Neural Plasticity and Cognitive Reserve

Abstract

Neural plasticity in the context of normal aging and dementia can be evaluated on a number of levels. Traditionally there has been much focus on cellular dysfunction, which is evidenced by the plaques and tangles that are the hallmarks of Alzheimer type dementia. Now, more than ever, there is an emerging spotlight on the preservation of functional levels despite failing cognition be it from normal aging, mild cognitive impairment (MCI) or diagnosed dementia. Neural plasticity can be viewed as the complex interaction between the neurons' electrical, biochemical and physical structure and the individual's behavioural, psychological and sociological activities[1]. This article will briefly review the neurobiology of cognition and the sequence of events that lead to its demise. The remainder of this review concentrates on tangible, evidence based strategies to uphold clinical cognition through the aging process.

Keywords: *neural plasticity, aging, dementia, cognition, neurons*

...there were neurons in her head, not far from her ears, that were being strangled to death, too quietly for her to hear them. Some would argue that things were going so insidiously wrong that the neurons themselves initiated events that would lead to their own destruction. Whether it was molecular murder or cellular suicide, they were unable to warn her of what was happening before they died.

-Still Alice
Lisa Genova

Cellular Neural Plasticity

Memory, even in its simplest depiction, is a complex process involving multiple structures in the brain as well as the use of key neurotransmitters. Using a time classification structure, memory can be divided into very short term, short term and long-term memory. It can further be subdivided into explicit (conscious recollection), episodic (temporal recollection), semantic (conceptualized paradigms), implicit (unconscious recollection), perceptual

About the authors

Zahra Bardai, BSc, MD, CCFP, MHSc, FCFP, *Community Family Physician, Lecturer, University of Toronto, Assistant Clinical Professor (Adjunct), Department of Family Medicine, McMaster University, Hamilton, ON.*

(symbolic imaging), procedural (habitual rules), associative (operative conditioning), non-associative (stimulus sensitization), and operational or working memory.[2-3] The basic mechanics of memory formation in the above domains involves the exposure to information or experiences and their subsequent transfer, storage and retrieval from memory. The part of the brain responsible for this function is comprised primarily of the hypothalamus and amygdala. There is also significant interplay of these limbic structures with the prefrontal cortex and the entorhinal/parahippocampal cortexes of the medial temporal lobe. Added to this is the role of neurotransmitters (NT), particularly acetylcholine, and the muscarinic and nicotinic receptors that modulate NT pathways.

...THE BRAIN ATTEMPTS TO BALANCE CELL FORMATION AND DESTRUCTION BY CONTINUOUSLY REFASHIONING SYNAPTIC CONNECTIONS.

Key Point

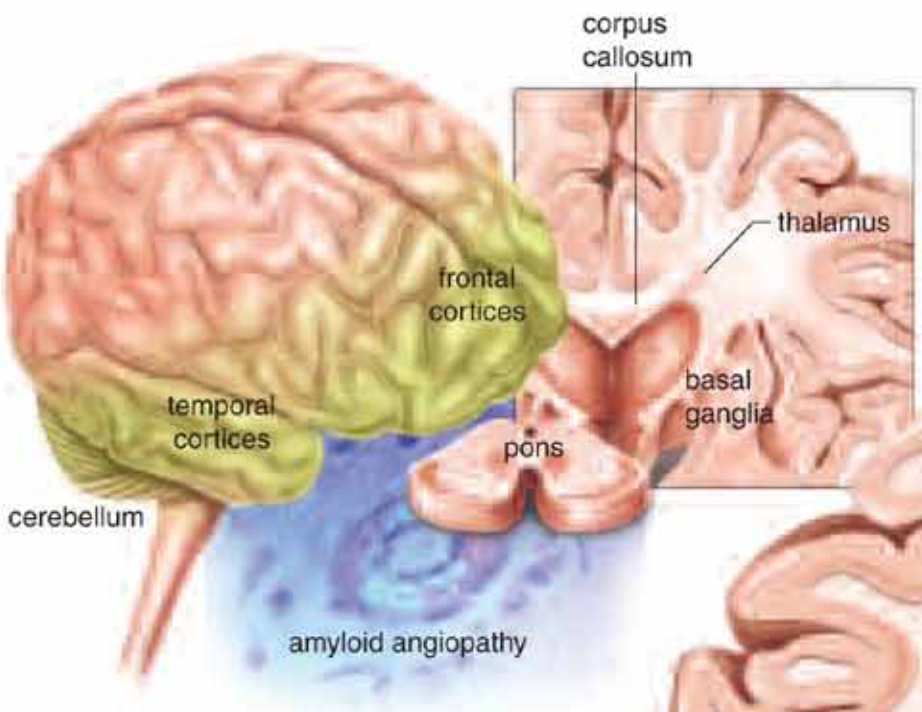
Re-routing brain cellular function, while initially compensatory, can lead to age related and pathological changes in brain cellular function.

With aging, it is postulated that a restricted loss of neurons occurs in key cortical areas involving memory.[4] As with many of the body's organs, the brain attempts to balance cell formation and destruction. It does so by continuously refashioning synaptic connections. Thus, at the cellular level, neural plasticity is a response to injury. As neurons undergo apoptosis, their base structural components, namely the axons, dendrites and synapses continuously remodel albeit in maladaptive patterns. The brain has a limited ability to restore this disrupted synaptic circuitry. Neurite sprouting and retraction along with sequestration of dysfunctional neurons can create a plasticity burden that eventually leads to degeneration. Specifically, a misguided synaptogenesis ensues, leading to an up regulation of tau (τ) protein phosphorylation and turnover of amyloid precursor proteins.[5] Moreover, there is an extensive loss of cholinergic stimulation in the limbic system, particularly the hippocampus.[6] The end result is the formation of neurofibrillary tangles and amyloid plaques that eventually manifest themselves as neuronal cellular death. Recent research also supports the premise that vascular and endothelial cell dysfunction aggravates underlying neuronal degeneration.[7] This has lead to the postulate that vascular risk factors interconnect with cellular neural plasticity and eventually lead to clinical symptomatology and memory loss.

Neuroplastic changes in the brain do not necessarily translate into an equal ratio of clinical cognitive decay. There are modulating features that protect the brain's function in spite of the neurobiological changes taking place. These factors, constructed under the

Figure 1:

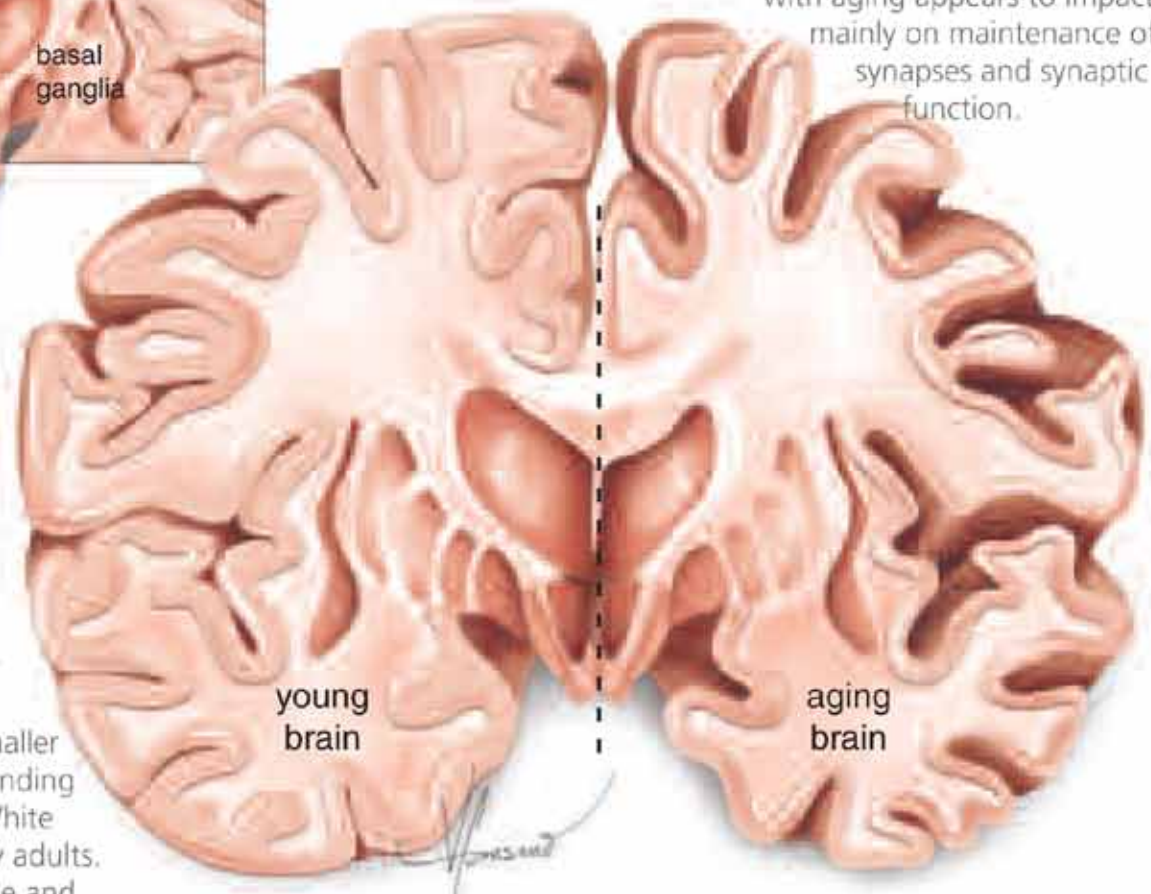
Morphological and Cellular Aspects of the Aging Brain



cellular morphology

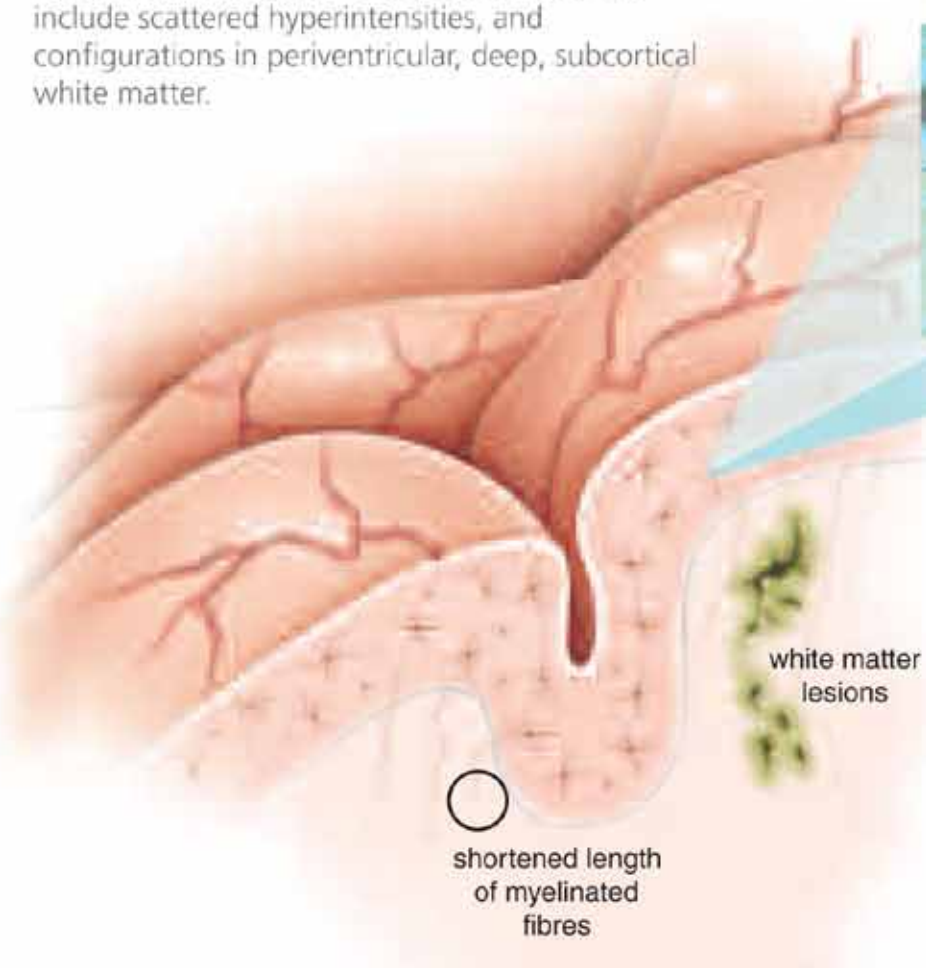
Most atrophy occurs in the frontal cortices, followed by the cerebellum, then perisyvian and temporal cortices, corpus callosum and thalamus, then basal ganglia, occipital cortex and the pons.

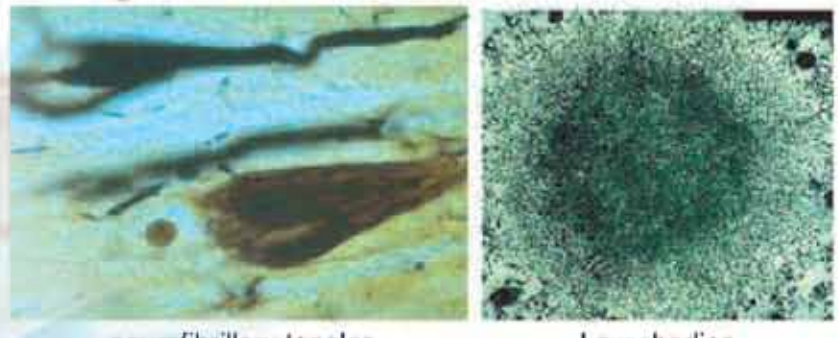
Neuronal densities increase while perikaryal size diminshes – numbers of neurons change very little with age in the neocortex. The functional effect of cellular change occurring with aging appears to impact mainly on maintenance of synapses and synaptic function.



changes in white matter

Between the ages of 20 and 80 years, a decline in white matter volume of approximately 23% occurs. The number and total length of myelinated fibres declines by 45%. The loss affects the smaller myelinated fibres and this explains the finding of a reduction in the density of fibres. White matter lesions commonly exist in healthy adults. Patterns of involvement are quite variable and include scattered hyperintensities, and configurations in periventricular, deep, subcortical white matter.





neurofibrillary tangles

Lewy bodies

neuropathology

With age, a large number of morphologic lesions are found in neurologically normal individuals. Such lesions include excessive accumulation of lipofuscin pigment and abnormal deposits and inclusions such as neurofibrillary tangles, senile plaques of amyloid, Lewy bodies, colloid inclusions, among others. In addition, several vascular lesions are found in a majority of people over 60, about half of which have no clinical or other neuropathological correlate. The common vascular lesions are atherosclerosis of the Circle of Willis, arteriosclerosis, arteriosclerosis, cerebral amyloid angiopathy, and small hemorrhages.

framework of cognitive reserve, provide not only an explanation for the variability in clinical expression of dementia but also open up avenues for preserving brain function in spite of pathological neurocellular dysfunction.

Preserving Cognitive Reserve

Lifestyle choices, achievement of higher education, cognitive pursuits, physical activity, and social interaction, can reduce the slowing of mental speed, and age related decline in executive function.[8-9] While there are no modifications to prevent or cure dementia, there is some evidence to suggest that there are interventions that may delay the appearance of clinical symptoms of memory decline when initiated in the preclinical stages.

The effect of cognitive engagement and stimulation in preserving the brain has been an area that has received considerable attention. A systematic review of randomized clinical trials on the use of cognitive exercises in the prevention of dementia[10] as well as a systematic review of the literature on cognitive intervention in MCI,[11] and population based epidemiological studies[12-14] have demonstrated a reduction in the odds of developing AD over a longitudinal period of up to 5 years by increasing the frequency of cognitive activity such as reading, playing musical instruments, attending cultural events, completing puzzles like crosswords and sudoku or participating in strategy games like chess. While most researchers agree that there are improvements in memory performance with cognitive stimulation, what is less well known is whether there are specific mental training protocols that can be implemented with reliable intensity, frequency and duration to achieve long-lasting memory gains.[15-16] Many of these studies have been criticized for their inability to show improved executive function on standardized testing with the skills gained in cognitive stimulation exercises. However, in the ACTIVE (Advanced Cognitive Training for Independent and Vital Elderly) RCT study,[17] at 5 year follow up, there was less functional decline in the group undergoing active problem solving training than the control group. It has also been difficult to tease out the independent effect of cognitive stimulation while controlling for variables such as pre-study higher educational or occupational achievement, although the latter two factors seem to provide their own independent protection from intellectual decomposition.[18]

Aside from the effect of cognitive stimulating activity, there are other factors that have been emerging as modulators in the development of cognitive deterioration. Physical activity is one such fac-

Key Point

Neuronal deterioration in the brain does not necessarily equate to clinical cognitive change.

Summary of Key Points

Re-routing brain cellular function while initially compensatory can lead to age related and pathological changes in brain cellular function.

Neuronal deterioration in the brain does not necessarily equate to clinical cognitive change.

Protective factors in preserving cognitive reserve include regular participation in cognitive enhancing activities, physical activity, targeting cardiac risk factors, and getting involved in social activities

tor. RCTs on exercise and cognitive waning demonstrated positive associations between engaging in physical activity and delaying cognitive decline in areas of cognitive speed, motor function and auditory/visual attention.[19-20] Case controlled, cross sectional and longitudinal epidemiologic studies[21] as reviewed by Rolland et al., have echoed these findings.

Given the influence of endothelial disruption on neural function, it is becoming more apparent that lifestyle modifications and the targeting of risk factors for cardiac health are also good for brain health. A meta-analysis on prospective cohort studies demonstrated an elevated risk of dementia in smokers.[22] Moreover, vascular risk factors like hypertension, hyperlipidemia, diabetes and obesity have been implicated in the development of dementia.[16]

The last factor to be addressed in this article is that of social interactions. Building varied and rich social connections has been associated with improved cognitive reserve. Population studies in Sweden and America have shown that frequent social engagement was related to a reduced incidence of dementia and that conversely those with limited social associations had an increased risk of developing dementia by as much as sixty percent.[23-24]

Key Point

Protective factors in preserving cognitive reserve include regular participation in cognitive enhancing activities, physical activity, targeting cardiac risk factors, and getting involved in social activities

Conclusion

Mild memory loss has long been associated with the aging process. This is differentiated from the pathological deterioration of dementia. While dementia is not curable or preventable, early cognitive decline prior to the onset of clinical dementia can be slowed down through the practice of healthy lifestyle management strategies, particularly physical exercise and a reduction of cardiac risk factors. Furthermore, building rich social networks and engaging in cognitive activity is beneficial in delaying cognitive decline and promoting healthy brain aging.

Clinical Pearls

Engaging in active problem solving training with the use of language and numerical puzzle and strategy exercises can delay the progression of age related memory loss.

Regular physical activity consisting of 150 min weekly for all adults as defined by the Canadian Physical Activity Guidelines promotes positive cognitive function.

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Opening Quote

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