Review Article

The Impact of Aging on Neurological Function and Cognitive Decline

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ABSTRACT

One of the most significant changes that occur as people grow older is the decline in neurological function and cognitive abilities. This decline can manifest in various ways, including memory loss, difficulty with problem-solving, and a decrease in reaction time. The impact of aging on neurological function and cognitive decline is a topic that has garnered a lot of attention in recent years. Advancements in medical technology have allowed researchers to study the brain and its functions in greater detail than ever before, shedding light on the complex processes that occur as we age. One of the most significant factors that contribute to cognitive decline is the loss of neurons in the brain. Neurons are the cells responsible for transmitting information throughout the brain and body. As we age, these cells begin to die off, leading to a decrease in brain function. This decline can be exacerbated by a variety of factors, including genetics, lifestyle choices, and environmental factors. Another contributing factor to cognitive decline is the buildup of plaque in the brain. This plaque is made up of proteins that can interfere with the normal functioning of neurons, leading to a decline in cognitive abilities. Additionally, changes in the brain's structure, such as a decrease in the size of the hippocampus, can also contribute to cognitive decline. The impact of aging on neurological function and cognitive decline is a complex topic that requires further research to fully understand. While there is no cure for cognitive decline, there are steps that individuals can take to mitigate its effects. By maintaining a healthy lifestyle and engaging in mentally stimulating activities, we can help to keep our brains healthy and functioning optimally as we age.

Keyword: neurological and cognitive function, ageing, neurological changes, geriatrics, Cognitive Decline.

Introduction

The impact of aging on neurological function and cognitive decline is a critical area of study in neuroscience, with significant implications for understanding the aging process and developing strategies to mitigate its effects on cognitive health [1].

In the lives of the elderly, mental abilities are crucial for everyday tasks. Regrettably, as aging occurs, some of these mental skills, like memory, the ability to solve problems, and quick thinking, tend to weaken. Various contributing factors are known to affect this decline in

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Mental sharpness [2]. These factors are categorized as either changeable or unchangeable. Factors that can't be altered include one's age, ethnic and racial background, gender, and genetic makeup. Interestingly, studies have shown that about 60% of our overall mental capacity is determined by genetics [3]. On the other hand, factors that can be modified include conditions such as diabetes, traumatic brain injuries, one's lifestyle choices, and their level of education. Recent inquiries have elucidated that senescence impacts the neurological efficacy of the peripheral nervous system, with metabolic elements such as glycemic indices exerting influence, even when these indices remain within normative bounds [4, 5]. This diminution in neurological efficiency may be a precursor to augmented morbidity and a diminished standard of living in the geriatric population [6]. Intriguingly, academicians from UCSF have discerned that the decrement in peripheral neural functionality attributable to senescence might correlate with subdued inflammatory responses and perturbations in glucose metabolism, intimating that these factors could expedite the waning of neural efficacy [7]. Furthermore, their observations indicate that senescence differentially affects the neural structures of males more profoundly than females in advanced years, suggesting a gender-specific divergence in neurological senescence [8-10]. Cognitive senescence, a natural and incremental diminution in cognitive faculties concurrent with advancing age, presents a significant impediment to sustaining life quality and vocational engagement [10]. A pivotal characteristic of this phenomenon is the erosion of working memory capacity, often the earliest to manifest among age-correlated cognitive impairments. The prefrontal cortex (PFC) is critically implicated in executive functionalities, notably in working memory. Research delineates that the degeneration of working memory in elderliness is intertwined with functional impairments in the PFC and disrupted synaptic interplay between the PFC and other regions crucial for task execution [7]. Neuroimaging comparisons between younger and older cohorts underscore this decline, evidencing alterations in the PFC encompassing deceleration in axonal fiber pathways, retraction of apical dendrites, synaptic attrition, and a reduction in dendritic spine density on pyramidal neurons [11]. Obesity and type 2 diabetes not only heighten the likelihood of various concurrent health issues but are also linked to a reduction in cognitive abilities, and may even lead to dementia in later years. This is particularly alarming given that, as established, even the most robust adults experience a natural decrease in basic mental functions with age [12]. This includes slower mental processing, short-term memory capacity, logical reasoning, and the ability to recall past events. Should obesity further exacerbate this cognitive decline, its impact would be most pronounced in older age, a time when mental capacities naturally diminish. It's also noted that with age comes a consistent growth in general knowledge, indicating that accumulated experience and wisdom can somewhat aid in maintaining daily functional abilities despite age-related cognitive challenges [12]. An investigation employing calcium imaging and optogenetic techniques in murine subjects revealed that aging is marked by a decline in the proportion of neurons in the medial prefrontal cortex (mPFC) that encode action plans, as well as a diminution in the action-plan signal strength of individual neurons [2]. This phenomenon results in a decreased ability to decode the action plan at the collective neuronal level. In the mPFC of younger adult mice, collective neural activities exhibit distinguishable yet intermingling patterns for tactile and auditory stimuli, facilitating the encoding of crossmodal memories alongside modality-specific memories [7]. Nevertheless, in middle-aged specimens, the capacity for crossmodal memory encoding wanes, although modality-specific encoding persists; both forms of memory encoding exhibit degeneration in advanced age. This study crucially underscores that functional changes in the prefrontal circuitry, pivotal for memory-guided behavior, become apparent in middle age and progressively worsen, marking a characteristic aspect of cognitive aging [11]. These findings collectively indicate that both neurological function and cognitive abilities are significantly impacted by the aging process, influenced by a combination of biological, metabolic, and possibly modifiable factors. Understanding these mechanisms is crucial for developing interventions to maintain neurological and cognitive health in the aging population [12].

Neurological Function and Aging

Peripheral Nervous System and Aging: Aging significantly alters the peripheral nervous system (PNS), both in structure and function. Morphologically, older individuals show a decline in myelinated and unmyelinated nerve fibers, coupled with abnormalities in myelinated fibers such as demyelination and remyelination, which are linked to reduced production of major myelin proteins [9]. Functionally, aging leads to slower nerve signal transmission, diminished muscle strength, impaired

sensory discrimination, weaker autonomic responses, and reduced blood flow in nerve coverings. Additionally, the aging PNS exhibits a decreased capacity for nerve regeneration and repair post-injury, attributable to altered responses in neurons, nerve fibers, Schwann cells, and immune cells [1]. The processes of nerve degeneration and regrowth are slower in the elderly, with a reduced release of growth factors from Schwann cells and target tissues, leading to diminished nerve fiber density and reduced sprouting of new nerve endings. While the ability for nerve regeneration and reconnection persists throughout life, these processes become increasingly delayed and less effective with advancing age [13]. While certain neurologic indicators are commonly associated with polyneuropathy, they may also manifest in individuals devoid of any health anomalies. The challenge in distinguishing between neuropathic dysfunction attributable to disease and natural variations owing to senescence stems from an incomplete comprehension of the normal aging process of the peripheral nervous system [14]. A comprehensive study was undertaken to elucidate the changes in neurological examination and nerve conduction as people age within the general populace. The investigation encompassed 4,179 subjects, averaging 64.5 years of age, with 54.9% being female. Among these participants, devoid of polyneuropathy, the incidence of standard results in neurological assessments diminished progressively with age. This decline was most pronounced in the vibration perception at the big toe and the non-elicitation of Achilles tendon reflexes. Contrastingly, superficial pain perception and patellar tendon reflexes demonstrated constancy over time. Furthermore, the amplitude of sural sensory nerve action potentials (SNAP) also reduced with advancing age, with nonrecordable SNAP amplitudes observed more frequently in individuals over 80, particularly in males compared to females [14].

Brain Aging: Brain age, a biomarker predicted using neuroimaging features, can indicate age-related brain changes. Studies have shown that psychiatric and neurologic diseases are commonly associated with accelerated brain aging. The most common changes associated with aging are brain atrophy, a reduction in white matter integrity and volume, and abnormal functional connectivity. These phenotypes can be considered signs of accelerated aging or an underlying disease process [15]. With aging, neural activity in the brain, especially in regions like the prefrontal cortex during high-level tasks, becomes both less integrated and more widespread rather than concentrated. This contrasts with younger adults, who tend to activate more specific brain areas for these tasks and more effectively connect these areas with other regions of the brain [16]. Interestingly, older individuals displaying this more spread out neural activity often demonstrate better cognitive performance compared to their peers with more localized brain activity. This suggests that such delocalization might be an adaptive response of the brain to aging. These patterns indicate that the complex, higher-order functioning of the brain undergoes significant changes as a result of normal aging, even in the absence of any disease [16]. The study of preclinical Alzheimer's disease has led to the development of a conceptual framework focusing on two mechanisms: resistance and resilience. Brain resistance refers to the brain's capacity to withstand pathological changes, which is indicated by either an absence or lower levels of Alzheimer's disease (AD) pathology than expected [17]. On the other hand, brain resilience is about the brain's ability to manage and adapt to AD pathology. This is measured by cognitive performance, brain structure, or function that is better than expected, given a certain level of AD pathology [17]. While the loss of neurons in most areas of the brain is minimal in normal aging, changes in the synaptic functions of aging neurons could lead to differences in how they connect and integrate at higher levels. Studies examining gene expression in the brains of aging mice, rats, monkeys, and humans have revealed significant alterations in genes related to synapses [18]. Notably, in the human and rhesus macaque prefrontal cortex, many genes responsible for inhibitory neurotransmission, particularly those involving GABA (γ-aminobutyric acid), show a marked decrease with age. This reduction could shift the balance between inhibitory and excitatory neurotransmission. Such a shift might result in increased neural activity in the prefrontal cortex of older individuals [4]. While this increase in activity might initially act as a compensatory mechanism, over time it could lead to increased susceptibility to excitotoxicity and neurodegenerative diseases [16]. Neurological interplay between the gastrointestinal (GI) tract's Enteric Nervous System (ENS) and the Central Nervous System (CNS) predominantly transpires via the vagus nerve, which imparts parasympathetic signals, and spinal nerves, responsible for sympathetic inputs. Intriguingly, this interaction is primarily unidirectional, with approximately 90% of the vagus nerve's fibers being afferent, underscoring the brain's role mainly as a

recipient of information from the gut. These afferent fibers of the vagus nerve connect to the brain stem's nucleus tractus solitarius, subsequently conveying data to various CNS areas, including those implicated in cognitive functions [19, 20]. Similarly, the afferent spinal nerve fibers associated with the GI tract predominantly infiltrate the CNS through the spinothalamic tract, integrating at the thalamus before disseminating information across the brain. Remarkably, the vagus nerve possesses receptors for specific hormones and neurotransmitters produced in the GI tract, such as serotonin, cholecystokinin (CCK), peptide YY (PYY), and ghrelin, along with receptors for bacterial derivatives like lipopolysaccharides (LPS). These receptors play a crucial role in updating the brain about the gut's condition [21, 22]. Furthermore, the gut's microbiota-generated short-chain fatty acids can activate the vagus nerve's afferent fibers. Emerging research indicates that a vagotomy, the severing of the vagus nerve, can impede the beneficial neurobehavioral outcomes usually prompted by probiotics. Additionally, there is increasing evidence that stimulation of the vagus nerve may bolster cognitive capabilities, highlighting the significance of this neuroanatomical communication in overall cerebral health and functionality [23]. In the context of aging and cognitive deterioration, the hippocampus stands out as a crucial area of focus. This brain region is not only integral for memory formation and learning but also plays a key role in regulating emotions and mood. Remarkably, it retains the ability for both functional and structural changes, like neurogenesis, even in later life stages [24]. The aging hippocampus undergoes several neurobiological changes, including heightened oxidative stress, increased neuroinflammation, changes in cell signaling and gene activity, alongside a decline in both neurogenesis and the adaptability of synapses. These alterations are believed to be linked to the cognitive decline associated with aging [23]. Fortunately, non-invasive methods such as diet control, regular physical activity, and stimulating environments have proven effective in reversing many of these age-related changes in the hippocampus. These techniques could therefore be beneficial in mitigating the negative impact of aging and in defending the brain from the progression of age-related neurodegenerative conditions [24].

Cognitive Decline and Aging

General Impact of Aging on Cognition: Senescence is recognized for precipitating the degeneration of cognitive faculties and stands as a principal contributor to the onset of widespread neurological ailments such as Alzheimer's disease. The regression of cognitive abilities with age targets particular memory types and cerebral structures in both human and animal paradigms. Mild Cognitive Impairment (MCI), impacting a substantial segment of the aged demographic, potentially escalates into dementia. The intensity of cognitive debilitation bears a direct correlation with hospitalization rates and profoundly affects life quality [25]. The presence of amyloid-β and tau proteins in the brain and the proposed alterations in neuronal functioning don't fully account for the complexities of Alzheimer's disease (AD) pathology. This is highlighted by the unsuccessful outcomes of extensive immunization trials and autopsy findings showing that individuals without cognitive impairments can possess substantial AD-related pathological changes. This discrepancy has led to investigations into why certain individuals exhibit a heightened resistance to dementia despite having considerable AD pathology, as identified through neuroimaging [6]. Studies have found that in people with significant AD pathology, the variance between those with normal cognitive function and those with dementia can be attributed to differences in overall brain and hippocampal size. It's suggested that larger brain volumes might provide a greater cognitive reserve or a higher baseline capacity, allowing more AD pathology to accumulate before cognitive impairments become apparent [26]. Moreover, individuals who are cognitively normal but have high levels of AD pathology might possess compensatory mechanisms that guard against neurodegeneration. These could include variations in the number of synaptic connections or differences in the cellular processes that lead to programmed cell death [26].

In a study that investigated whether cognitive activities throughout life are linked to slower cognitive decline in later years, independent of common neuropathological disorders. Participants in a longitudinal study rated their cognitive activity levels in both early and late life. After an average of 5.8 years, 294 participants passed away and underwent neuropathologic examinations, assessing factors like infarcts, neocortical Lewy bodies, β-amyloid burden, and tau tangle density [27]. The results, adjusted for various factors including age, sex, and education, showed that both frequent late-life and early-life cognitive activities were associated with slower cognitive decline. Together, these activities explained 14% of the variability in cognitive decline not related to neuropathological burden. Specifically, cognitive

activities during childhood and middle age, but not young adulthood, contributed to this association [27].

Numerous deliberations have been centered around evidence-based strategies for preserving cognitive prowess, with Mindfulness being one of the discussed approaches. A study was initiated to evaluate whether mindfulness-based stress reduction (MBSR), physical exercise, or their amalgamation could enhance cognitive faculties, particularly episodic memory and executive function, in the elderly. The study engaged 585 older adults aged between 65 and 84 years who had subjective cognitive concerns but no diagnosis of dementia. At the primary six-month checkpoint, neither the mindfulness training nor the physical exercise regimen demonstrated a significant impact on episodic memory or executive function. This lack of significant effect persisted at the 18-month secondary evaluation [28]. Furthermore, there was no notable interplay between mindfulness training and physical exercise. Additionally, none of the five secondary parameters, which included hippocampal volume and dorsolateral prefrontal cortex thickness and surface area, registered significant enhancements following either intervention. Consequently, the study concluded that among older adults with subjective cognitive concerns, neither mindfulness training, exercise, nor a combination thereof resulted in notable improvements in episodic memory or executive function at the six-month mark. These outcomes do not endorse the application of these methods for cognitive enhancement in this specific age group [28]. However, another study aimed to assess the effectiveness of musical activities in improving the physical, mental health, and cognitive abilities of people with dementia (PWDs). The interventions included singing or listening to familiar songs, vocal exercises, rhythmic movements, reminiscence, and discussions, along with musical exercises at home [29]. The results showed that compared to usual care, both singing and music listening improved mood, orientation, and remote episodic memory, and to a lesser extent, attention, executive function, and general cognition. Singing specifically enhanced short-term and working memory and improved caregiver well-being, while music listening positively impacted QOL. These findings suggest that regular musical activities can offer long-term cognitive, emotional, and social benefits in mild/moderate dementia, indicating their potential utility in dementia care and rehabilitation [29]. Another study focused on how multitasking, which can be challenging due to inherent limitations in processing information, affects different age groups. It was observed that by engaging older adults (aged 60-85) in training using an adaptive, custom-designed 3D video game (NeuroRacer), significant improvements were noted. These adults outperformed untrained 20-year-olds in multitasking, and the improvements lasted for six months. Additionally, training ameliorated age-related cognitive control deficits, evident in changes in brain activity patterns (enhanced medial frontal theta potency and fronto-occipital theta synchrony) [30]. Crucially, the advantages of this regimen were not confined to multitasking, but also extended to unpracticed cognitive skills such as prolonged focus and working memory. The augmentation in medial frontal theta dynamics correlated with these broader benefits and the preservation of multitasking abilities after a six-month period. This research highlights the exceptional plasticity of the aging brain's prefrontal cognitive control mechanism and emphasizes the utility of specially tailored video games as instruments for evaluating and augmenting cognitive abilities throughout different stages of life [30].

Lifestyle-cognition hypothesis

Studies reveal that approximately 60% of overall cognitive capacity is influenced by genetic factors, yet medical conditions, psychological aspects, and sensory deficits, such as auditory and visual impairments, can hasten cognitive deterioration with advancing age. This raises the inquiry of whether environmental elements could contribute to delaying or averting such decline [5]. The lifestyle-cognition hypothesis posits that an active lifestyle and engagement in particular activities over a lifetime could counteract age-associated cognitive diminishment and dementia. Support for this theory is derived from observations indicating that elderly individuals with higher cognitive functions tend to participate more in specific activities compared to those with lower cognitive abilities [15]. Longitudinal research, including the Seattle, Bronx Aging, and Victoria Longitudinal Studies, have investigated the potential of certain activities to slow cognitive decline, utilizing measures such as cognitive test performance and brain structure evaluations, including hippocampal volume and alterations in grey and white matter. These studies have pinpointed a range of activities associated with successful cerebral aging [2].

Cognitive Function Variability

Cognitive faculties are unevenly influenced by aging, with certain capabilities like vocabulary remaining stable or experiencing enhancement, while others, including abstract reasoning, information processing velocity, and memory, undergo deterioration [4]. The

disparity in the rates of cognitive decline among different individuals is prominent, and the hastening and subsequent erosion of cognitive abilities are associated with the emergence of age-related ailments. Memory deficits are broadly preserved across various species. Elderly humans and animals exhibit challenges in spatial orientation, increasingly depending on self-referential strategies owing to changes in specific brain areas affected during the aging process [6, 13]. An interesting study that contrasts brain aging in humans with that in chimpanzees, our closest living relatives, by examining various brain structures. While human brains show noticeable volumetric decline in areas like the hippocampus and frontal lobe, it wasn't clear if chimpanzees experienced similar changes. Using MRI, the study measured brain volumes in 99 chimpanzees aged 10 to 51 years and compared these with measurements from 87 adult humans aged 22 to 88 years. The findings revealed a stark difference: unlike humans, who exhibited a decrease in all brain structures over their lifespan, chimpanzees did not show significant age-related changes. Further analysis indicated that the pronounced aging effects in human brains were due to the inclusion of individuals older than the maximum lifespan of chimpanzees. The study concludes that the greater extent of brain shrinkage in human aging is a recent evolutionary development, likely linked to our longer lifespans. These findings provide insights into the cellular and molecular mechanisms underlying these changes [31].

Conclusion

In summary, the impact of aging on neurological function and cognitive decline is influenced by a combination of genetic, lifestyle, health, and disease factors. The trajectory of aging varies within the population, and age-related changes are evident in both structural and functional aspects of the brain. Understanding these changes is crucial for developing interventions to maintain neurological and cognitive health in the aging population.

Conflict of Interest

None

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