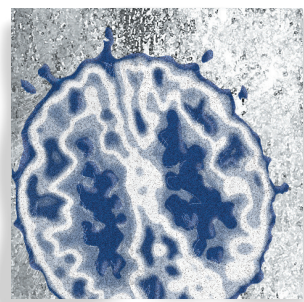


# Translational research

## *Neuropathological approaches to cerebral aging and neuroplasticity*

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### Introduction

“Healthy” aging is defined as aging without disease. With the current attempts to increase the life span, understanding the molecular interactions and mechanisms involved in normal brain aging continues to be a challenge. Cerebral aging is a complex and heterogenous process that is associated with a high degree of interindividual variability. The last 20 years have witnessed a great

*Cerebral aging is a complex and heterogenous process related to a large variety of molecular changes involving multiple neuronal networks, due to alterations of neurons (synapses, axons, dendrites, etc), particularly affecting strategically important regions, such as hippocampus and prefrontal areas. A substantial proportion of nondemented, cognitively unimpaired elderly subjects show at least mild to moderate, and rarely even severe, Alzheimer-related lesions, probably representing asymptomatic preclinical Alzheimer's disease, and/or mixed pathologies. While the substrate of resilience to cognitive decline in the presence of abundant pathologies has been unclear, recent research has strengthened the concept of cognitive or brain reserve, based on neuroplasticity or the ability of the brain to manage or counteract age-related changes or pathologies by reorganizing its structure, connections, and functions via complex molecular pathways and mechanisms that are becoming increasingly better understood. Part of neuroplasticity is adult neurogenesis in specific areas of the brain, in particular the hippocampal formation important for memory function, the decline of which is common even in “healthy” aging. To obtain further insights into the mechanisms of brain plasticity and adult neurogenesis, as the basis for prevention and potential therapeutic options, is a major challenge of modern neurosciences.*

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increase in our knowledge of its basic mechanisms. Functional analyses have identified signaling pathways acting as master regulators of aging and lifespan that are conserved in many animals, suggesting that the rate of aging is not inevitably fixed, but is plastic and open to modifications. Based on experimental evidence, the evolution of aging is probably the result of determinants of neuronal vulnerability, which include altered protein interaction networks, mitochondria, reactive oxidative species and intracellular calcium homeostasis, autophagy, signal transduction pathways, stem cell proliferation, and stress resistance mechanisms.<sup>1,2</sup> Perturbations in the functional state of these processes may lead to a state of decreased homeostatic reserve, where the aged neurons could still maintain adequate function during normal activity, although they become vulnerable. Neurons have significant homeostatic control of essential physiological functions like synaptic excitability, gene expression, and metabolic regulation. Any deviation in these physiological events can have severe consequences, as observed in aging.<sup>3</sup> A recent study in a large cohort of >10 000 persons showed that a measurable decline in generalized cortical function is already present by 45 to 49 years of age, with evidence of faster decline in older people.<sup>4</sup> Dementia due to Alzheimer's disease (AD) is preceded by about 5 to 6 years of accelerated decline of multiple cognitive functions; by contrast, little decline is evident in persons who do not develop AD. Compromised brain energy metabolism/oxygen delivery to neurons and blood flow differences in the regions most vulnerable to neurodegeneration are possible mechanisms of progression from healthy to "unhealthy" brain aging.<sup>5</sup> The human brain is uniquely powerful with respect to cognitive abilities, yet many neuronal networks, in particular the hippocampal and neocortical circuits that mediate such complex functions, are highly vulnerable to aging. Loss of neurons, now recognized to be more modest than previously suggested, mainly involves these specific neuroanatomical areas. Cognition and its decline associated with brain aging also seems to be variable and possibly open to modifications.<sup>1</sup> Studies in humans and animal models suggest that age-related cognitive decline is more likely to be associated with alterations in synaptic connectivity than with neuronal loss and white matter changes.<sup>6,7</sup> According to recent studies, alterations of intracellular  $\gamma$ -secretase mediated signaling pathways may be involved in synaptic pathogenesis of AD,<sup>8</sup> and apolipoprotein E is suggested to enhance the toxic

effects of oligomeric amyloid beta ( $A\beta$ ), causing synapse loss, a major correlate of cognitive decline in AD.<sup>9</sup> Although dementia-associated hallmarks of AD pathology (neuritic plaques and neurofibrillary tangles) become less prominent with increasing age, synaptic marker abnormalities in dementia remain constant and may represent an independent substrate of dementia spanning all ages.<sup>10</sup> These and other changes induce functional network disruptions in degenerative dementia,<sup>11,12</sup> suggesting that disease progress is transmitted by neural pathways.<sup>13</sup>

Age-related brain changes are widely documented. Postmortem and in vivo magnetic resonance imaging (MRI) studies of healthy brains have reported different location, extent, and severity of these changes with aging, some brain regions with greater activation being linked to better cognitive performance. Besides hemispheric asymmetry reduction they indicated increased activity in (pre)frontal regions, suggesting posterior-anterior shift models of functional brain aging.<sup>14</sup> There is a strong relationship between cognitive ability and cortical fine structure in the prefrontal cortex.<sup>15</sup> Postmortem studies of human brains revealed more prominent age-related changes in the anterior and posterior white matter, but not in gray matter volumes, histology showing less severe changes than the imaging methods.<sup>16</sup> While in previous studies postmortem MRI of white matter lesions (WMLs) was less sensitive than pathology, more recent ones showed that postmortem MRI is a valid tool for the assessment of subcortical pathologies.<sup>17</sup> MRI investigations showed widespread age-related changes in prefrontal cortex and white matter, somatosensory cortex, and, to a lesser degree, in motor cortex, the prefrontal white matter being most susceptible to the influence of age.<sup>18</sup> In cognitively normal elderly subjects, WMLs were inversely correlated with gray matter volume, with greatest volume loss in the frontal cortex. Both advancing age and hypertension predict higher WML load, which is itself associated with gray matter atrophy.<sup>19</sup> Low white matter grade and ventricular grade on MRI are powerful determinants of long-term survival among older individuals.<sup>20</sup> Recent functional neuroimaging studies indicated reduced cortical activation in the default-mode network for mild cognitive impairment patients, compared with age-matched healthy elderly persons, mainly in the retrosplenial region/posterior cingulate cortex, left hippocampus, and bilateral inferior and middle frontal areas, while increased activation for patients was

observed in the medial prefrontal and bilateral middle temporal/angular cortex, probably as a compensatory mechanism.<sup>21</sup> Resting state networks have been found to be hierarchically organized.<sup>22</sup>

Age-related atrophy is observed in the hippocampal region.<sup>23</sup> This region is of particular interest given its contribution to memory function, working memory decline being a common complaint in healthy aging<sup>24</sup> and one of the earliest signs of AD. Impaired hippocampal synaptic function is an early detectable pathologic alteration, well before amyloid plaque accumulation and cell death.<sup>25</sup> Positive relationships emerged consistently between the hippocampal formation, global cognition, and memory, and between frontal measures and executive function.<sup>26</sup> The hippocampal formation and the Papez circuit are targeted differentially by diseases of late life.<sup>27</sup> Volumetric MRI of temporal and parietal brain structures distinguishes AD patients from healthy subjects, volumetry of the left and right hippocampus providing the highest diagnostic accuracy in separating these groups.<sup>28</sup> Recent advances in imaging techniques (diffusion tensor imaging [DTI] and magnetization transfer imaging [MTI]) indicate that age-related small-vessel disease is a diffuse process affecting the whole brain and that WMLs are probably only the tip of the iceberg,<sup>19,29-31</sup> while decreased gray matter diffusivity might be a potential new biomarker for early AD.<sup>32</sup> A $\beta$ -associated cortical thinning has been observed in clinically normal elderly subjects.<sup>33</sup> Age-related neuronal dysfunction involves a host of subtle changes such as reduction in the complexity of dendritic arborization and length, decrease in spine numbers and related synaptic densities, changes involving receptors, neurotransmitters, cytology, electric transmission, vascular or Alzheimer-related changes, and myelin dystrophy. Together, these multiple alterations in the brain may lead to age-related cognitive dysfunction.<sup>1,2</sup> However, every lesion in the nervous system triggers an endogenous neuroprotective reaction, combining neuroplasticity and neurogenesis, which are initiated and regulated by neurotrophic factors in a multimodal way.<sup>34</sup> Extrusion of misfolded and aggregated (toxic) proteins may be a protective strategy of aging neurons.<sup>35</sup>

### Neuropathology findings in cognitively normal aged subjects

It is increasingly recognized that the correlation between neuropathological lesions and cognition is modest and

accounts for about a quarter of the variance in cognition of older adults. Concerning factors that modify or mediate the association between neuropathology and cognition, it was hypothesized that the concept of resilient aging can be useful to understand mechanisms that underlie healthy aging amidst disease-related pathology.<sup>34</sup> Some individuals maintain normal cognitive function despite significant brain pathology, while others suffer varying degrees of cognitive and neurological deterioration. Many aged people do not exhibit cognitive impairment or other symptoms of disease and live “normal” lives, but nonetheless display pathological changes that are characteristic of AD, Parkinson’s disease (PD), cerebrovascular disease (CVD), or other disorders.<sup>36-38</sup> Although the best morphologic correlates of cognitive impairment/dementia are; (i) the number of neocortical neurofibrillary tangles (NFTs)<sup>39-43</sup>; and (ii) loss of synapses,<sup>44-47</sup> between 8% and 45% of nondemented, often cognitively stable older adults were found to have AD-related pathologies.<sup>38,43,48-58</sup> Many of them showed only minimal to mild neuritic changes corresponding to Braak tau stages 0-IV,<sup>59</sup> while 31% to 88% showed National Institute for Aging and Reagan Institute (NIA-RI) criteria of no likelihood for AD criteria.<sup>51,53</sup> The frequency of intermediate likelihood of AD criteria ranged from 11.9% to 35.8%,<sup>37,53,56</sup> and only 1.5 to 3% were scored as having a high likelihood of AD.<sup>53</sup> The presence of AD lesions in nondemented aged individuals may represent AD at a stage prior to clinical expression (presymptomatic or unrecognized early forms).<sup>54,55,58,60,61</sup> This is supported by observations that the mechanisms responsible for these changes in nondemented elderly appear similar if not identical to those found in AD,<sup>60,62</sup> and their distribution corresponds to the hierarchical topographical procession associated with symptomatic AD.<sup>48,49,61</sup> The concept of “preclinical” AD<sup>58,60,61</sup> pathology has been further solidified in biomarker studies using CSF A $\beta$ -42<sup>63</sup> and more directly in vivo positron emission tomography (PET) amyloid scanning, demonstrating that 20% to 30% of healthy elderly subjects have elevated PIB signals indicative of extensive amyloid deposition.<sup>64</sup> These data suggest a high frequency of preclinical AD pathology in normal elderly similar to that seen in clinico-pathologic cohorts.<sup>65,66</sup> They further suggest that preclinical changes are not static, but progress over time.<sup>67,68</sup>

Among 555 nondemented persons with false-positive pathological NIA-RI high likelihood for AD, only 1.6%

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corresponded to Braak stage V, 0.5% to stage VI, and 2.6% to stage V-VI,<sup>41</sup> while in other studies between 35% and 88% were NIA-RI negative<sup>43,51</sup>; 18% to 25% met the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria for AD.<sup>51,52,56</sup> Review of the data from National Disease Coordinating Center (NDCC) database and the Nun Study emphasized that there may be no documented example of truly end-stage neurofibrillary pathology with intact cognition.<sup>69</sup> Although in the Adult Changes in Thought (ACT) and Nun Studies, nondemented seniors with severe AD pathology (mean age of 89.15±6.9 to 90.80±5.2 years) amounted to 8% and 12%, respectively, most of them showed neuritic Braak stage V, and frontal NFT counts were slightly lower than in a comparable dementia group.<sup>49</sup> Moreover, review of clinical data from those studies revealed that most of the seniors classified as nondemented were indeed significantly memory-impaired.<sup>49</sup> A recent study of nondemented elderly demonstrated 62% with low and 28% with high NFT levels<sup>70</sup>; 87 nondemented elderly (mean age 87±5.9 years; mean MMSE 28.3) showed mean Braak stage 3.0 ± 0.9, a total NFT score of 4.5±2.5, and mean neuritic density of 1.3±1.1, whereas AD cases showed much higher cortical neuritic and striatal amyloid plaque scores.<sup>71</sup> The 90+ study revealed significantly less severe A $\beta$ ,  $\alpha$ -synuclein, and TPD-43 pathologies, and hippocampal sclerosis in nondemented subjects, while A $\beta$  distribution showed no essential differences; nondemented individuals had limited hippocampal tau and neocortical A $\beta$  pathology.<sup>72</sup>

A recent clinicopathologic study of 296 persons without cognitive impairment of the Religious Order Study (ROS) and the Memory and Aging Project (MAP) showed a common presence of AD pathology and macroscopic infarctions. Amyloid load was related to global cognition ( $P < 0.05$ ), with only a trend for NFTs ( $P = 0.08$ ), while NFTs and macroscopic infarctions were related to episodic memory ( $P = 0.03$  and 0.02, respectively); AD pathology and A $\beta$  load to working memory ( $P = 0.02$  and 0.03, respectively).<sup>73</sup>

Comparing the biochemistry of AD and nondemented nonagenarians revealed the lack of clear amyloid-related pathological/ biochemical determination between both groups.<sup>74</sup> A personal retrospective study of 100 nondemented elderly (mean age 81.23±5.47 years, mean Mini Mental State Examination (MMSE) score 29) revealed negative Khachaturian criteria and CERAD stage 0 in 83% and 86%, respectively, only 13% with CERAD

stage A and 1% stage B. Braak neuritic stages ranged from 0 to IV, with an average score of 2.3±0.8. 12% were scored NIA-RI low, and only 2% intermediate likelihood for AD.<sup>37</sup> Thus, mounting evidence from clinicopathologic studies support the view that AD is a continuous spectrum between asymptomatic lesions in cognitively normal elderly and dementia, with mild cognitive impairment (MCI) as a transition phase between them.<sup>75</sup> Although correlations between cognitive deficits and the severity and extension of senile plaques (SP) and NFTs (see ref 42) have been found, at least in those brains without other pathologies, the distinction between "physiological" (in nondemented subjects) and "pathological" aging (PA) is difficult. A postmortem classification for individuals reported to be cognitively normal before death, their brains showing plaque pathology similar in extent to AD with only minimal cortical tau pathology, may also be difficult.<sup>76</sup> Recent biochemical studies found extensive overlap with only subtle quantitative differences between A $\beta$  levels, peptide profiles, solubility, and oligomeric assemblies in PA and AD brains, suggesting that PA represents an initial prodromal stage of AD and that these individuals would eventually develop clinical symptoms, if they lived long enough, or an inherent individual resistance to the toxic effects of A $\beta$ .<sup>77</sup> Recent studies suggest that two independent processes (synapse-mediated and ApoE-mediated) may contribute to region-specific A $\beta$  accumulation in nondemented individuals, and may influence the mechanisms of the regional vulnerability to A $\beta$  accumulation, which is prevented by ApoE.<sup>78</sup> A coding mutation (A673T) in the APP gene that reduces the  $\beta$ -cleavage of APP may protect against AD and also against cognitive decline in the elderly without AD.<sup>79</sup>

Older persons with overall normal cognitive function and preclinical AD changes by brain autopsy usually have lower scores on cognitive function tests, particularly episodic and working memory.<sup>24,54</sup> A $\beta$  biomarker studies also confirmed the relations between preclinical AD and cognition,<sup>80,81</sup> and a clinicopathologic study indicated that elders with AD changes but without overt dementia are more likely to have memory complaints.<sup>82</sup>

The definition of nondemented subjects with AD pathology raises important questions regarding the cognitive profile of these people who are relatively protected from the devastating effects of AD-related lesions. A default hypothesis for AD is that it is a part of a "normal aging process," such that plaques and tangles are secondary to



aging or that the primary aging effect is on synapses and neurons independent of these morphological AD markers. AD is indeed a disease that accompanies human aging, but it is not an inevitable consequence of it.<sup>83,84</sup> However, the suggestion that plaques and tangles may “cause” this disorder is oversimplified or even wrong, since accumulating evidence suggests that AD pathology represents effect rather than cause or at least a host response to injury, equaling adaptive or neuroprotective reactions.<sup>85</sup>

Many studies emphasize multiple additional pathologies in nondemented elders, in particular cerebrovascular lesions (CVLs), eg, small or large cerebral infarctions, lacunes, WMLs, in 22 up to almost 100%.<sup>36,49,51-53</sup> Evaluation of 336 cognitively normal (CN) seniors from four studies revealed moderately to frequent neuritic plaque density in 47%; of these 6% also had Braak stages V or VI; medullary, nigral, and cortical Lewy bodies in 15%, 8%, and 4%, respectively; cerebral microinfarcts in 33% and high-level cerebral microinfarcts in 10%. The burden of brain lesions and comorbidities varied widely within each study but was similar across studies.<sup>86</sup> Among 418 nondemented participants of the Religious Order study (mean age 88.5±5.3 years), 35% showed macroscopical infarcts, 8% microinfarcts, 14.8% arteriosclerosis, 5.7% both, only 37.5% being free of CVLs.<sup>87</sup> Up to 75% of CN seniors had various degrees of cerebral amyloid angiopathy (CAA),<sup>53</sup> occasional hippocampal sclerosis,<sup>53,56</sup> Lewy body pathologies in up to 18%,<sup>36,37,51-53,56,57</sup> argyrophilic grains in up to 23%,<sup>53</sup> and mixed pathologies in 7% to 14.8%.<sup>36,57</sup> In a small autopsy series of CN elders, only 16% showed no additional pathology.<sup>55</sup> Among 100 nondemented seniors, mild, moderate and severe intracranial atherosclerosis was present in 31%, 17%, and 6%, respectively, lacunar state in basal ganglia and/or white matter in 73%, hippocampal sclerosis in 3%, whereas only 9% were free of CVLs. Lewy bodies were observed in 5%, tau pathology in brain stem in 60%, and mixed cerebral pathologies (CVLs and moderate neuritic Braak stages) in 6%.<sup>37</sup> A recent British nondemented sample (n = 53; mean age 81.5±7.4 years; MMSE score 27-30) showed maximum score neuritic plaques in 32% to 49%, NFTs in hippocampus and neocortex in 81% and 30.8%, respectively, white matter changes 55% to 83.7%, small vascular disease 45%, infarcts 13.7%, lacunes 6%, and hemorrhages 10%.<sup>88</sup> Thus, clinically silent pathology is widespread in normal aging, and the term “healthy aging” is inappropriate at

the cellular level, and is manifested by regional heterogeneity in the scenario of general volume loss in the human brain.

### Brain aging and neuroplasticity

Aging is associated with progressive loss in function across multiple systems, including sensation, cognition, memory, motor control, and affect. The traditional view has been that functional decline in aging is unavoidable because it is a direct consequence of brain machinery wearing down over time. In recent years, however, an alternative perspective has emerged that, based on extensive experimental work, argues that as people age, brain plasticity processes with negative consequences begin to dominate brain functioning. Four core factors—reduced schedules of brain activity, noisy processing, weakened modulatory control, and negative learning—interact to create a self-reinforcing downward spiral of degraded brain function. These interrelated functions promote plastic changes in the brain that result in substantial improvement in function and/or recovery from functional losses.<sup>89</sup> Neuroplasticity can be defined as the ability of the nervous system to respond to intrinsic and extrinsic stimuli by reorganizing its structure, function, and connections. It is both a substrate of learning and memory and a mediator of responses to neuronal attrition and injury (compensatory plasticity). This continuous process in reaction to neuronal activity and injury involves modulation of structural and functional processes of dendrites, axons, and synapses. Plasticity is an intrinsic property of the brain across the lifespan. However, mechanisms of neuroplasticity may vary with age, and occur in many variations and in many contexts, while common areas of plasticity that emerge across diverse CNS conditions include experience dependence and circuit training.<sup>70</sup>

### The concept of “cognitive reserve”

Contrary to assumptions that changes in brain networks are possible only during crucial periods of development, recent research has supported the idea of a permanent plastic brain. Novel experience, altered afferent input due to environmental changes, and learning new skills are now recognized as modulators of brain function and underlying neuroanatomic circuitry.

Results in animal experiments and discovery of increases in gray and white matter in the adult human brain as a

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result of learning and exercise have reinforced the old concept of “cognitive reserve,” that is, the ability to reinforce brain volume in certain areas and thus provide a greater threshold for age-dependent deficits, or the capacity of the brain to manage pathology or age-related changes, thereby minimizing clinical manifestation.<sup>90-94</sup> The concept of “cognitive reserve” and a broader theory of “brain reserve” was originally proposed to help explain epidemiological data indicating that individuals who engaged higher levels of mental and physical activity via education, occupation, and recreation were associated with slower cognitive decline in healthy aging and are at lower risk of developing AD and other forms of dementia.<sup>95-98</sup> The aging process that results in loss of synapses and possible neurons may be far more detrimental for those with little brain reserve as compared with those with a high one.<sup>99</sup>

The construct of “cognitive reserve” is a set of variables including intelligence, education, and mental stimulation which putatively allows the brain to adapt to underlying pathologies by maintaining cognitive function despite underlying neuronal changes. It also indicates a resilience to neuropathological damage, and could be defined as the ability to optimize or maximize performance through effective recruitment of brain networks and/or alternative cognitive strategies. Childhood cognition, educational attainment, and adult occupation all contribute to cognitive reserve independently. Enriched environment and physical activity influence the rate of neurogenesis in adult animal model hippocampi.<sup>100</sup> In people with high reserve, deterioration occurs rapidly once the threshold is reached.<sup>101</sup>

Structural and functional brain imaging studies have revealed selective changes in aging brain that reflect neural decline as well as compensatory neural recruitment, representing possible neural substrates of cognitive reserve, but its neural basis is still a topic of ongoing research.<sup>102</sup> While aging is associated with reductions in cortical thickness, white matter integrity, transmitter activity, and functional engagement in the hippocampus and occipital areas, there are compensatory increases in frontal functional engagement that correlate with better behavioral performance in the elderly.<sup>103,104</sup> Those cortical regions most consistently shrinking in aging—prefrontal and parietal cortices—are the same regions showing increased regional activation in aging, suggesting that losses in regional brain integrity drive functional reorganization through changes in processing strategy.<sup>105</sup> Cognitive reserve allows individuals greater neural efficacy, greater neural

capacities, and the ability for compensation via the recruitment of additional brain regions.<sup>106</sup> Frontal and supramarginal cortical activity has been suggested to compensate for an age-related decrease in inferior-frontal junction recruitment of verbal fluency processing. Larger brain and hippocampal values, and neuronal hypertrophy<sup>107</sup> were associated with preserved cognitive function despite a high burden of AD pathology (asymptomatic AD).<sup>108</sup> The structural and functional imaging correlates of cognitive and brain reserve hypothesis have recently been reviewed.<sup>109</sup> A complementary hypothesis of “metabolic” reserve is characterized by neuronal circuits that respond adaptively to perturbations in cellular energy metabolism and thereby protect against declining function, mediated by neurotrophic factor signaling, and glucose metabolism.<sup>93</sup> Increased basal forebrain metabolism in MCI is an evidence for brain reserve in incipient dementia.<sup>110</sup> Neuroprotective effects of noradrenaline both in vivo and in vitro suggest noradrenaline's key role in mediating cognitive reserve—by disease compensation, modification, or a combination of both, a viable hypothesis.<sup>111</sup>

## Structural basis of neuroplasticity

The structural elements that embody plasticity include synaptic efficacy and remodeling, synaptogenesis, neurite extension including axonal sprouting and dendritic remodeling, neurogenesis, and recruitment from neural progenitor cells. Phenomenological processes that manifest plasticity are: synapse, neurite, neuronal cell bodies, anterograde and retrograde transport, cell interactions (neuron-glia), neuronal networks, and related activities.<sup>35</sup> They include intraneuronal, interneuronal, and intercellular signaling through glia, and involve extracellular matrix molecules, immunoglobulins, myelin-associated inhibitors, tyrosine kinase receptors, neurotrophic and growth factors, inflammatory cytokines, and neurotransmitters.<sup>110</sup> These processes are regulated by cell-autonomous and intercellular programs that mediate responses of neuronal cells to environmental input. By generating energy and regulating subcellular  $\text{Ca}^{2+}$  and redox homeostasis, mitochondria may play important roles in controlling fundamental plasticity processes,<sup>112</sup> including neuronal and synaptic differentiation, neurite outgrowth, neurotransmitter release, and dendritic remodeling. Receptor protein tyrosine phosphorylase  $\zeta$  (RPTP $\zeta$ ) regulates synapse structure, function, and plasticity.<sup>113</sup> Emerging data suggest that mitochondria emit

molecular signals, eg, reactive oxygen species, proteins, and lipid mediators that can act locally or travel to distant targets. Disorders in mitochondrial functions and signalling may play roles in impaired neuroplasticity and neurodegeneration.<sup>114,115</sup>

Both aging and A $\beta$  that as a normal product of neuronal metabolism has an essential regulatory function at the synapse, independently decrease neuronal plasticity.<sup>116</sup> The major growth of A $\beta$  burden occurs during a preclinical stage of AD, prior to the onset of AD-related symptoms.<sup>117</sup> It is associated with lower cognitive performance both in AD patients and normal elderly, but the association is modified by cognitive reserve, suggesting that this may be protective against amyloid-related cognitive impairment.<sup>80</sup> On the other hand, endogenous A $\beta$  is necessary for hippocampal plasticity and memory within the normal CNS, due to regulation of transmitter release, activation of nicotinic acetylcholine receptors, and A $\beta$ -42 production. The basis of age-related toxicity partly resides in mitochondrial dysfunction and an oxidative shift in mitochondrial and cytoplasmic redox potential. In turn, signaling through phosphorylated extracellular signal-regulated protein kinases is affected along with an age-independent increase in phosphorylated cyclic adenosine monophosphate (cAMP) response element-binding protein.<sup>118</sup> Furthermore, the production of inflammatory mediators (inflammatory cytokines, interleukins, neurotrophins), activation of glia and other immune cells disrupting the delicate balance needed for the physiological action of immune processes produces direct effects on neural plasticity and neurogenesis, facilitating many forms of neuropathology associated with normal aging as well as neurodegenerative diseases.<sup>119</sup> Recent evidence shows that key regulations of communication between neuron and microglia disruption in the aged brain may be one of the factors that precedes and initiates the increase in chronic inflammatory states underlying age-related impairments of cognition and hippocampal neurogenesis.<sup>120</sup> Effective treatments that dampen inflammatory activity are expected to have beneficial effects on cognitive performance and neural plasticity.<sup>121</sup>

Functional recovery of synaptic circuitry requires that reactive synaptogenesis not exacerbate dysfunction, since aberrant misconnection by innervating the wrong target may cause misguided synaptogenesis, and inhibition of sprouting may be protective by sequestering dysfunctional neurons. Hippocampal synaptic plasticity in AD has been observed in transgenic models.<sup>25</sup> Aberrant,

excessive, insufficient, or mistimed plasticity may represent the pathogenic cause of neurodevelopmental and neurodegenerative disorders.<sup>122</sup> Neuroplasticity is impaired in patients with AD and PD as a result of diminished growth factor expression<sup>123</sup> and failure of delayed nonsynaptic neural plasticity mechanisms.<sup>124</sup>

Understanding normative changes in brain structure that occur as a result of environmental changes is pivotal to understanding the ability of the brain to adapt.<sup>125</sup> Neuroplastic changes in cerebral gray matter may be induced by training.<sup>126</sup> Studies in animals and humans revealed dramatic effects of environmental enrichment, increased physical exercise documenting positive effects of mental and physical exercise, mediating brain and cognitive reserve,<sup>127-129</sup> thus showing no compromise in daily life despite higher A $\beta$  plaque load.<sup>130</sup> Other studies in animal models showed preventive or therapeutic action of environmental enrichment counteracting A $\beta$  pathology by different molecular mechanisms<sup>131</sup> and by mitigating Alzheimer-like pathology, and increasing synaptic immunoreactivity<sup>132,133</sup> due to reduction of cerebral oxidative stress.<sup>134</sup>

Examination of synaptic physiology revealed that environmental experience significantly enhanced axonal transport in hippocampal and cortical neurons after enrichment, enhanced hippocampus long-term potentiation, without notable alterations in synaptic transmission. These data suggest that environmental modulation can rescue the impaired phenotype of the AD brain and that induction of brain plasticity may represent therapeutic and preventive avenues in AD.<sup>135,136</sup>

Recent studies demonstrated that the magnitude of the contribution of education is greater than the negative impact of either neuropathological burden of AD or CVLs with standardized regression weights of  $-0.14$  for hyperintensities and  $-0.20$  for hippocampal atrophy.<sup>137</sup> However, a large clinicopathologic study at 27 AD centers found no evidence of larger education-related differences in cognitive function when AD pathology was more advanced, suggesting that the advances of cognitive reserve may ultimately be overwhelmed by AD pathology.<sup>138</sup>

### Neurogenesis in the aging brain

Neurogenesis or the birth of new neural cells was thought to occur only in the developing nervous system, but recent studies have demonstrated that it does indeed

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continue into and throughout adult life. However, the age of olfactory bulb neurones, that are assumed to be derived from neuroblasts via the rostral migratory stream (RMS), has been assessed recently by measuring the levels of nuclear bomb test-derived <sup>14</sup>C in genomic DNA. Data from this study suggest that there is very limited, if any, postnatal neurogenesis in the human olfactory bulb.<sup>139</sup> Certain areas of the brain may retain pluripotent precursors with the capacity to self-renew and differentiate into new neural lineages in adult mammals, nonhuman primates,<sup>140</sup> and humans.<sup>141</sup> Physical activity causes a robust increase in neurogenesis in the dentate gyrus of the hippocampus, a process that would implement a form of network plasticity analogous to that at the synaptic level, but occurring at the cellular network level.<sup>142,143</sup>

Neurogenesis represents a key factor of adult brain to response to environmental stimuli,<sup>144</sup> and abnormalities in neurogenesis have been detected in neurodegenerative disorders such as AD.<sup>145,146</sup> It occurs in the subventricular zone and the subgranular layer of the hippocampus, and follows a multistep process probably in five stages, including proliferation, differentiation, migrating, targeting, and integration phases, respectively.<sup>147,148</sup> Stimuli that entail an increase in neuronal activity have been shown to stimulate neurogenesis and enhance survival of new neurons in the adult mammalian hippocampus.<sup>149</sup> The incorporation of functional adult-generated neurons into existing neural networks provides higher capacity for plasticity, while they favor the encoding and storage of certain types of memories.<sup>150-152</sup> Although neurogenesis continues throughout life, its rate declines with increasing age,<sup>153,154</sup> and the proportion of neuronal stem cells that survive to become mature neuronal cells is reduced.<sup>155</sup> This may be due to intrinsic decline in neuronal stem cell responsiveness to stimulating environmental cues, to a decrease in or disappearance of these environmental cues, or to accumulation of inhibitory factors.<sup>156</sup> Intrinsic properties of neural progenitor cells such as gene transcription and telomere activity change with age, which may contribute to decline in neurogenesis. While most studies indicated a correlation between decreased hippocampal neurogenesis and impaired performance in hippocampus-dependent cognitive tasks in age mice, few have demonstrated that young and aged mice are equivalent in their cognitive ability. The lack of neuronal ability to divide may be overcome by replacing damaged neurons or by restoring their function. Thus, Kittappa et al<sup>157</sup> revisited the

molecular mechanisms responsible for neuronal renewal from stem cells, which are present in specific niches within the adult brain. The authors provided the novel notion that even non-terminally differentiated neural stem cells play roles in the regeneration of neurons and their synaptic function by mechanisms beyond mere cell replacement. These cells signal specific survival pathways that are worth investigating in search for novel therapeutic strategies against neurodegeneration. According to this notion, noninvasive tools to follow up synaptic function in the living brain are therefore essential for our better understanding of neuronal regeneration.

Although neuronal turnover is reduced in every neurogenic region of the aged brain, neuronal precursor cells clearly survive, remain responsive to growth factors and other physiological stimuli, and can increase their activity in response to damage.<sup>157</sup> Exploration of the regulation of neuronal progenitor cells in the aging brain is critical not only for understanding age-related cognitive deficits, but also for progress toward the goal of using the brain's regenerative potential to restore functional loss. Dysregulated or impaired neurogenesis may compromise plasticity and neuronal function in the hippocampus and other neuronal systems, and exacerbate neuronal vulnerability. Interestingly, increasing evidence suggests that molecular players in AD, including presenilin1, amyloid precursor protein, and its metabolites, play a role in adult neurogenesis, while alterations in tau phosphorylation may interfere with the potential role of tau proteins in neuronal maturation and differentiation. This indicates a crosstalk between signaling molecules involved in both neurogenesis and neurodegeneration, and the ways by which AD-linked dysfunction of these signaling molecules affect neurogenesis in the adult brain.<sup>158,159</sup> In AD, both increased and decreased neurogenesis has been reported and cholinergic activity may be involved in neurogenesis. However, most of these new neurons die, and fibrillar A $\beta$ -42 seems to be involved in generating an inappropriate environment for those neurons to mature. These findings open up prospects for new strategies that can increase neurogenesis in pathologic processes in the aging brain.<sup>160</sup> Recent studies confirming the assumption that cholinergic pathology has a detrimental influence on neurogenesis<sup>161</sup> suggest an attenuation of stem cells together with compensatory increased proliferation that, however, does not result in an increased number of migratory neuroblasts and differentiated neurons in AD.<sup>162</sup>



There are indications that neurogenesis is impaired in PD, which might be due to a lack of dopamine in the subventricular zone, but recent studies did not find evidence that dopamine has a direct effect on human stem cell proliferation *in vitro*. Thus, it was concluded that the number of adult neural stem cells is probably not diminished, and the proliferative capacity of the subventricular zone is maintained in the parkinsonian brain.<sup>163</sup> Neural stem cells have been identified also in areas where neurogenesis does not occur under physiological conditions, such as the midbrain and striatum, suggesting that they may have the potential to be used as a non-

invasive cell replacement therapy in PD. Recent studies have shown that the deleterious effects of  $\alpha$ -synuclein on newly generated neurons, in particular on their dendritic outgrowth and spine development, thus having negative impact on adult neurogenesis and neuronal maturation.<sup>164</sup> Further elucidation of the mechanisms regulating the synaptic integration of adult-born neurons is not only crucial for our understanding of the age- and disease-related neuroplasticity/brain plasticity, but also provides a framework for the manipulation and monitoring of endogenous adult neurogenesis as well as grafted cells potential therapeutic applications.<sup>165-167</sup>

- Cerebral aging is a complex and heterogenous process of high-degree intraindividual variability involving neuronal and synaptic functions, signal transduction, mitochondrial dysfunctions, oxidative stress, energy failure, neurotransmitter changes, and many other factors inducing functional network disruptions.
- Neuroimaging studies of the aging brain show hemispherical and hippocampal atrophy, white matter changes, and subcortical small-vessel disease.
- Cognitive decline in aged subjects is more likely associated with synapse dysfunction/loss than with neuronal loss and white matter changes.
- Nondemented, cognitively unimpaired elderly subjects frequently show only mild to moderate Alzheimer's disease (AD)-related lesions and frequent mixed pathologies/comorbidities.
- The best morphological correlates of cognitive impairment/dementia are the severity of neocortical tau pathology (neurofibrillary tangles, neuritic plaques) and loss of synapses. In the oldest-old, however, plaques and tangles are less important, dementia being only moderately related to AD pathology, while non-Alzheimer and other (cerebrovascular) pathologies are more important. Thus, the distinction between "normal" and "pathological" aging (asymptomatic AD) may be difficult.
- Neuroplasticity, defined as the ability of the neuronal system to respond to intrinsic and external stimuli by reorganizing its structure, connections, and functions, is of great importance for the aging brain.
- Cognitive reserve is a set of variables including intelligence, education, and mental stimulation to adapt the brain to underlying pathologies by maintaining cognitive functions and to minimize clinical manifestations.
- Recent neuroimaging data have provided changes in aging brain that reflect compensatory mechanisms or neuronal restitution. Larger brain and hippocampal volumes and neuronal hypertrophy were associated with preserved cognition despite a high burden of AD pathology.
- The structural basis of neuroplasticity includes synaptic and dendritic remodeling, axonal sprouting and neurogenesis induced by biochemical changes (endogenous  $\beta$ -amyloid, receptor protein kinases, growth factor changes, etc).
- Environmental modulations and both physical and mental activities can induce brain plasticity.
- Neurogenesis originating from pluripotent precursor cells does occur in the adult brain and is a key factor to response to environmental mental stimuli.
- Neurogenesis continues throughout life but declines with increasing age due to reduction of the proportion of neuronal stem cells that may become mature neurons.
- Dysregulated or impaired neurogenesis may compromise neuronal plasticity and functions and exacerbate neuronal vulnerability.
- The cholinergic system, severely involved in AD, that has a detrimental influence on neurogenesis, together with fibrillary  $\beta$ -amyloid, causes a decrease of neuronal differentiation and early death of newly formed neurons.
- Resilience to AD is related to genetic factors (APOE  $\epsilon$ 2), increased premorbid brain volume, hypertrophy of neurons, and compensatory metabolic changes.
- Understanding how brain reserve may be influenced to minimize the impact of pathologies associated with dementia has enormous public health implications, and further research is warranted to understand how lifestyle, physical, and mental activities could mitigate the negative impact of pathology on the aging brain as a basis for potential prophylactic and therapeutic options.

**Table I.** Summary of key points on cerebral aging.

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## Conclusions and outlook

A major problem in studying aging is how to separate the effects of aging from disease. Cerebral aging is a complex and heterogeneous process that is associated with a high variety of molecular interactions, morphological, and functional changes, summarized in *Table I*. The interrelations between them need further elucidation. Brain aging results in loss of synapses and possible neurons, which is associated with structural changes in cerebral areas and neural networks that are essential for cognitive and memory function. Many cognitively unimpaired elderly subjects are involved by Alzheimer-related or other pathologies of various severity and extent. Knowing the substrate of the resilience to cognitive decline in the presence of abundant AD and/or mixed pathology might be crucial not only for the understanding of the pathophysiology of nondemented aged people, but also to discover new prophylactic and/or therapeutic targets for aging processes. As expected from the significant clinicopathologic correlations of synaptic and neuronal loss in AD, “high-pathology nondemented” controls have preserved densities of synaptophysin-labeled presynaptic terminals and dendritic spines as compared with AD dementia patients with a similar burden of plaques and tangles.<sup>99,168</sup> Greater amounts of specific presynaptic proteins and distinct protein-protein interactions may be components of cognitive reserve that reduce the risk of dementia with aging.<sup>168</sup> They may have no significant neuronal loss, not even in vulnerable regions, such as the entorhinal cortex and hippocampus,<sup>54,169</sup> and have lower levels of neuroinflammatory markers than pathology-matched AD patients.<sup>170</sup> This resistance to AD pathology has also been related to a nucleolar, nuclear, and cell body hypertrophy of the hippocampal and cortical neurons, suggestive of a compensatory metabolic activation to face the neurotoxic effects of AD lesions.<sup>108,171</sup> Resilience to AD is also attributed to genetic factors, particularly apolipoprotein E2 and combinations of other genetic polymorphisms.<sup>172</sup> Premorbid brain volume has been found to provide protection against clinical manifestation of dementia despite evidence of AD pathology, supporting the brain reserve hypothesis of resilience to AD.<sup>173</sup> Although multiple factors and possible interventions may influence cognitive reserve and susceptibility to dementia, much work is required on the mechanisms of action in order to determine which, if any, may improve the clinical and epi-

demiological picture.<sup>174</sup> On the other hand, the unique observation of a cognitively intact woman aged 115 years with only slight tau pathology corresponding to Braak stage II, almost no plaques or vascular changes, and normal neuron count in the locus ceruleus indicates that the limits of human cognitive function extend far beyond the range that is currently enjoyed by most individuals and that brain disease, even in supercentenarians, is not inevitable.<sup>175</sup> The association between “vulnerability” and “protective” factors varies with age, since the effects of these factors on the risk for AD may differ in younger (age <80) versus older (age >80) individuals. The understanding of the dynamic of these factors at different age periods will be essential for the implementation of primary prevention treatments for AD.<sup>176</sup>

The importance of understanding ageing and the complex interplay of multiple influences on successful cognitive ageing is clear.<sup>176,177</sup> Understanding how brain reserve might be influenced to minimize the impact of neuropathologies associated with dementia could have enormous public health implications. This is a crucial prerequisite to meaningful research in dementia and illustrates how life-long intellectual engagement can mitigate the negative impact of brain pathology even on healthy ageing.<sup>178</sup> The neuronal underpinning of the dynamic compensatory mechanism opens the possibility for strategic interventions based on environmental approaches.

Future work should measure the contribution of more diverse influences on cognitive reserve that might operate in early and midlife, such as socioeconomic conditions and social relationships, which might be modified through public education in order to have a positive impact on the looming public health disaster that is dementia. Recent studies in a nondemented population have shown that intellectual and physical activity lifestyle factors were not assessed with AD biomarkers, while intellectual lifestyle factors explained the variability in the cognitive performance, providing evidence that lifestyle activities may delay the onset of dementia, but do not significantly influence the expression of AD pathophysiology.<sup>179</sup>

The neuropathological distinction between nondemented, cognitively intact, and cognitively impaired/demented subjects, elucidation of the relationship of additional pathologies with minor—often clinically latent—AD lesions observed in many but not all elderly persons without cognitive impairment is important, allowing further

insights into the mechanisms of brain plasticity and the basic mechanisms of adult neurogenesis warrants further experimental and prospective, well documented clinico-pathological studies of elderly individuals. In this continuously growing field, new acquisitions, derived from basic research and clinical grounds, on cognitive reserve mechanisms, neuroplasticity, and the potential application of novel therapeutic targets in neurodegeneration and aging disorders are necessary.<sup>180</sup> As a basis for potential pro-

phylactic and therapeutic options for brain aging, they are major challenges for modern neurosciences. □

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### **Enfoques neuropatológicos del envejecimiento y la neuroplasticidad cerebral**

*El envejecimiento cerebral es un proceso complejo y heterogéneo que se relaciona con una gran variedad de cambios moleculares que involucran múltiples redes neuronales, a causa de alteraciones en las neuronas (sinapsis, axones, dendritas, etc.), que particularmente afecta regiones estratégicamente importantes como el hipocampo y las áreas prefrontales. Una proporción significativa de sujetos no dementes y cognitivamente no deteriorados muestran a lo menos lesiones leves a moderadas o rara vez graves que se relacionan con el Alzheimer; lesiones que representan probablemente la Enfermedad de Alzheimer preclínica asintomática y/o patologías mixtas. Si bien el sustrato de la resiliencia para la declinación cognitiva en diversas patologías ha sido poco claro, la investigación reciente ha reforzado el concepto de reserva cognitiva o cerebral, basado en la neuroplasticidad o la capacidad del cerebro de controlar o contrarrestar los cambios o patologías relacionadas con la edad al reorganizar su estructura, conexiones y funciones a través de complejas vías y mecanismos moleculares que están siendo cada vez mejor comprendidos. Parte de la neuroplasticidad es la neurogénesis adulta en áreas específicas del cerebro, en particular en la formación hipocámpica; esta área es importante para la función de memoria y se reduce con frecuencia incluso en el envejecimiento "saludable". La obtención de mayores conocimientos sobre los mecanismos de plasticidad cerebral y neurogénesis adulta, como base para la prevención y potenciales opciones terapéuticas, constituye un importante desafío para las modernas neurociencias.*

### **Approche neuropathologique de la neuroplasticité et du vieillissement cérébral**

*Le vieillissement cérébral est un processus complexe et hétérogène associé à de nombreuses modifications moléculaires impliquant de multiples réseaux neuronaux en raison d'altérations de neurones (synapses, axones, dendrites, etc.) touchant particulièrement des régions stratégiques comme l'hippocampe et le cortex préfrontal. Un pourcentage important de sujets âgés non déments et sans troubles cognitifs présentent des lésions de type Alzheimer de niveau au moins léger à modéré et plus rarement sévère, témoignant probablement d'une maladie d'Alzheimer préclinique asymptomatique et/ou de troubles mixtes. Le substrat de la résilience du déclin cognitif au cours de nombreuses pathologies n'est pas clair mais des recherches récentes ont renforcé le concept de réserve cérébrale ou cognitive sur la base de la neuroplasticité ou de la capacité du cerveau à maîtriser ou à s'opposer aux modifications ou aux pathologies liées à l'âge en réorganisant ses structures, ses connexions et ses fonctions grâce à des mécanismes et des voies moléculaires complexes de mieux en mieux compris. La neurogenèse adulte fait partie de la neuroplasticité dans des aires cérébrales spécifiques comme l'hippocampe, important pour la mémoire, qui décline de façon courante même chez le sujet « sain ». Mieux comprendre les mécanismes de la plasticité cérébrale et de la neurogenèse adulte, comme base de la prévention et des solutions éventuelles de traitement, est un défi majeur pour les sciences modernes.*

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# Translational research

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