:53–65.
[13] Avery RA, Franowicz JS, Studholme C, van Dyck CH, Arnsten AF. The alpha-2A-adrenoceptor agonist, guanfacine, increases regional cerebral blood flow in dorsolateral prefrontal cortex of monkeys performing a spatial working memory task. Neuropsychopharmacy 2000;23(3):240–9.
[14] Ball K, Beard B, Roenker D, Miller R, Griggs D. Age and visual search: expanding the useful field of view. J Optical Soc Am 1988;5:2210–9.
[15] Bar T. The vascular system of the cerebral cortex. Berlin: Springer, 1980.
[16] Barnes CA, Nadel L, Honig WK. Spatial memory deficit in senescent rats. Canad J Psychol 1980;34(1):29–39.
[17] Baron A, Mattila W. Response slowing of older adults: effects of time limit contingencies on single and dual-task performance. Psychol Aging 1989;4:66–72.
[18] Barres BA. New roles for glia. J Neurosci 1991;11(12):3685–94.
[19] Baylor A, Spirduso W. Systematic aerobic exercise and components of reaction time in older women. J Gerontol: Psychological Sci 1988;43:121–6.
[20] Bennett EL, Diamond MC, Krech D, Rosenzweig MR. Chemical and anatomical plasticity of brain. Science 1964;146:610–9.
[21] Birren JE, Schaie KW. Handbook of the psychology of aging. San Diego, CA: Academic Press, 1996.
[22] Black JE, Isaacs KR, Anderson BJ, Alcantara AA, Greenough WT. Learning causes synaptogenesis, whereas motor activity causes

angiogenesis, in cerebellar cortex of adult rats. Proc Natl Acad Sci USA 1990;87:5568–72.
[23] Black JE, Polinsky M, Greenough WT. Progressive failure of cerebral angiogenesis supporting neural plasticity in aging rats. Neurobiol Aging 1989;10:353–8.
[24] Black JE, Zelazny AM, Greenough WT. Capillary and mitochondrial support of neural plasticity in adult rat visual cortex. Exp Neurol 1991;111(2):204–9.
[25] Blomstrand E, Perrett D, Parry-Billings M, Newsholme EA. Effect of sustained exercise on plasma amino acid concentrations and on 5-hydroxytryptamine metabolism in six different brain regions in the rat. Acta Physiol Scand 1989;136(3):473–81.
[26] Blumenthal JA, Madden DJ. Effects of aerobic exercise training, age, and physical fitness on memory search performance. Psychol Aging 1988;3:280–5.
[27] Botwinick J, Thompson L. Age difference in reaction time: an artifact? Gerontologist 1968;8:25–8.
[28] Brezun JM, Daszuta A. Depletion in serotonin decreases neurogenesis in the dentate gyrus and the subventricular zone of adult rats. Neuroscience 1999;89(4):999–1002.
[29] Brezun JM, Daszuta A. Serotonin may stimulate granule cell proliferation in the adult hippocampus, as observed in rats grafted with foetal raphe neurons. Eur J Neurosci 2000;12(1):391–6.
[30] Briones T, Shah P, Juraska J, Greenough WT. Effects of prolonged exposure to and subsequent removal from a complex environment on corpus callosum. Soc Neurosci Abst 1999;25:638.
[31] Bulinski SC, Thompson KJ, Powell SK, Sikorski AM, Swain RA. Increased immunolabeling of flk-1 receptors in primary motor cortex of the adult rat following exercise. Soc Neurosci Abst 2000;26:1735.
[32] Bulinski SC, Thompson KJ, Powell SK, Swain RA. Exercise increases immunolabeling of the Flk-1 receptor in the adult rat cerebellum. Soc Neurosci Abst 1999;25:1640.
[33] Bunce DJ, Barrowclough A, Morris I. The moderating influence of physical fitness on age gradients in vigilance and serial choice responding. Psychol Aging 1996;11:617–82.
[34] Cabeza R, Grady CL, Nyberg L, McIntosh AR, Tulving E, Kapur S, et al. Age-related differences in neural activity during memory encoding and retrieval: a positron emission tomography study. J Neurosci 1997;17:391–400.
[35] Cabeza R. Functional neuroimaging of cognitive aging. In: Cabeza R, Kingstone A, editors. Handbook of functional neuroimaging of cognition. Cambridge MA: MIT Press, 2001.
[36] Caley DW, Maxwell DS. Development of blood vessels and extracellular spaces during postnatal maturation of rat cerebral cortex. J Comp Neurol 1970;138:31–48.
[37] Cameron HA, McKay RD. Restoring production of hippocampal neurons in old age. Nat Neurosci 1999;2(10):894–7.
[38] Chapman C, Trepel C, Ivanco T, Froc D, Wilson K, Racine R. Changes in field potentials and membrane currents in rat sensorimotor cortex following repeated tetanization of the corpus callosum in vivo. Cerb Cort 1998;8:730–42.
[39] Cheresh DA. Human endothelial cells synthesize and express an Arg-Gly-Asp-directed adhesion receptor involved in attachment to fibrinogen and von Willebrand factor. Proc Natl Acad Sci USA 1987;84:6471–5.
[40] Cheresh DA. Structure, function and biological properties of integrin alpha v beta 3 on human melanoma cells. Cancer Metastasis Rev 1991;10:3–10.
[41] Chodzko-Zajko W, Moore KA. Physical fitness and cognitive function in aging. Exer Sport Sci Rev 1994;22:195–220.
[42] Churchill JD, Ivanco TL, Patel S, Norr D, DeRidder M, Greenough WT. Learning induced neurophysiological modifications in the rat cortex: are they LTP like? Soc Neurosci Abst 2000;26:36.
[43] Clarkson P, Kroll W. Practice effects on fractionated response time related to age and activity level. J Mot Behav 1978;10:275–86.
[44] Clarkson-Smith L, Hartley A. Relationships between physical exercise and cognitive abilities in older adults. Psychol Aging 1989;4:183–9.
[45] Clarkson-Smith L, Hartley A. Structural equation models of relationships between exercise and cognitive abilities. Psychol Aging 1990;5:437–46.
[46] Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. Psychological Sci, in press.
[47] Conn G, Bayne ML, Soderman DD, Kwok PW, Sullivan KA, Palisi TM, et al. Amino acid and cDNA sequences of a vascular endothelial cell mitogen that is homologous to platelet-derived growth factor. Proc Natl Acad Sci USA 1990;87(7):2628–32.
[48] Cook N, Albert M, Berkman L, Blazer D, Taylor J, Hennekens C. Interrelationships if peak expiratory flow rate with physical and cognitive function in the elderly: MacArthur foundation studies of aging. J Gerontol: Med Sci 1995:317–23.
[49] Corotto FS, Henegar JR, Maruniak JA. Odor deprivation leads to reduced neurogenesis and reduced neuronal survival in the olfactory bulb of the adult mouse. Neuroscience 1994;61(4):739–44.
[50] de la Torre JC, Stefano GB. Evidence that Alzheimer's disease is a microvascular disorder: the role of constitutive nitric oxide. Brain Res Rev 2000;34(3):119–36.
[51] de la Torre JC. Impaired cerebromicrovascular perfusion: summary of evidence in support of its causality in Alzheimer's disease. Ann N Y Acad Sci 2000;924:136–52.
[52] Del Rey P. Effects of contextual interference on the memory of older females differing in levels of physical activity. Percept Mot Skills 1982;55:171–80.
[53] Dustman R, Shearer ER. Physical activity, age, and cognitive neuropsychological function. J Aging Phy Act 1994;2:143–81.
[54] Dustman RE, Emmerson RY, Ruhling RO, Shearer DE, Steinhaus LA, Johnson SC, et al. Age and fitness effects on EEG, ERPs, visual sensitivity, and cognition. Neurobiol Aging 1990;11:193–200.
[55] Dustman RE, Ruhling RO, Russell EM, Shearer DE, Bonekat W, Shigeoka JW, et al. Aerobic exercise training and improved neurophysiological function of older adults. Neurobiol Aging 1984;5:35–42.
[56] Emery CF, Huppert FA, Schein RL. Relationships among age, exercise, health, and cognitive function in a British sample. Gerontologist 1995;35:378–85.
[57] Emery CF, Schein RL, Hauck ER, MacIntyre NR. Psychological and cognitive outcomes of a randomized trial of exercise among patients with chronic obstructive pulmonary disease. Health Psychol 1998;17:232–40.
[58] Engert F, Bonhoeffer T. Dendritic spine changes associated with hippocampal long-term synaptic plasticity. Nature 1999;399:66–70.
[59] Eriksson PS, Perfilieva E, Bjork-Eriksson T, Alborn AM, Nordborg C, Peterson DA, et al. Neurogenesis in the adult human hippocampus. Nat Med 1998;4(11):1313–7.
[60] Evans DA, Beckett LA, Albert MS, Hebert LE, Scherr PA, Funkenstein HH, et al. Level of education and change in cognitive function in a community population of older persons. Ann Epidemiol 1993;3:71–7.
[61] Farkas E, De Jong GI, de Vos RA, Jansen Steur EN, Luiten PG. Pathological features of cerebral cortical capillaries are doubled in Alzheimer's disease and Parkinson's disease. Acta Neuropathol 2000;100(4):395–402.
[62] Farkas E, Luiten PGM. Cerebral microvascular pathology in aging and Alzheimer's disease. Prog Neurobiol 2001;64(6):575–611.
[63] Ferrara N, Henzel WJ. Pituitary follicular cells secrete a novel heparin-binding growth factor specific for vascular endothelial cells. Biochem Biophys Res Commun 1989;161(2):851–8.
[64] Floeter MK, Greenough WT. Cerebellar plasticity: modification of Purkinje cell structure by differential rearing in monkeys. Science 1979;206:227–9.
[65] Fordyce DE, Farrar RP. Enhancement of spatial learning in F344 rats by physical activity and related learning-associated alterations in hippocampal and cortical cholinergic functioning. Behav Brain Res 1991;46(2):123–33.

[66] Fordyce DE, Farrar RP. Physical activity effects on hippocampal and parietal cortical cholinergic function and spatial learning in F344 rats. Behav Brain Res 1991;43:115–23.
[67] Fordyce DE, Wehner JM. Physical activity enhances spatial learning performance with an associated alteration in hippocampal protein kinase C activity in C57BL/6 and DBA/2 mice. Brain Res 1993;619(1/2):111–9.
[68] Forgays DG, Forgays JW. Crucial periods for free-environmental experience in the rat. J Comp Physiol Psychol 1962;55:816–8.
[69] Forgays DG, Forgays JW. The nature of the effect of free-environmental experience in the rat. J Comp Physiol Psychol 1952;45:322–8.
[70] Fox PT, Raichle ME. Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects. Proc Natl Acad Sci USA 1986; 83:1140–4.
[71] Geinisman Y, deToledo-Morrell L, Morrell F. Induction of long-term potentiation is associated with an increase in the number of axospinous synapses with segmented postsynaptic densities. Brain Res 1991;566:77–88.
[72] Globus A, Rosenzweig MR, Bennett EL, Diamond MC. Effects of differential experience on dendritic spine counts in rat cerebral cortex. J Comp Physiol Psych 1973;82:175–81.
[73] Gomez-Pinilla F, Dao L, Vannarith S. Physical exercise induces FGF-2 and its mRNA in the hippocampus. Brain Res 1997;764:1–8.
[74] Gomez-Pinilla F, So V, Kesslak JP. Spatial learning and physical activity contribute to the induction of fibroblast growth factor: neural substrates for increased cognition associated with exercise. Neuroscience 1998;85(1):53–61.
[75] Gould E, McEwen BS, Tanapat P, Galea LA, Fuchs E. Neurogenesis in the dentate gyrus of the adult tree shrew is regulated by psychosocial stress and NMDA receptor activation. J Neurosci 1997;17(7):2492–8.
[76] Gould E, Reeves AJ, Fallah M, Tanapat P, Gross CG, Fuchs E. Hippocampal neurogenesis in adult Old World primates. Proc Natl Acad Sci USA 1999;96(9):5263–7.
[77] Gould E, Reeves AJ, Graziano MS, Gross CG. Neurogenesis in the neocortex of adult primates. Science 1999;286(5439):548–52.
[78] Green EJ, Greenough WT, Schlumpf BE. Effects of complex or isolated environments on cortical dendrites of middle-aged rats. Brain Res 1983;264:233–40.
[79] Greenough WT, Madden TC, Fleischmann TB. Effects of isolation, daily handling, and enriched rearing on maze learning. Psychonomic Sci 1972;27:279–80.
[80] Greenough WT, McDonald JW, Parnisari RM, Camel JE. Environmental conditions modulate degeneration and new dendrite growth in cerebellum of senescent rats. Brain Res 1986;380:136–43.
[81] Greenough WT, West RW, DeVoogd TJ. Sub-synaptic plate perforations: changes with age and experience in the rat. Science 1978;202:1096–8.
[82] Greenough WT, Wood WE, Madden TC. Possible memory storage differences among mice reared in environments varying in complexity. Behav Biol 1972;7:717–22.
[83] Grinvald A, Lieke E, Frostig RD, Gilbert CD, Wiesel TN. Functional architecture of cortex revealed by optical imaging of intrinsic signals. Nature 1986;324:361–4.
[84] Gyllensten L. Influence of oxygen exposure on the postnatal vascularization of the cerebral cortex in mice. Acta Morph Neerlando-Scan 1959;2:289–310.
[85] Harik SI, Hritz MA, LaManna JC. Hypoxia induced brain angiogenesis in the adult rat cerebellum. J Physiol 1995;485:525–30.
[86] Hart B. The effect of age and habitual activity on the fractionated components of resisted and unresisted response time. Med Sci Sport Exer 1981;13:78.
[87] Hawkins H, Kramer A, Capaldi D. Aging, exercise and attention. Psych Aging 1992;7(4):643–53.
[88] Hebb DO. The effects of early experience on problem-solving at maturity. Am Psychol 1947;2:306–7.
[89] Hebb DO. The organization of behavior. New York: Wiley, 1949.
[90] Hengemihle JM, Abugo O, Rifkind J, Spangler E, Danon D, Ingram DK. Chronic treatment with human recombinant erythropoietin increases hematocrit and improves water maze performance in mice. Physiol Behav 1996;59(1):153–6.
[91] Hill RD, Storandt M, Malley M. The impact of long-term exercise training on psychological function in older adults. J Gerontol: Psych Sci 1993;1:12–7.
[92] Isaacs KR, Anderson BJ, Alcantara AA, Black JE, Greenough WT. Exercise and the brain: angiogenesis in the adult rat cerebellum after vigorous physical activity and motor skill learning. J Cereb Blood Flow Metab 1992;12(3):533 [Erratum]. J Cereb Blood Flow Metab 1992;12(1):110–9.
[93] Juraska JM, Greenough WT, Elliot C, Mack K, Berkowitz R. Plasticity in adult rat visual cortex: an examination of several cell populations after differential rearing. Behav Neur Biol 1980;29: 157–67.
[94] Juraska JM, Henderson C, Muller J. Differential rearing experience, gender, and radial maze performance. Dev Psychobiol 1984;17(3):209–15.
[95] Juraska JM, Kopcik JR. Sex and environmental influences on the size and ultrastructure of the rat corpus callosum. Brain Res 1988;450(1/2):1–8.
[96] Juraska JM. Sex differences in dendritic response to differential experience in the rat visual cortex. Brain Res 1984;295(1):27–34.
[97] Kaplan MS, Hinds JW. Neurogenesis in the adult rat: electron microscopic analysis of light radioautographs. Science 1977;197:1092–4.
[98] Kaplan MS. Neurogenesis in the 3-month-old rat visual cortex. J Comp Neurol 1981;195:323–38.
[99] Kaplan MS. Proliferation of subependymal cells in the adult primate CNS: differential uptake of DNA labeled precursors. J Hirnforsch 1982;23:23–33.
[100] Kempermann G, Kuhn HG, Gage FH. Experience-induced neurogenesis in the senescent dentate gyrus. J Neurosci 1998;18(9):3206–12.
[101] Kempermann G, Kuhn HG, Gage FH. More hippocampal neurons in adult mice living in an enriched environment. Nature 1997;386(6624):493–5.
[102] Kleim JA, McNamee D, Blankstein EJ, Greenough WT. Interdependent changes in synapse size and number across the course of learning. Soc Neurosci Abst 1997;23:221.
[103] Kleim JA, Pipitone MA, Czerlanis C, Greenough WT. Structural stability within the lateral cerebellar nucleus of the rat following complex motor learning. Neurobiol Learn Mem 1998;69(3):290–306.
[104] Kleim JA, Swain RA, Armstrong KA, Napper RM, Jones TA, Greenough WT. Selective synaptic plasticity within the cerebellar cortex following complex motor skill learning. Neurobiol Learn Mem 1998;69(3):274–89.
[105] Kleim JA, Swain RA, Czerlanis CM, Kelly JL, Pipitone MA, Greenough WT. Learning-dependent dendritic hypertrophy of cerebellar stellate cells: plasticity of local circuit neurons. Neurobiol Learn Mem 1997;67(1):29–33.
[106] Kleim JA, Vij K, Ballard DH, Greenough WT. Learning-dependent synaptic modifications in the cerebellar cortex of the adult rat persist for at least 4 weeks. J Neurosci 1997;17(2):717–21.
[107] Klintsova AY, Cowell RM, Swain RA, Napper RMA, Goodlett CR, Greenough WT. Therapeutic effect of complex motor skill learning on neonatal alcohol-induced motor performance deficits. I. Behavioral results. Brain Res 1998;800:48–61.
[108] Knighton DR, Hunt TK, Scheutenstuhl H, Halliday BJ. Oxygen tension regulates the expression of angiogenesis factor by macrophages. Science 1983;221:1283–5.

[109] Kornack DR, Rakic P. Continuation of neurogenesis in the hippocampus of the adult macaque monkey. Proc Natl Acad Sci USA 1999;96(10):5768–73.
[110] Kramer AF, Hahn S, Cohen NJ, Banich MT, McAuley E, Harrison CR, et al. Aging, fitness and neurocognitive function. Nature 1999;400:418–9.
[111] Kramer AF, Hahn S, Gopher D. Task coordination and aging: explorations of executive control processes in the task switching paradigm. Acta Psychol 1999;101:339–78.
[112] Kramer AF, Larish J, Weber T, Bardell L. Training for executive control: task coordination strategies and aging. In: Gopher D, Koriat A, editors. Attention and performance, vol. XVII. Cambridge, MA: MIT Press, 1999.
[113] Kramer AF, Larish J. Training for attentional control in dual-task settings. In: Rogers W, Fisk A, Walker N, editors. Aging and skilled performance: advances in theory and applications. Hillsdale, NJ: Erlbaum, 1996.
[114] Kuhn HG, Dickinson-Anson H, Gage FH. Neurogenesis in the dentate gyrus of the adult rat: age-related decrease of neuronal progenitor proliferation. J Neurosci 1996;16(6):2027–33.
[115] Ladoux A, Frelin C. Hypoxia is a strong inducer of vascular endothelial growth factor mRNA expression in the heart. Biochem Biophys Res Commun 1993;195(2):1005–10.
[116] Laurin D, Verreault R, Lindsay J, MacPherson K, Rockwood K. Physical activity and risk of cognitive impairment and dementia. Arch Neurol 2001;58:498–504.
[117] Madden DJ, Blumenthal JA, Allen PA, Emery CF. Improving aerobic capacity in health older adults does not necessarily lead to improved cognitive performance. Psychol Aging 1989;4:307–20.
[118] Madden DJ, Turkington TG, Provenzale JM, Denny LL, Hawk TC, Gottlob LR, et al. Adult age differences in functional neuroanatomy of verbal recognition memory. Hum Brain Map 1999;7:115–35.
[119] Maki PM, Resnick SM. Effects of estrogen on patterns of brain activity at rest and during cognitive activity: a review of neuroimaging studies. Neuroimage 2001;14(4):789–801.
[120] Malberg JE, Eisch AJ, Nestler EJ, Duman RS. Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. J Neurosci 2000;20(24):9104–10.
[121] Maletic-Savatic M, Malinow R, Svoboda K. Rapid dendritic morphogenesis in CA1 hippocampal dendrites induced by synaptic activity. Science 1999;283:1923–6.
[122] Marsh JT, Brown WS, Wolcott D, Carr CR, Harper R, Schweitzer SV, et al. rHuEPO treatment improves brain and cognitive function of anemic dialysis patients. Kidney Int 1991;39(1):155–63.
[123] Marshall RS, Lazar RM, Pile-Spellman J, Young WL, Duong DH, Joshi S, et al. Recovery of brain function during induced cerebral hypoperfusion. Brain 2001;124(Pt 6):1208–17.
[124] Mennerick S, Zorumski CF. Glial contributions to excitatory neurotransmission in cultured hippocampal cells. Nature 1994;368:59–62.
[125] Moul J, Goldman B, Warren B. Physical activity and cognitive performance in the older population. J Aging Phy Act 1995;3:135–45.
[126] Nedergaard M. Direct signalling from astrocytes to neurons in cultures of mammalian brain cells. Science 1994;263:1768–71.
[127] Neeper SA, Gomez-Pinilla F, Choi J, Cotman C. Exercise and brain neurotrophins. Nature 1995;373:109.
[128] Nissenson AR. Epoetin and cognitive function. Am J Kidney Dis 1992;20(1 (Suppl 1)):21–4.
[129] Normand R, Kerr R, Metivier G. Exercise aging and fine motor performance: an assessment. J Sports Med 1987;27:488–96.
[130] Offenbach S, Chodzko-Zajko W, Ringel R. Relationship between physiological status cognition and age in adult men. Bull Psychonomic Soc 1990;28:112–4.
[131] Opitz E. Increased vascularization of the tissue due to acclimatization to high altitude and its significance for the oxygen transport. Exp Med Surg 1951;9:389–403.
[132] Otto T, Eichenbaum H, Wiener S, Wible CG. Learning-related patterns of CA1 spike trains parallel stimulation parameters optimal for inducing hippocampal long-term potentiation. Hippocampus 1991;1(2):181–92.
[133] Panton LB, Graves JE, Pollock ML, Hagberg JM, Chen W. Effect of aerobic and resistance training on fractionated reaction time and speed of improvement. J Gerontol: Med Sci 1990;45:26–31.
[134] Park DC, Polk TA, Mikels JA, Taylor SF, Marshuetz C. Cerebral aging: integration of brain and behavioral models of cognitive function. Dialogues in clinical neuroscience: cerebral aging, in press.
[135] Patterson II JC. Cerebellar perfusion abnormalities correlated with change in cognitive and affective state in a 78-year-old man. Am J Geriatric Psych 2001;9(3):309–14.
[136] Pencea V, Bingaman KD, Wiegand SJ, Luskin MB. Infusion of brain-derived neurotrophic factor into the lateral ventricle of the adult rat leads to new neurons in the parenchyma of the striatum septum thalamus and hypothalamus. J Neurosci 2001;21(17):6706–17.
[137] Powell R, Pohndorf R. Comparison of adult exercisers and nonexercisers on fluid intelligence and selected physiological variables. Res Q 1971;42:70–7.
[138] Pysh JJ, Weiss GM. Exercise during development induces an increase in Purkinje cell dendritic tree size. Science 1979;206: 230–1.
[139] Radak Z, Kaneko T, Tahara S, Nakamoto H, Pucsok J, Sasvari M, et al. Regular exercise improves cognitive function and decreases oxidative damage in rat brain. Neurochem Int 2001;38(1):17–23.
[140] Reuter-Lorenz PA, Jonides J, Smith EE, Hartley A, Miller A, Marshuetz C, et al. Age differences in the frontal lateralization of verbal and spatial working memory as revealed by PET. J Cog Neurosci 2000;12:174–87.
[141] Rikli R, Edwards D. Effects of a 3-year exercise program on motor function and cognitive processing speed in older women. Res Q Exer Sport 1991;62:61–7.
[142] Rioult-Pedotti MS, Friedman D, Hess G, Donoghue J. Strengthening of horizontal cortical connections following skill learning. Nat Neurosci 1998;1(3):230–4.
[143] Rogers RD, Monsell S. Costs of a predictable switch between simple cognitive tasks. J Exp Psychol General 1995;124:207–31.
[144] Rosenzweig MR, Bennett EL, Diamond MC. Cerebral effects of differential experience in hypophysectomized rats. J Comp Physiol Psych 1972;79:56.
[145] Rowan RA, Maxwell DS. Patterns of vascular sprouting in the postnatal development of the cerebral cortex of the rat. Am J Anat 1981;160:247–55.
[146] Russo-Neustadt A, Ha T, Ramirez R, Kesslak JP. Physical activity-antidepressant treatment combination: impact on brain-derived neurotrophic factor and behavior in an animal model. Behav Brain Res 2001;120(1):87–95.
[147] Rympa B, D'Esposito M. Isolating the neural mechanisms of age-related changes in human working memory. Nat Neurosci 2000;3:509–15.
[148] Sadamoto Y, Igase K, Sakanaka M, Sato K, Otsuka H, Sakaki S, et al. Erythropoietin prevents place navigation disability and cortical infarction in rats with permanent occlusion of the middle cerebral artery. Biochem Biophy Res Commun 1998;253(1):26–32.
[149] Salthouse T. The processing-speed theory of adult age differences in cognition. Psychol Rev 1996;103:403–28.
[150] Satake S, Kuzuya M, Miura H, Asai T, Ramos MA, Muraguchi M, et al. Up-regulation of vascular endothelial growth factor in response to glucose deprivation. Biol Cell 1998;90(2):161–8.
[151] Schwarz RD, Callahan MJ, Coughenour LL, Dickerson MR, Kinsora JJ, Lipinski WJ, et al. Milameline (CI-979/RU35926): a muscarinic receptor agonist with cognition-activating properties: biochemical and in vivo characterization. J Pharmacol Exp Ther 1999;291(2):812–22.

[152] Shay KA, Roth DL. Association between aerobic fitness and visuospatial performance in healthy older adults. Psychol Aging 1992;7:15–24.
[153] Shetty AK, Turner DA. In vitro survival and differentiation of neurons derived from epidermal growth factor-responsive postnatal hippocampal stem cells: inducing effects of brain-derived neurotrophic factor. J Neurobiol 1998;35(4):395–425.
[154] Sholl DA. Organization of the cerebral cortex. Methuen, London, 1956.
[155] Shweiki D, Itin A, Soffer D, Keshet E. Vascular endothelial growth factor induced by hypoxia may mediate hypoxia-initiated angiogenesis. Nature 1992;359(6398):843–5.
[156] Simpson IA, Chundu KR, Davies-Hill T, Honer WG, Davies P. Decreased concentrations of GLUT1 and GLUT3 glucose transporters in the brains of patients with Alzheimer's disease. Ann Neurol 1994;35(5):546–51.
[157] Sirevaag AM, Greenough WT. Plasticity of GFAP-immunoreactive astrocyte size and number in visual cortex of rats reared in complex environments. Brain Res 1991;540:273–8.
[158] Sokoloff L, Reivich M, Kennedy C, Des Rosiers MH, Patlak CS, Pettigrew KD, et al. The [^{14}C] deoxyglucose method for the measurement of local glucose utilization: theory, procedure, and normal values in the conscious and anesthetized albino rat. J Neurochem 1977;28:897–916.
[159] Stones M, Kozma A. Age exercise and coding performance. Psychol Aging 1988;4:190–4.
[160] Swain RA, Harris AB, Wiener EC, Dutka MV, Morris HD, Theien BT, et al. Prolonged exercise induces angiogenesis and increases cerebral blood volume in primary motor cortex of the rat. J Neurosci, in press.
[161] Swain RA, Harris AB, Wiener EC, Dutka MV, Morris HD, Lauterbur PC, et al. fMRI and immunohistological evidence of capillary plasticity in motor cortex of adult rats following exercise. Soc Neurosci Abst 1998;24:1168.
[162] Swain RA, Harris AB, Wiener EC, Morris HD, Swain CR, Lauterbur PC, et al. fMRI of rat motor cortex following physical exercise. Soc Neurosci Abst 1994;20:147.
[163] Swain RA, Theien BE, Dutka MV, Wiener EC, Greenough WT. Rapid induction of cerebellar angiogenesis in the adult rat following exercise. Soc Neurosci Abst 1997;23:1575.
[164] Szeligo F, Leblond CP. Response of the three main types of glial cells of cortex and corpus callosum in rats handled during suckling or exposed to enriched, control and impoverished environments following weaning. J Comp Neurol 1977;172(2): 247–64.
[165] Uylings HBM, Kuypers K, Diamond MC, Veltman WAM. Effects of differential environments on plasticity of dendrites of cortical pyramidal neurons in adult rats. Exp Neurol 1978;62:658–77.
[166] Van Boxtel M, Langerak K, Houx P, Jolles J. Self-reported physical activity, subjective health, and cognitive performance in older adults. Exp Aging Res 1996;22:363–79.
[167] Van Boxtel M, Paas F, Houx P, Adam J, Teeken J, Jolles J. Aerobic capacity and cognitive performance in a cross-sectional aging study. Med Sci Sports Exer 1997;10:1357–65.
[168] van Praag H, Kempermann G, Gage FH. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. Nat Neurosci 1999;2(3):266–70.
[169] Verhaeghen P, Marcoen A, Goossens L. Improving memory performance in the aged through mnemonic training: a meta-analytic study. Psychol Aging 1992;7:242–51.
[170] Vissing J, Andersen M, Diemer NH. Exercise-induced changes in local cerebral glucose utilization in the rat. J Cereb Blood Flow Metab 1996;16:729–36.
[171] Volkmar FR, Greenough WT. Rearing complexity affects branching of dendrites in the visual cortex of the rat. Science 1972;176(42):1145–7.
[172] West R. An application of prefrontal cortex function theory to cognitive aging. Psychol Bull 1996;120:272–92.
[173] Williams P, Lord SR. Effect of group exercise on cognitive functioning and mood in older women. Aust N Z J Public Health 1997;21:45–52.
[174] Willis SL, Nesselroade CS. Long-term effects of fluid ability training in old-old age. Dev Psychol 1990;26:905–10.
[175] Willis SL, Schaie . Training the elderly on the ability factors of spatial orientation and inductive reasoning. Psychol Aging 1986;1(3):239–47.
[176] Yaffe K, Barnes D, Nevitt M, Lui LY, Covinsky K. A prospective study of physical activity and cognitive decline in elderly women—women who walk. Arch Int Med 2001;161:1703–8.