Review Article

Alzheimer's Disease – Not an Exaggeration of Healthy Aging

Krishnendu Ghosh, Pratibha Agarwal, Greg Haggerty

ABSTRACT

The world population is becoming older now. The boom of the elderly population comes from public health efforts to improve living conditions and prevent disease, and from improved medical interventions. People more than 65-year-old who are representing 12.9% of the population now is expected to grow to be 19% of the population by 2030. Very few numbers of diseases will have such socioeconomic burden on society in the newer world. Although Alzheimer's disease (AD) has been studied very well recently, still its exact etiopathogenesis is unknown. Currently there are no available tests for the definitive diagnosis of AD. So the clinical diagnosis of AD remains a diagnosis of exclusion. This limits the potential for early intervention. The difference between normal degenerative processes of brain and preclinical changes of AD is a gray zone and there is no particular way to distinguish between the two. Now several modalities like functional magnetic resonance imaging (fMRI), positron emission tomography (PET) scan, electrophysiological tests and cerebrospinal fluid (CSF) biomarkers for tauopathy and Aβ have shown to be promising in the development of early diagnostic tools for neurodegenerative changes and help us to differentiate between healthy aging and pathological aging. In this article we tried to discuss about the differences between pathological and physiological aging process from radiological, pathological, biochemical, and electrophysiological point of view. However, differentiating between physiological and pathological dementia still remains a challenge.

Key words: *Alzheimer's disease, cerebrospinal fluid, functional magnetic resonance imaging, positron emission tomography scan, prefontral corex, subjective cognitive complains, whole brain volume*

INTRODUCTION

An inescapable fate of growing old is the gradual slowing of the cognitive and mental capacities. Human development is an ongoing process. In most cases, subjective complains start in the fifth or sixth decade of life, indicating the possibility that dementia comes in 20–30 years earlier. Even before the stage of SCI, by 3rd decade of life our cognitive function starts declining and healthy aging starts. This article will present and discuss the available cognitive, electrophysiological, radiological and pathological and biochemical evidences of healthy aging Also we will try to delineate natural process of aging from pathological aging.

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CHANGES IN MEMORY WITH AGING

A healthy older adult experiences mild decline in some areas of cognition. These changes may occur in the areas of visual and verbal memory, visuospatial abilities, immediate memory, or the ability to name objects. Non-verbal memory impairments are also considered to be a common cognitive deficit associated with

Department of Psychiatry and Behavioral Sciences, Von Tauber Institute for Global Psychiatry, Nassau University Medical Center, NY, USA

Address for correspondence: Dr. Krishnendu Ghosh
200 Carman Avenue, Apt 3A, East Meadow, NY, 11554, USA. E-mail: kghoshmd@yahoo.com

aging. Risk factors for cognitive decline and dementia are similar. Biologists believe that our bodies begin to degenerate from the third decade of life and so does our brain. Research carried out in the last two decades have suggested the possibility to recognize Alzheimer's disease (AD) or pathological aging many years before the mildest symptoms appear. AD is an age-related disease, but it is not age dependent.[1] AD is itself a subtle process; it does not spread like a forest fire rather it starts slowly, grows daily, and is eventually followed by dementia. Seeding for AD occurs long before it becomes clinically apparent. The initial stage of AD starts with the stage of subjective cognitive complains (SCI), one review[2] found the prevalence of SCI among aged 65-year old or more varied from 25% to 56%.

No single theory explains the neurocognitive changes that occur during aging. Several authors have suggested a two-component view of aging, in which one component is associated with normal aging processes, while a second component indicates pathological processes. The first component studies revolve around changes in the volume and function of the following areas of our brain, prefrontal cortex-related frontal-Striatal, and prefrontal cortex-related frontal-parietal circuits, and their associated neurotransmitter systems, including dopamine.[3,4] The neural circuits in this component are associated with high-level cognitive operations referred to as executive control. Executive control is the ability to modulate and coordinate multiple component processes. These processes help us to maintain focus on task-relevant information at the time of distraction, an ability which fades up with aging.[5] Neurophysiological test suggest that prefrontal cortex (PFC) contributes in working memory. Patients with frontal lobe lesion show impairment of short term memory, difficulty with selective attention, and executive function such as planning and organization of information. The effects of aging on this component could be because of age-related structural changes and volumetric decline in the PFC. During memory tasks, healthy older people showed a reduced activation in the PFC while the same region was most activated in the younger group.[6-8] However, both groups sometimes may show equivalent activation. Older adults often display greater bilateral PFC activation on tasks in which younger adults have unilateral activation.[9,10] This pattern is known as reduced hemispheric asymmetry. It is a well-documented phenomenon in the cognitive neuroscience of aging.[11,12] This age-related phenomenon is a sign of compensatory function, implying that older adults recruit homologous regions in the contralateral hemisphere to boost performance with declining neural efficiency. Working memory performance has been found to be associated with Wisconsin Card Sorting Task (WCST). WCST an effective tool to test working memory has found to be particularly sensitive to dysfunction in dorsolateral prefrontal cortex (DLPFC). Another tool Raven's Progressive Matrices (RPM), test general intelligence by using abstract reasoning tasks. Both of these tests displayed a significant negative correlation with aging.[13] This study also showed decreased activation of DLPFC starting at 20 years of age during working memory test by WCST tools.

The second component involves pathological age-related changes. In contrast to the changes observed during normal aging, pathological changes are centered in the medial temporal lobes that are primarily associated with AD. Volume loss begins in the entorhinal cortex (EC), an important relay between the hippocampus and associated cortex. It progressively affects the hippocampus proper. The progression from normal aging to frank AD can occur in a graded fashion, lasting perhaps a decade or longer.

With aging comes general cognitive slowing, attention or working memory decline and loss of new learning activities. Reaction time gets slower as we become older. A study done among academic professors of 31-70 years old age group showed slowing of reaction time by 3.9 ms per year. The slowing can be observed in a variety of task and decision making.[14] Fluid types of cognition abilities which include problem solving, spatial manipulation, and mental speed, peek in the mid 20s, and then decline gradually until 60s, when more rapid decline takes place.[15] Recently research has shown that some aspects of age-related cognitive decline begin in healthy educated adults when they are in their 20s and 30s. Three tests on reasoning, speed of thought and spatial visualization were conducted to find out the earliest age at which performance starts declining. These tests showed that peak scores were at 27 years of age and then they started declining. Memory was shown to decline from the average age of 37 years.[16]

The cognitive aging depends on various causes and cognitive outcome depends on education level and health. Education, good health, absence of the APOE 4 allele, and physical activity may be protective and prevent cognitive decline. Cognitive processing speeds and memory retrieval speeds decline by as much as 20% by age of 40 years and 40-60% by age 80 years. Crystallized cognitive abilities, however, increase well into the later decades of life and only decline at advanced ages.[17]

ELECTROPHYSIOLOGICAL CHANGES WITH AGING

It is important to introduce techniques that would give us more insight into natural brain aging and could possibly differentiate it from pathological neurodegeneration.

Interestingly some studies showed that in the same age group, higher α-wave frequency activity is related to higher cognitive ability in normal healthy as well as demented population. High-frequency α-wave reflects the oscillation of specific neural systems for the elaboration of sensorimotor or semantic information whereas low frequency α-wave is primarily related to subject's global attentive readiness.A gradual decrease of α-wave and a global slowing of the background EEG are noted with aging.[18] From early childhood up to puberty α-frequency increases but then starts to decline with age. A young adult, 20-year-old will have an a-wave with the highest frequency, a frequency of 10.89 Hz and then α-wave frequency declines gradually in a liner manner; at 70-years of age α-wave shows a drop of 2.65 Hz down to a frequency of 8.24 Hz.[19]

A study[20] in a large number of different age grouped participants showed that older age group had delta waves in the occipital area and α-1 and α-2 waves in the parietal, occipital, and temporal regions. Limbic areas have less magnitude of α-1 and α-2 waves in older age group compared to younger participants. Compared to healthy normal elderly subjects, AD patients have high amplitude of delta and theta wave frequencies and low amplitude of α- and β-wave frequencies. A decrease of α- and β-wave frequency was found in AD patients compared to the same age mild cognitive impairment (MCI) subjects. α- and β-activities are more common anteriorly in AD patient's brain compared to both the controls and MCI subjects. No significant difference in α-wave was found between MCI and controls. α- and θ-wave amplitude when combined were the best variables to differentiate between AD patients and controls; it is also an important tool by which we can differentiate between AD and MCI subjects.[21]

Polysomnography (PSG) is a comprehensive recording of the biophysiological and electrophysiological changes that occur during sleep. A study done by Lauer[22] of individual from 18 to 65 years of age showed significant polysomnographic changes with aging; decrease of Sleep time period, decrease of total sleep time, decrease of sleep efficiency index. Sleep onset latency and intermittent time awake were found to increase with aging, similarly, duration of stage 1 sleep increase with aging while the slow wave activity of sleep decreased with aging. Throughout aging Stage 2 sleep remained unchanged. With aging sleep becomes more fragmented and lighter; stage 1 sleep increases and percentage of slow wave sleep (SWS) decreases.

In patient with AD it could be look like changes are exaggeration of normal aging but that is not true. In patients with AD we see more wakefulness and it is because of increased in duration of stage 1 sleep, we can even see decrement changes in SWS in AD patient which is not a feature for same aged control. In mild to moderate stage of AD stage 2 sleeps loses its own texture, K complex and sleep spindles no more make this stage distinguishable from other stage of the sleep. Subsequently stage 1 and stage 2 sleep patterns starts look like same and new stage of sleep emerges and is known as indeterminate NREM sleep. REM latency was found to decrease while first REM period significantly increased with advancing age but continuous decrement in the percentage of REM sleep with the progression of disease process is also typical feature of AD which is not seen in normal healthy aging as total REM sleep percentage remains stable.[23]

Magneto encephalography is a potential investigation of choice which can help us understand the cortical rhythm in pathological aging. It was seen that the frequency of delta and theta waves increases in the AD group compared to healthy control and slow wave activity differs significantly between temporoparietal regions of both hemispheres. Temporoparietal δ and θ sources are enhanced in amplitude in AD compared to old subjects in association with hippocampal atrophy.[24]

RADIOLOGICAL CHANGES WITH AGING

Aging originates from a diverse group of mechanism that makes a gray zone between normal aging and pathological aging process.[25] Normal aging is associated with some degree of neuron loss and volume loss with increasing adjacent glial cells.[26] Recent studies have shown that loss of brain volume is due to loss of neuronal cell size rather than loss of cell volume,[27] and the cognitive decline associated with normal aging is because of dysfunction rather than loss of neurons or synapses. Decrease in the amount of synaptic proteins involved in structural plasticity of axons and dendrites have suggested that disturbed mechanism of plasticity may contribute to cognitive dysfunction during aging.[28] Noninvasive technique like volumetric MRI has shown a progressive decline in cerebral hemisphere by 2-3% a decade and increase in ventricular volumes by 2% a decade.[29-32] There was also a whole brain volume (WBV) decline by 0.22 a year between the ages of 20-80 years with hastened decline with advancing age.[29,33] Healthy volunteers, an age-related decline in the volume of the prefrontal cortex, insula, anterior cingulategyrus, superior temporal gyrus, inferior parietal lobule, and precuneus was found. These decreases might contribute to the cognitive changes during normal aging. In patients with AD, a significant reduction of gray matter volume in the hippocampalformation and EC bilaterally was noted. The changes in regional volume are not uniform. Some regions, such as the PFC, show particularly dramatic changes in volume, while other regions, such as

the occipital cortex, are relatively unaffected by normal aging.[3,34-36] The largest age-related volumetric changes in older adulthood appear to occur in the PFC,[35,37] approximately average volume loss of approximately 5% per decade starts from 3rd decade of life.[36] The biggest age-related volume loss occurs in the lateral PFC, with an estimated rate of loss of 0.91% per year.[37] Orbito-frontal PFC declination were nearly as large as lateral PFC, with an estimated annual loss of 0.85%.[37] But in case of Alzheimer's disease greatest degeneration is seen in the inferior PFC.[38] Also gradual volume loss is observed in the striatum. It is heavily enriched with dopaminergic neuron, which connects it to the PFC. Striatal volume declines at about 3% per decade,[39] while caudate volume declines at approximately 0.75% per year.[37]

Medial temporal lobe consists of the hippocampus and adjacent, anatomically related cortex, including entorhinal, perirhinal, and parahippocampal cortices. These structures, presumably by virtue of their widespread and reciprocal connections with neocortex, are essential for establishing long-term memory for facts and events. These volumes also decline during normal aging. Adult lifespan studies (with participants in their 20s to 80s) with intervals of 5 years have estimated the rate of decline in hippocampal volume at 0.79-0.86% per year.[3,40] The declination in EC volume however, was smaller- with the estimated rate of change being approximately 0.33%, although this accelerates somewhat in later life.[40]

Longitudinal measurements of hippocampal atrophy increase many-fold from a range of 0.2-3.8% per year in normal elderly to a range of 4.9-8.2% per year in AD.[41] Decline in EC volume in MCI patients is twice, compared to age-matched controls.[42] In general, these results suggest that normal aging has modest structural effects on the hippocampus and adjacent medial temporal lobe structures. Pathological processes related to MCI and AD, however, have severe effects within the EC even early in disease progress, which reduces the potential for effective hippocampal involvement in memory function.

Brain areas which are involved with cognitive processes affected in AD showed robust relationship with white matter degeneration and gray matter (GM) degeneration. Therefore, cortical function and white matter (WM) degeneration are related in aging and dementia. A study done by Yulin[43] measured both absolute and fractional %GM and %WM volumes in healthy adults aged of 20–86 years and evaluated the data by age and sex. This study showed that the rate of change in %GM and %WM with aging does not depend on sex, although female subjectshave slightly higher %WMs, compared to male subjects. This study also found a 4.9% difference in %GM between the younger groupand the older groups. The decline of volume of %GM occurs by a relatively young age (age 20 years), and the decline occurs constantly in a linear fashion. While the %WM, in contrast, shows a quadratic pattern of change, volume increases until an age of around 40 years. But once WM degeneration starts at age of 40, the loss is more consistent and faster than GM.

Modern noninvasive imaging techniques are an excellent means to examine age-related changes from pathological changes. CT scan and MRI help us gain detailed assessment of brain structures. The functional state of brain can be best detected by PET scan; Flurrine-18-fluorodeoxyglucose has been used before to reveal alteration of regional metabolic rate of normal aging and other psychiatric disorders.[44] Various regional metabolic activities varied among subjects within same age group as well as over decades. The anterior posterior gradient changes over the time and with advancing age, because of significant decrease in frontal lobe activity in later years. Less frontal lobe activity becomes more notable after age of 30 years, but more dramatic decline of frontal brain metabolic activity occurs after age of 60, and this is the time when temporal lobe metabolic activity also starts to decline.[45] Cerebellum to cerebral cortex metabolic activity ratio tends to increase with age, and it is consistent with decrease metabolic activity of cerebral cortex, which becomes more prominent after age of 40 years. At the same time cerebellum's metabolic activity remains constant up to age of 40 years.[46] Findings from other research[47] showed that metabolic activity of frontal, temporal and parietal brain decreases with aging but this decline is more rapid in case of frontal lobes.[48] One study was done[49] to detect cerebral metabolites like N-acetyl aspartate (NAA), and choline (Cho) and creatine (Cr) *in vivo* by newer proton magnetic resonance spectroscopy. NAA is a specific neuron marker, as it is found at high concentration almost only in neurons.[50] The major findings of this study were: A) Hippocampal NAA/Cho and NAA/Cr decreases with advancing age, whereas Cho/Cr remains relatively stable. This implies that NAA ratio declines are mainly due to decreases of NAA. B) Hippocampal volume decreases with age, C) Hippocampal NAA ratios and volume change occurs at similar relative rates with advancing age. This is consistent with the view that hippocampal volume loss is due to neuronal loss. Metabolites ratio and volume of hippocampus decrease starts consistently from age of 36 years, and it occurs in a linear fashion with aging.

PATHOLOGICAL CHANGES WITH AGING

Pathological hallmark of AD is amyloid peptide (Aβ),

the sticky plaque which was first discovered around the meningeal blood vessels of individuals with Down's syndrome who developed AD nearly 20 years earlier.[51] Later, the same Aβ peptide was recognized as the primary component of the senile (neuritic) plaques of brain tissue of people with AD. These discoveries initiated the beginning of the modern era of research on this common, devastating neurodegenerative disease. Amyloid and tau deposition starts up long before the development of first AD symptoms. Deposition of amyloid and tau protein is limited to specific brain regions. With the recent advancement in neuroradiology it is now possible to look into the pathological changes that occur in AD much before the onset of clinical symptoms. Most commonly used approach is PIB-PET scan. PIB-PET scan displayed that amyloid plaque deposition occurs with high frequency (about 30%) in non-demented elderly.[52] The frequency of individual with high Mean cortical binding potentialfor PIB was 0% at age 45-49 years, 5.7% at 50-59 years, 195% at 60-69 years, 25.8% at age 70-79 years, and 30.3% at age 80-89 years, and CSF Aβ42 was 18.2% at age 45-49 years higher than 14% at age 50-59 years.[53] It demonstrates that ongoing degenerative process of central nervous system is detectable as early as, in the 5th decade of life. CSF markers are now well-validated: Reduced CSF-A β and raised CSF-tau have a strong relationship with early stage of AD. Another study has shown that changes in CSF biomarkers already reach a plateau in a preclinical phase, before cognitive decline begins, that is, even before MCI can be diagnosed.[54]

AD developmental process has been distinguished by three histopathological stages. Initial changes are seen in the basal cortex, most frequently in the poorly myelinated temporal areas such as perirhinal and Enterorhinal fields (stage A), in stage B, AD changes occur in the neocortical area and in the hippocampal formation. Finally deposits are found all over cortex (stage C). Early amyloid deposition occurs in poorly myelinated areas of the basal neocortex.[55,56] After that AD pathology spreads to cortical region (that is temporal, parietal and frontal), leading to early signs of pathological changes. Neurofirillary tangles (NFTs), Neutrophil threads (NTs), and neuritic plaques (NPs) are different types of intraneuronal change can be seen in AD. In general NPs changes occur later than NFT or NT changes. Some young individuals develop first neurodegenerative changes in brain, in their 3rd decade of life. One case showed stage A amyloid changes among 61 individuals of 26-30 years age group; however, 11 cases among 61 individuals of the same age group showed stage I/II intraneuronal changes.[57]

In normal aging, a few NFT can be observed in layer II of the EC and NFT are occasionally encountered in the stratum pyramidale of the CA1 field. The inferior temporal cortex (ITC) and superior frontal cortex (SFC) remain devoid of NFT. There is no neuronal loss in normal aging. In contrast, very mild AD is characterized by higher NFT densities in the EC and CA1, and NFT are consistently observed in layer III of the ITC. The neocortical areas show no neuronal loss, but a significant degree of neuronal loss is present in layer II of the EC and in the CA1 field. In severe AD, NFT are found in high densities in layer II of the EC, in the CA1 field, and in layers III, V, and VI of the ITC, with moderately high density in SFC as well. The degree of neuronal loss parallels NFT densities in these regions, although NFT numbers alone cannot account for the total loss of neurons, indicating that not all dying neurons necessarily undergo NFT formation.[58]

One of the most significant features of AD is substantial neural loss in hippocampus and cerebral cortex, the regions which are involved in memory and cognition. Studies have shown that high hippocampal diffusivity values in the hippocampal formation of healthy elderly individuals beyond their 50s, predicts memory decline.[59] Myelin breakdown is predicted to be an important aspect of AD.[60-62] According to this hypothesis, late myelinating fibers are the earliest ones to get involved in AD. Corpus calosum which connects two cerebral hemispheres is the largest white matter bundle in the human brain and this is where early degeneration begins. It contains late myelinating fibers in genu and early myelinating fiber in splenium. One study[63] has shown that reduction in genu size occur even in the preclinical stage of dementia which reinforced the theory of late myelinating fibers get affected in AD first.

BIOCHEMICAL CHANGES WITH AGING

Our body is mostly dependent on aerobic metabolism which takes place in mitochondria; the powerhouse of a cell. Myelinataion is an energy consuming event. With aging changes occur in cellular organelles.Mitochondria also undergo functional and morphological changes. This may disrupt the energy supply for myelinataion, which may explain the metabolic theory of AD. A study[64] measured effects of age on pH in brain tissue. It showed a significant age associated decrease in brain pH (–0.53% per decade). This acidification not only induces apoptosis but also substantially alters enzyme activities and promotes the development of AD.

A study by Smith[65] on postmortem brain showed that Carbonyl content rises exponentially with aging, double in rate in the frontal pole compared to occipital pole. It also showed decreases in glutamine synthetase and creatine kinase activities in the frontal compared to occipital pole. This study also proved that oxidation

vulnerable enzymes activity decrease with aging and protein oxidation products accumulate in the brain. Glutamine synthetase enzyme plays an important role in the regulation of cellular acid-base balance. Decrease in intracellular pH can change position of intracellular iron, which can eventually result in production of oxygen free radicals and further protein oxidation. Only glutathione synthetase activity in the frontal cortex is significantly decreased in AD which was another differentiating factor between healthy aging and AD.

In addition to the volumetric and functional age-related changes in the PFC, various neurotransmitter systems in the PFC and striatum also undergo age-associated changes. Of these, three are very important, dopaminergic system, cholinergic system and glutaminergic system. The dopamine system which plays an important role in attention or executive control of memory also loses its efficiency with aging. Age-related declines have been observed in dopamine concentration, transporter availability. D2 and D3 receptor density also found to decline with aging.[49,50,66] Studies showed[67] that there is age-related decrease in dopaminergic receptors in the caudate nucleus and the substantianigra.The rate of neuronal loss in the substantianigra which is mostly dopaminergic, found to be about 6% per year.[68]

This loss of dopaminergic neuron is responsible for cognitive decline and many neurological symptoms that increase in frequency with age, such as - decreased arms swing and increased rigidity. The dopamine level in the human striatum declines to 50% with advance aging. Postsynaptically, the density of D-2 dopamine receptors also decline by 25–50% in human striatum. On the contrary, the amount of D-1 receptor has been found to be incremental with advancing age.[69] The decline of the number of D2 receptors begin at age of 40 years and it occurs at the rate of approximately 8% per decade. Lower level of D2 receptors is also associated with a low glucose metabolism in the PFC.[50,70] By age 60, normal older adults display 58% decline compared to younger adults in striatal uptake of a dopaminergc analog (In subjects with Parkinsonism, decline is about 85%)[46]. Also, dopamine transporter availability has been estimated to decline at a rate of 4.9% per decade in the caudate nucleus and 4.2% per decade in the putamen.[49] Now comparing health aging with AD at dopamine level shows not much change. One research[71] was done to investigate dopaminergic activities in post-mortem brains of patients with various types of dementia and brain of healthy elderly people. It showed in the caudal putamen level Dementia with Lew body (DLB) patients showed significantly low (57% of normal level) dopamine uptake compared to control, but patients with Parkinson's disease had the lowest level (75% of normal level), and it was unchanged in Alzheimer's disease. This study also showed D3 receptor binding capacity in the patients with AD was 20% higher than control at caudal striatum. Same kind of result came out with another study[72] where *in vivo* dopamine (D2/D3) receptor availability was examined by [(11)C] raclopride (RAC) PET scan in patients with mild and moderate AD with delusion. It showed increased striatal dopamine (D2/D3) receptor availability in delusional AD compared to same aged control group.

Age-related changes also take place in cholinergic circuit of brain. Nucleus Basalis of Meynert (NBM) is a group of distinct neurons which is rich in acetylcholine and choline acetyltransferase. It is a major source of cholinergic innervation of the cerebral cortex. In various types of dementia, this nucleus undergoes degeneration. Patients with low acetyl choline show general decrement of mental capacity and learning and cognition. Even elderly patients on anticholoinregic medication showed difficulty with cognition. Anticholinergic activity accelerates Alzheimer's pathology and reduces cognitive function. A study[73] on postmortem brains of patients with AD and senile dementia showed profound diminishment of cholinergic neurons in the cortex. This study also showed neurons of the Nucleus Basalis of Meynert underwent a profound (greater than 75%) selective degeneration in AD patients. But it is not documented when degeneration starts.

In AD choline acetyltransferase activity is reduced to 35-50% of normal level.[74-77] Furthermore, synaptic reuptake of choline, which is essential for the synthesis of ACh molecules, is reduced to ~60% of normal levels in AD.

Nicotinic receptors in the frontal cortex undergo changes with aging.[78,79] But in the hippocampus, $\alpha 4$ subunit receptor numbers remains constant, though $\alpha 7\beta 2$ subunit significantly decreases with age.[68] These findings suggest that nicotinic receptors decrease during aging with differing vulnerability between subunits and brain regions, which may contribute to the reduced cognitive function with aging. In AD both types of cholinergic receptors, nicotinic receptors and muscarinic receptors binding property decrease to their 60-70% and 80-100%, respectively.

Other important receptor for memory perspective would be N-methyl-D-aspartate (NMDA) receptors, which are seen in high density throughout the cerebral cortex and hippocampus and play an important role in learning and memory. Calcium flux through NMDARs is thought to play a critical role in synaptic plasticity, a cellular mechanism for learning and memory. The capacity for thinking and remembering is derived

from various input and output pathways between the hippocampus and the neocortex,[80] pyramidal cells which accounts for more than 70% of all connection use glutamate for this process. In healthy individuals, the glutamatergic neurotransmission cycle begins in the mitochondria of hippocampal neurons, where the enzyme glutaminase catalyzes the conversion of glutamine to glutamate. NMDA antagonist drug has shown benefits in case dementia, as it slows the progression. These receptors are also negatively affected by the aging process.[81]

It has been hypothesized that constant activation of NMDA receptors leads to neuronal over activity which contributes to an unfavorable signal-to-noise ratio during glutamatergic neurotransmission and, hence, to the absence of long-term potentiation.[82] In patients with AD, available evidence points to a disruption in the glutamatergic neurotransmission cycle at the point of glial cell reuptake of free glutamate from the synapse. Neuropathological studies have documented reduced levels of glutamate reuptake in the frontal and temporal cortices of patients with AD, possibly due to oxidative modification of the glutamate transporter molecule[83] which is not common in healthy aging. Furthermore, diminished uptake by vesicular glutamate transporter (which mediates the packaging of these glutamate molecules into vesicles) has been reported in patients with AD.[84]

CONCLUSIONS

The difference between healthy brain aging and changes of AD remains a gray zone. In this article we tried to discuss about the differences between pathological and physiological Neurodegenerative process from radiological, pathological, biochemical, electrophysiological perspective. We can see distinctive pathological changes, radiological changes and electrophysiological changes in AD compare to healthy degenerative aging of brain. Healthy aging of brain starts from 3rd decade of life which begins 30 years before the SCI or first pathological changes of brain. Though AD has been studied very well recently, still its exact etiopathogenesis is unknown. Currently there are no available tests for the definitive diagnosis of AD. Not much study has been done to discover or differentiate if the pathological aging in AD is the continuation of healthy aging process, but hopefully with new early diagnostic tools we will be able to delineate preclinical AD from healthy aging in the near future.

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