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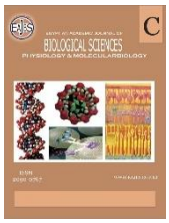

Structural and Functional Changes in Cerebral Aging

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ABSTRACT

Many structural and physiological alterations occur in cerebral aging, exposing elderly subjects to impaired cerebral functions and several brain diseases. The senile narrowing of the brain is an obvious structural manifestation, which is easily diagnosed in imaging and may be global or focal (i.e. touching the whole of particular regions of the brain). The physiological chained reactions of aging require adaptation from the brain cells; otherwise, authentic diseases may evolve, such as tumors, stroke, or brain-wasting diseases like Parkinson's and Alzheimer's. On the other hand, some studies demonstrated that the aging process and its consequent effects on the brain could be slowed or delayed by some preventive measures, such as regular physical activity, a balanced diet and life environment, sustained cognitive training and some herbal products. All these factors would have a positive effect on the preservation of brain integrity and should be integrated into brain aging management, as well as pharmacological treatments.

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INTRODUCTION

Aging can be defined as the process by which organisms proceed through a physical deterioration of the body (Garthwaite, S., *et al.*,1986). According to the World Health Organization (WHO), there will be more individuals aged over 65 years than kids aged less than 5 in the coming few years (WHO). With the expanding lifespan, survival analyses estimate the number of centenarians at around 3.2 million worldwide by 2050, more than 18-fold higher than the turn of the 21st century (Bernadett M. 2013). For these reasons, it is becoming crucial for all health actors, including authorities and researchers, to deploy the needed efforts in order to draw better approaches regarding aging and multiple aging-related disabilities.

Indeed, unavoidable physiological changes occur during aging, implying the progressive switch of the organisms from a steady normal state to a steady dysfunctional state. All living beings are concerned with this process, including unicellular organisms and plants. However, till today, research has not revealed all the features of aging changes yet and many details of this process remain unknown.

In a strict physiological term, body aging is almost parallel to body development, which means that this process may actually start at birth and only ends up at death. During aging, several physiological modifications occur, such as a lessening in the number of cells, diminution of the metabolic rate, increment of the sickness and loss of flexibility. These modifications are degenerative processes, whose severity and speed of onset depend not only on ecological determinants but also on individual factors, such as stress, dietetics, smoking and exposure to daylight (Harman D. 1981).

Theories of Aging:

Many theories have been suggested to explain the global essence of aging, among which two seem fundamentally distinct. The first of these two fundamental theories is the hereditary programming speculations of aging, stipulating that both the lifespan and maturation rate of living organisms are hereditarily predetermined. The second one is the theory of essential damage, stipulating that aging occurs as a consequence of cumulative damage over the lifetime, progressively consuming the biological reserves of the organism. All the other theories, which will be exposed below, are likely to be incorporated into the theory of essential damage (Harman D. ,1981; Albert MA. & Funkenstein HH.,1992).

1-Genetic Theory:

Is lifespan hereditarily based? Many arguments support this claim; mainly the fact that lifespan is likely species-specific, which indicates that each species, including humans, is genetically programmed for a maximal lifespan. Indeed, despite the increase in the average lifespan, we did not observe any increase in the maximal lifespan. These observations are valid for humans, as well as for other animal and vegetal species. Thus, according to this theory, the term of life would be predetermined, in the same way, fetal life is predetermined with the birth term.

Partisans of this theory conceptualize the aging process as the expression of senescence genes, resulting in a slowdown or break of chemical and bio-cellular metabolic pathways. These genetic expressions are scheduled in timelines that differ across types of tissues and cells.

Furthermore, lifespan differences within the same species seem also explained by some genetic differences. The New England Centenarian Study, founded in 1994, in its genetic findings, reported the association of a locus in chromosome 4 to familial longevity (Sebastiani P., and Perls TT., 2012). Another Genome-Wide Association Study described another locus located in TOMM40 at chromosome 19q13.32, to be determining familial longevity (Deelen J., 2011).

2-Wear-and-Tear Theory:

According to the wear-and-tear theory, the human body is subject to aging effects as a result of damage from accidents, diseases, radiation, toxic substances, food,

and many other harmful circumstances when it is used for a long time, much like machines that are subject to damage and break down when utilized for a certain period of time. This notion, however, has been disproved because even protected animals have aging changes that have no bearing on how long they live (Harman D.,1981 and Albert MA. & Funkenstein HH.1992). This shows that such damages cannot represent the underlying causes of aging, only time-dependent alterations.

3-Telomere Theory:

The lifespan of an organism is intimately dependent on the lifespan of its cells. When human fibroblasts are continuously sub-cultured, the lifespan of cell division is estimated to be 50-100 times approximately. Such observations support the thesis that the lifespan of the cells is pre-programmed. Moreover, subsequent research has identified the responsible shortened telomeres at the chromosomal ends.

Repetitive DNA sequences, six-nucleotide sequences (TTAGGG), are present at the terminus of all human chromosomes. They are about 12 kbp in length and lose telomeres when going through around 100 times of cell division. The length is very similar to the lifespan of in-vitro-cultured cells. Telomerase, the enzyme that prevents telomere shortening, is highly expressed in immortalized cells and cancer cells. Therefore, telomere shortening takes place constantly by the enzyme so that immortalization or proliferation of cancer cells would be ongoing (Wong JM., Collins K., 2003).

4-Endocrine Theory:

The endocrine theory supposes that impairment of hypothalamus- pituitary gland-endocrine systems, regulating the body's homeostasis, are the main responsible cause of aging, with many broad effects on several physiological functions. In general, endocrine hormones are involved in regulating growth, metabolism, temperature, inflammation, and stress. This theory is suggested through some animal studies that showed that the lifespan of animals with menopause, andropause, and somatopause (decreased GH/IGH-1) is extended when the corresponding hormones are provided. Since the endocrine system takes part in the maintenance of life and the species plays significant roles, there are not many changes induced by aging when the hormone system for maintaining the species is greatly altered by aging (Tatar M., *et al.*, 2003).

5-DNA Damage Hypothesis:

According to the DNA damage theory, the absence of or incomplete repair of the DNA with free radical-derived damage would reduce gene expression as well as cell death. It would then interfere with the proper functioning of the tissues eventually so that the progression of aging is stimulated. A study, reporting that albino rats, (shorter lifespan than humans), urinate 10 to 15 times more of oxidatively-damaged nucleotides than humans, and the increase in damaged DNA in brains by aging also supports the hypothesis. In addition, it is assumed that the faculty to repair DNA alterations is directly associated with the lifespan of species and that it is impaired in normal cells with the progression of aging (Bohr VA. and Anson RM., 1995).

6-Error Catastrophe Theory:

The procedures including replication of the DNA, transcription of the gene to produce mRNA, and translation of the message to produce the protein are required in protein synthesis. The theory hypothesizes that if there are any errors in any of those procedures, incorrect genes, mRNA, and proteins would be produced so order to support this theory. Even though the accumulation of these errors is partially eliminated by the repair system, such a repair system would not operate perfectly and permanently because errors may be accumulated in the repair system as well (Weinert BT. and Timiras PS., 2003). the cells would be impaired; however, more studies need to be done in this area in

7-The Rate of Living Theory:

The rate of living theory suggests that energy expenditure is inversely proportional to the lifespan, and in particular,

animal studies have shown that the lifespan is shorter when the energy expenditure is higher, and vice versa. In the case of poikilotherms such as nematodes, insects, and fish, their lifespan is generally increased as the habitat temperature is elevated while it is decreased as the temperature is lowered. The lifespan of a housefly at 20°C is twice that of a housefly at 28°C. Similar to the housefly, the lifespan of a minnow at 10°C is 1.4 times higher than that of a minnow at 20°C. Another study investigating the relationship between the lifespan of *Drosophila* and temperature showed that approximately 25 days, 50 days, 100 days, and 150 days of lifespan was exhibited at 30°C, 27°C, 21°C, and 18°C, respectively, which is in agreement with this theory. This may be because the metabolic rate would slow down as the temperature is decreased. However, the theory is not applicable to homeotherms as they are mostly independent of the temperature (Park DC., *et al.*, 2013).

8-The Mitochondrial Theory:

The mitochondrial theory hypothesizes that mitochondria are relevant to aging as mitochondrial DNA where free radicals are produced maximally is not properly protected due to external antioxidants, and mitochondria are very susceptible to damage from external toxic molecules and radioactive materials. Especially, since repair enzymes for the damaged DNA do not exist in mitochondria, that damage has significant implications. The damaged mitochondrial DNA leads to a decrease in energy production, an increase in free radical production, and the accumulation of harmful molecules. Several aging phenotypes are exhibited when mitochondrial DNA is studied in animal studies done with mice. When mitochondrial DNA polymerase deletion exists, it is known that the aging process is expedited thereby shortening the lifespan. Aging induces alterations in mitochondrial morphology as well as functional impairments. It further reduces ATP generation and therefore elevates oxidative stress (Trifunovic A., 2004 and Balaban RS., 2005).

9-Free Radical Theory:

Several free radicals—superoxide (O2-) and hydroxyl (OH-) anions, nitric oxide (NO), and peroxynitrite (ONOO-)—that may be inadvertently created during regular metabolic processes cause oxidative damage to organisms. According to the free radical theory, the buildup of these kinds of damage eventually causes aging. The notion is indirectly supported by other findings from animal experiments demonstrating that oxidatively damaged tissue by free radicals, such as lipofuscin, lipid hydroperoxides, malondialdehyde, carbonyl group, and 8-hydroxy-2-deoxyguanosine, was manifested more when the animals were older. If the free radical theory is accurate, providing antioxidants to experimental animals should increase lifespan by reducing the oxidative damage caused by free radicals. However, even though many researchers have attempted to prove the hypothesis, no positive results have been shown yet.Organisms possess various defense systems in order to protect themselves from the toxicity of free radicals. As the primary defense system for the prevention of damage, there are antioxidant compounds including vitamin E, β-carotene, ascorbic acid, and uric acid as well as antioxidant enzymes including superoxide dismutase, glutathione peroxidase, glutathione reductase, DT-diaphorase, and catalase.Lipolytic enzymes (phospholipase A2), proteolytic systems (proteinases and peptidases), and DNA and RNA repair systems (endonucleases and exonucleases) are included in the secondary defense system to remove or repair the damaged products (Beckman KB., Ames BN.,1998 and Croteau DL, Bohr VA., 1997).

10-Cell Death: Necrosis and Apoptosis:

While cellular senescence, or a permanent withdrawal from cell division, may be a mechanism to prevent the development of cancer, cell death may represent another way in which the body protects itself from abnormal cells. Cell death can take two forms including necrosis and apoptosis (Kumar V., *et al.*,2005). Necrosis is thought to result from massive cell injury that

is accidental and is always pathological. An example would be when cells of the heart muscle undergo necrosis because of ischemia, or lack of blood flow, during a myocardial infarction. Apoptosis is more of a controlled cell death, what some call ‘‘programmed’’ cell death, in response to a stimulus. It is thought to be genetically driven. In contrast to necrosis, apoptosis is thought to be physiological and may be a means of ridding the body of unwanted cells. An example of this is seen in the immune system, whereby T lymphocytes undergo cell death in what is thought to be a reaction to the recognition of self-antigens that might cause autoimmune diseases (Troen BR., 2003). Death of neuronal cells is seen in many degenerative diseases, including Alzheimer’s disease.

11-Immune Theory:

Some biologists feel that the nervous, endocrine, and immune systems coordinate all the other systems in the body and that aging is tied to an overall declining ability to deal with stressors (McEwen BS., 2003). Some believe that the master ‘‘biological clock’’ is ultimately in the hypothalamus in the brain and that it is responsible for aging through hormonal pathways. There are decreases in hormones with normal aging, most notably the reproductive hormones such as estrogen and testosterone. There are also decreases in growth factors and in secretions of other hormones that affect the older individual’s ability to deal with stressors such as infection or dehydration.There is evidence that immune function declines with age. The function of T lymphocyte cells declines, increasing the chances of developing infection and cancer. This may be caused by an alteration in cytokines, which are molecules responsible for communication between immune cells.

Cerebral Aging:

In the functional front, cerebral aging is associated with impaired neuro-plasticity. Nevertheless, it has been hypothesized that these anatomical and physiological alterations are the result of gradual homeostatic perturbations affecting the cellular reserves and unbalancing the calcium-dependant nerve signaling (Yankner A., *et al.*,2008).

Furthermore, the senescence of the brain is also associated with modification in several biochemical functions and cumulative damage in cellular components such as DNA, mitochondria and mitochondrial DNA, in addition to the decreasing capacity of regeneration.These damages result in the deterioration of the brain's superior functions, such as memory, speech and cognition and the quality of sleep.

I- **Cerebral Aging Changes:**

As the aging brain is associated with a high risk of neurological disorders and traumatic brain injuries, it becomes essential to comprehend the different mechanisms involved in this process, for therapeutic purposes. As a consequence, many relevant studies were made possible by the development of novel techniques for the scientific study of the nervous system, such as neuroimaging, neurogenetics and neuroproteomics. These studies have highlighted the featured brain changes during aging, including anatomical, functional and metabolic changes, enzymatic and hormonal deregulations; and genetic and epigenetic modifications; in addition to inflammatory processes and oxidative stress. Further, some studies assessed the link between these alterations and the impairment of the cognitive or superior functions of the brain.

A-Anatomical Changes:

The main anatomical sign of a senile brain is the reduction of its global volume, with a frequent predilection for the frontotemporal cortex and some sub-cortical structures such as thalamic nucleai, nucleus accumbens and putamen.

In recent studies, MRI sections showed a loss in the grey matter in the front-parietal-temporal cortices, in the insula and in the superior parietal gyri (Berti V., *et al.,* 2011 and Taki Y., *et al.*,2011). These findings, observed in men as well as in women, lead to further explorations that revealed a similar loss in white matter, at diverse levels across the different brain regions (Sehmidt R., *et al.*, 2011).

Over the years of life, this shrinkage progresses at various rates according to the concerned region of the brain (Beason-Held LL., *et al.,* 2008).

Brain shrinkage is explained by the decline in the size of neurons, synaptic spines and myelinated axons; and the decrease in number of the synapses (Dickstein DL., *et al.,* 2007). Moreover, pyramidal cells of the aging human and primate cortex are subjected to the rarefaction of their dendrites (arborization and spines). In both species, up to 50% loss in spines was observed by electron microscope, in apical dendrites of prefrontal cortex (Barnes CA.,2011).Among the other remarkable changes, objectified in computed tomography, are the cortical atrophy and the enlargement of the ventricles (ventriculomegaly). The cortical atrophy can progress with up to 1.0% per year, as measured by the relative reduction of the cortical line.

Additionally, the brain activity was either raised or declined in old subjects in comparison with young controls, as assessed by functional MRI (Beason-Held LL., *et al.,* 2008); which further showed, in the prefrontal cortex, a reduction in the hemispheric lateralization (Woodard JL.,and Sugarman MA., 2012).

Furthermore, the blood-brain barrier becomes more permeable with aging (Farrall AJ., andWardlaw JM., 2007).

B-Molecular Changes:

Besides structural and anatomical changes, the understanding of molecular changes in cerebral aging and the detection of their corresponding biomarkers are crucial data for the optimal management of brain aging.

1-Chemical Changes:

Several enzymatic and hormonal modifications accompany cerebral aging, along with modifications in levels of neurotransmitters, such as dopamine, glutamate and serotonin; and metabolites.

1-a) Neurotransmitters:

For example, a reduction in the number of dopaminergic neurons results in a gradual decrease in dopamine levels (10% per 10 years) with subsequent cognitive and motor alterations. On the other hand, dopamine receptors are also subjected to a reduction in number and qualitative alteration with impairment of their binding proprieties (Ota M., *et al.,* 2006).

Similarly, reductions in of levels serotonin and glutamate are observed in the aging brain and are responsible for defects in synaptic plasticity (Yamamoto M., 2001 and Chang L., *et al.,* 2009).

Conversely, neurotransmitters regulating enzymes are increased in the cerebral aging process. High levels of monoamine oxidase are observed, for example, resulting in the release of high levels of free radicals overtaking the antioxidant capital (Esiri MM., 2007).

1-b) Hormones:

Hormonal changes have an additional role in cognitive alterations in cerebral aging; either by decline or increase, according to the hormone. Most important hormones subjected to decline, such as growth hormone (GH), melatonin, thyroxine, Dehydroepiandrosterone (DHEA) and both male and female sexual hormones (Veiga S., *et al.,* 2004 and, Schumacher M., *et al.,* 2003). Whereas, cerebral aging is associated with high levels of cortisol, which represents an additional risk of obesity and cardiovascular events, due to its activity as a stress hormone (Lupien SJ., *et al.,* 2009). In the brain, the expression of estrogen intracellular receptors α and β (ERα and ERβ) is regulated by GH and thyroid hormone, in addition to its specific ligand estrogen. In the aging brain, the decline in levels of these hormones impacts estrogen signaling, which is a mechanism highly involved in the impairment of brain structure and function (Thakur MK., Sharma PK.,2006).

Recent studies report an interaction of ERß with mitochondrial and nuclear proteins, within specific sites of casein kinase2, phosphokinase C and N- myristoylation. These interactions interfere with estrogen-dependent gene regulation and could open an interesting therapeutic option (Paramanik V.,Thakure MK.,2012).

1-c) Insulin and Energy Metabolism:

It has been largely reported that the speed of aging is significantly influenced by insulin and insulin-like growth factors (IGFs) (Sonntag WE., *et al.,* 2000). Hyperinsulinism and insulin resistance, more frequent in elderly life are associated with a high risk of dementia, due to the effect of both anomalies on energy metabolism and their negative impact on the integrity of the synapses and on cerebral vascularisation. Additionally, energy metabolism can be further worsened by the reduction of the sugar input in the brain cells resulting from the relatively inefficient vascular network (Cohen E.,Dillin A.,2008). Many studies have observed increased levels of lactate as an early indicator of an aging brain. These studies relate the increased level of lactate to a shift in the lactate dehydrogenase A/B ratio, considering this finding as a hallmark of aging (Ross JM., *et al.,* 2010).

1-d) Oxygen Metabolism:

The aging process is associated with a decrease in cerebral blood flow and oxygen metabolism in all brain regions, along with an increase in oxygen extraction fraction (OEF). It has been hypothesized that these changes are consequent to deactivation of brain tissue in some regions, resulting in declined metabolic demand in oxygen and abnormal raise in OEF.

2-Genetic Changes:

The recent progress in genetics and gene expression studies has brought much enlightenment to the study of cerebral aging. Genomic microarray helped elucidate the corresponding molecular anomalies involved in the cerebral aging alterations, such as stress-related molecules, inflammation and immunity mediators; and mineral molecules homeostasis such as calcium. Moreover, gene expression studies revealed also alterations in mitochondrial functions, growth factors, neuro-cellular vitality and synaptic plasticity.

Specificity Across Species:

Furthermore, comparable age-dependent changes in gene expressions (i.e. upregulation *versus* downregulation) were observed across different species, in studies comparing aging genomes of mice, monkeys and humans (Loerch PM., *et al.,* 2008). Age-upregulated genes included most remarkably apolipoprotein D gene 13, which has antioxidative proprieties and whose upregulation is greater in some neurological diseases such as Alzheimer's. Other genes are concerned with age-upregulation, such as stress-related genes, DNA repair genes and inflammation-related genes; while age-downregulated genes included mitochondrial genes (Yankner A., *et al.,* 2008 and Bishop NA., *et al.,* 2010).

Specificity across Brain Regions:

Other studies showed that these age-dependent changes in gene expression touch more specifically certain brain regions, in comparison with others. In the forebrain, for example, the superior frontal gyrus reveals more gene expression changes than the entorhinal cortex. Hippocampal region CA1 is another region most likely subjected to age-dependent gene alterations, concerning genes in relation to CA3 and the dentate gyrus; whereas immune-response genes and apoptosis genes are enriched (Zeier Z., *et al.,* 2001).

Nevertheless, the frontier of cerebral aging is crossed between the age of 60 and 70 years, as these changes become generalized to the whole cortex.

***Specificity across genders*:**

Sexual dimorphism has been observed in age-dependent changes in gene expression. Males' brains are more likely to be concerned with these gene expression changes, where a global reduction of catabolism and anabolism is observed, as well as a down-regulation of genes related to energy production. It is also observed, in a male's aging brain, a down-regulation of genes related to protein production and transport. On the other hand, a female's aging brain, in comparison with a male's, exhibits higher activation of immunity; though both sexes are concerned by this change in immune activity.

Specificity across Neurons*:*

Beyond being gender-specific and region-specific, age-dependent gene

expression changes show further specificity for certain neurons and glial cells. Studies suggest a large downregulation observed in neuronal-enriched genes related to synapse structural and functional proprieties, calcium regulation, signal transduction and transmembrane receptors. Conversely, there is an up-regulation in glial-enriched genes related to immune response and complement activation, as well as in astrocytic genes; while oligodendrocytic genes are down-regulated (Loerch PM., *et al.,* 2008).

Table 1: Summarizes some examples of age-dependent gene changes in humans.

Category	Example
Genes upregulated	
Stress response	Heat shock 70kD protein 2, mortalin, crystalline alpha B, hypoxia-inducible factor 1α (HOFIα), HIF-1 responsive RTP801, transglutaminase 2, p53 binding protein 2., retinoblastoma-associated protein 140.
DNA repair	8-oxoguanine DNA glucosylase, uracil-DNA glycosylase, topoisomerase 1 binding protein.
Mitochondrial function	Mitochondrial 3-oxoacyl-CoenzymeA thiolase
Inflammatory response	TNF-α, C type lectin, H factor (complement)-1, interferon gamma-inducible protein 16, interferon regulatory factor 7, integrin α5, interginß1.
Growth factors	Vascular endothelial growth factor, FGF receptor 2, FGF receptor 3
Synaptic transmission	SNAP23, synaptophysin-like protein
Myelin-related proteins/ lipid metabolism, growth-associated protein 43 (GAP-43),, activity-regulated cytoskeletal protein (Arc)	Amyloid precursors protein[a], oligodendrocyte lineage transcription factor 2, peripheral myelin protein 22, proteolipid protein 1, fatty acid desaturase 1, apolipoprotein D, low-density lipoprotein receptor-related protein 4, sterol carrier protein 2.
Metal ion homeostasis	Metallothionein IG, metallothionein 1B, metallothionein 2A, haem binding protein 2, haemoglobin β, hephaestin.
Genes downregulated	
Synaptic plasticity	BDNF, neurexin 1, synaptobrevin 1, synapsin II b
Synaptic transmission	(MEF2C
Vesicular transport	GABA vesicular transported (SL32A1), kinesin 1B, sortilin, dynein (DNCH1), dynamin, trans-Golgi network protein 2, Golgi reassembly stacking protein 2, phosphatidylinositol transfer protein β, clathrin.
Neuronal survival	Presenilin (PS) 1[b] MADS box transcription enhancer factor 2C (MEF2C), inositol polyphosphate-4-phosphatasel, inositol 1,4,5 trisphosphate 3 kinase A
Calcium homeostasis	Calmodulin 1 & 3, CAMkinase 11α and IV, calcineurin Bα, ATPase Ca^{2+} -transporting, plasma membrane 2 (ATP2B2)
Mitochondrial function	ATP synthase H+ -transporting mitochondrial F1α1, mitochondrial ribosomal protein L28, S12, cytochrome c synthase, translocase of inner mitochondrial membrane 17A.
Microtubule structure and function	Microtubule associated protein (MAP)1B, MAP2, tau J, RAN binding protein 9
G-protein coupled receptors	Rap2A, re gulator of G protein, signaling 4, G protein q polypeptide (GNAQ)
Protein turnover	ATPase H^+ -transporting lysosomal VI subunit H and A, ubiquitin-conjugating enzyme Ubch5, ubiquitin-conjugating enzyme E2M, ubiquitin carrier protein
Amino acid modification	Protein-L-isoaspartate O-methyltransferase, methionine adenosyltransferase 11α, β-1, 3-galactosyltransferase,s glutamate decarboxylase 1
Kinases and phosphatases	Protein kinase C isoforms (PKCβ1), PKCγ and PKCζ
Stress response	Stress 70 protein chaperone
Hormones	Proenkephalin, somatostatin, cholecystokinin β receptor, chromogranin B (secretogranin 1)
Voltage-gated channels	Voltage-gated Na channel IIb (SCN2BB), voltage-dependent calcium channel b2.
Genes unaltered	
Lipid transport	ApoE
Cytoskeletal elements	βtubulin III, neurofilament L chain,βActin
Glycolytic enzyme	GAPDH

[a] Sivanandam and Thakur 2011 [b] Thakur and Ghosh 2007.

1-Epigenetic Changes:

Along with genetic alterations in the aging brain, epigenetic mechanisms are similarly involved in the process, with alterations in histone and DNA, resulting in additional cellular and physiological perturbations. A study performed in aging rats revealed a downregulation in histone acetylation and in histone acetyltransferase with an upregulation in histone deacetylase 2 (HDAC 2), as concurrent mechanisms in loss of synaptic plasticity and hippocampal dendritic spines (Zeng Y., *et al.,* 2011). The role of brain-derived neurotrophic factor (BDNF) in these alterations was explored and revealed a downregulation in H3 and H4 acetylation in many promoter regions of BDNF gene. Consequently, BDNF expression declines significantly, thus reducing the downstream hippocampal signaling. Reduction of BDNF (as well as trkB receptors) could be prevented by inhibiting HDAC or by activating tfkB receptors with 7 8-dihydrolxyflavone; which increases the expression of BDNF and trkB receptors. Other genes concerned with age-related epigenetic modifications, such as Arc, xif268 and BDNF in the hippocampal region and prefrontal cortex, are involved in cognitive alteration Furthermore, age-dependent changes can be influenced by the dynamic structural changes of chromatin, which could either accelerate or slowdown the consequent alterations. However, studies in this field ambition to identify which of the known mechanisms constitutes the master piece in cognitive alterations.

A- Functional Changes

1- Melatonin and Circadian Cycle:

A-Oxydative Stress and Inflammation in Cerebral Aging:

Alterations in oxidative stress and inflammatory processes as well as mitochondrial dysfunctions participating in normal cerebral aging are also observed, at higher levels, in many age-related neurodegenerative diseases. Therefore, the application of melatonin in treating cerebral age-related pathologies has been explored in several animal experiments and in-vitro models, for its beneficial effects on oxidative stress and inflammation. Some studies even suggest a positive effect of melatonin in retarding physiological cerebral aging, by increasing antioxidant enzymes and reducing inflammatory events, which are important mechanisms in the aging process. On the other hand, the affordability of melatonin and its low toxicity makes it a valuable candidate in the treatment of cerebral aging and age-related neurologic diseases, which is worthy of more research investment.

a.Oxidative Stress:

Cerebral aging is associated with several phenotypic modulations, implying the cut of some specific portions of mitochondrial DNA (Melov S., *et al.,* 1999 and Wei YH., *et al.,* 2002), impaired oxidation homeostasis with decreased antioxidant activity, along with the pro-oxidant environment and impaired immunity (LeBel CP., Bondy SC. ,1992 and Calabrese V., 2000).

Moreover, some amyloid and other material depositions have also been observed in aging brains in healthy people, though these are characteristic of neurodegenerative diseases such as Alzheimer's (Price JL., *et al.,* 1991). The accumulation of such insoluble materials resistant to cellular proteolytic activity affects cellular functions in a similar way to genetic gangliosidoses.

Abnormally high pro-oxidant activity is involved in a big part of age-related cellular and bimolecular changes, especially macromolecules such as proteins, nucleic acids and lipids (Kim R., *et al.,*2006 and Roberts LJ II., *et al.,* 2001). However, the causal relationship of these changes with the supposedly consequent clinical disorders is more difficult to establish. Animal models using α-phenyl-*N-tert*-butyl nitrone (α-PBN), for its spin-trapping activity of free radicals, suggested an improvement of certain cognitive (Sack CA., *et al.,* 1996) and behavioral aptitudes (Butterfield DA., *et al.,* 1996)] that had been lost with the aging process. Other animal models using α-PBN have shown restitution of ischemic changes,

which guided the clinical testing of NXY-059[1] (Disodium 4-[(*tert*-butylimino) methyl] benzene-1, 3-disulfonate *N*-oxide.), an α-PBN derivate, in patients with acute ischemic stroke (Floyd RA., 2006).

b.Inflammation:

Different studies report the association of brain senescence with abnormally high and persistent immune activity, without appropriate stimuli (Terrazzino S., *et al.,* 1997 and Sharman E., *et al.,* 2004); but paradoxically, this immune activity is inefficient or diminished (Sharman KG., *et al.,* 2002) regarding exogenous stimuli and probably also regarding pathogens.In aged rats (Perry VH., *et al.,* 1993) and primates (Sloane JA., *et al.,* 1999), increased activation of the brain microglia has been observed, acting as the brain's macrophages and promoting an adverse inflammatory state. On the other hand, the inactivation of microglia is associated with reduced injury in dopaminergic neurons (Wu DC., *et al.,* 2002).These chronic sub-inflammatory subjects the brain tissue to a noxious environment, resulting in cumulative deteriorations and pathologic modifications, such as amyloid deposits and other insoluble materials.

Moreover, several epidemiological studies observed a reduced incidence of Alzheimer's disease in subjects with extensive use of anti-inflammatory drugs, as well as the use of antioxidant agents, supporting the roles of both inflammation and oxidative stress in brain degeneration (McGeer PL., *et al.,* 2007 and, Pitchumoni SS., Doraiswamy PM., 1998).

c.Mitochondrial Dysfunction:

Mitochondria are the cell respiratory site where oxygen is reduced to water. Consequently, mitochondrial injure results in the production and intra-cytoplasmic dissemination of free and reactive oxidizing radicals, along with an impairment in antioxidant mechanisms (Tian L., *et al.,* 1998). In physiological conditions, about 2% of the utilized oxygen is spared by the reduction process and liberated in an intermediate reactive form (Boveris A, Chance B., 1973). This proportion of reactive forms of oxygen is augmented in the aging cells, as a consequence of a decrease in mitochondrial respiratory functions (Harman D., 2002 and Liu J., Ames BN., 2005). Consequently, aging is associated with increased oxidative stress touching the mitochondrial structures, in the frontline (inner and outer membranes and mitochondrial DNA). In comparison with the nucleus DNA, mitochondrial DNA is more exposed to oxidative damage, as it contains no histones and is fitted with poorer regeneration mechanisms (Mecocci P., *et al.,* 1993). Such alterations are reported to be up to 15 times greater in the brains of old subjects (both human and mice), in comparison with young subjects (Mecocci P., *et al.,* 1997 and Wang E., *et al.,* 1997); which results in inefficient mitochondrial respiration (Sobreira C., *et al.,* 1996).

Several neurodegenerative diseases are associated with mitochondrial injuries and dysfunctions. This has been observed for example in Alzheimer, Parkinson's and Huntington's diseases and amyotrophic lateral sclerosis (Bowling AC., Beal MF., 1995). The latter association could be attributed to the susceptibility of the substantial gria to oxidative stress, because of the latent dopamine oxidative action, leading to selective DNA damage in dopaminergic midbrain neurons (Bender A., *et al.,* 2008). Similarly, mitochondrial DNA alterations are also characteristic of premature aging and are involved in several age-related anomalies (Vermulst M., *et al.,* 2008). It is further hypothesized that altered mitochondria, although dysfunctional, are fitted with a higher division rate (Corral-Debrinski M., *et al.,* 1994), in comparison with normally functional ones; which results in progressive dominion of altered mitochondria, along with aging (Fukui H., Moraes CT., 2009). Dysfunctional mitochondria are also highly involved in cellular programmed death (Kim

R., *et al.*, 2006; Poon HF., *et al.*, 2004 and Skulachev VP., 2006).

B-Melatonin in Cerebral Aging:

Many laboratories studying the pharmacodynamics and pharmacokinetics of melatonin have pointed out its beneficial effect on delaying oxidative process in cerebral aging, after reaching the brain in an unchanged form (Bondy SC., *et al.*, 2002 and Lahiri DK., *et al.*, 2004). One of the supposed mechanisms of melatonin protective action is the stimulation of antioxidant genes in the brain (Kotler M., *et al.*, 1998), explaining probably the reduction in lipopolysacharide (LPS) adverse inflammatory and anxiety-generating effects (Sohal RS., *et al.*, 1993 ; Sewerynek E., *et al.*, 1995 and Clapp-Lilly KL., *et al.*, 2001). Moreover, melatonin reduces the production of free oxygen radicals and interleukins (Clapp-Lilly KL., *et al.*, 2001 and Masilamoni JG., *et al.*, 2008).

Beyond the well-documented improvement of age-related biochemical changes, melatonin is also recognized to improve concomitant behavioral disorders in animal models (Sharman EH., *et al.*, 2002 and Reiter RJ., *et al.*, 2007).

On the other hand, surgical removal of the pineal gland (the main site of production of melatonin) is associated with premature signs of cerebral aging; whereas grafting of this gland delayed the age-related thymic deregulation. The latter effect was also observed after melatonin treatment. (Tian L., *et al.*, 1998; Reiter RJ., *et al.*, 1999 and Provinciali M., *et al.*, 1996).

The actions of melatonin in retarding cerebral aging have been investigated in three big axes, 1) systemic action, 2) specific action on non-pathologic cerebral-aging and 3) specific action on neurological diseases.

B.1. Systemic Action:

Melatonin treatment has been associated with an extended life span (Oaknin-Bendahan S., *et al.*, 1995 and Anisimov SV., Popovic N., 2004), which is mainly a result of its effects on reducing age-related oxidative stress and lipid peroxidation (Caballero B., *et al.*, 2009 and Akbulut KG., *et al.*, 2008). On the other hand, a reduced life span is observed after removal of the pineal gland.

In aged mice, melatonin was able to regenerate the reproductive cycle (Diaz E, *et al.*, 2000) and enhance the body's immune system (Akbulut KG., *et al.*, 2001). In addition, high levels of melatonin are associated with lesser damage to the DNA of different tissues of the organism, in correlation with a decrease in age-related oxidative stress (Morioka N., *et al.*, 1999). Altogether, these data suppose that the positive effect of melatonin in aging is not restricted to the brain.

B.2. Specific Action on Non-Pathologic Cerebral Aging:

As previously reported, melatonin improves the regulation of inflammatory and immune responses, both altered in non-pathologic aging of the brain. In addition, dietary melatonin delivered as a chronic treatment was associated with reduced age-related memory deficit and vascular changes, along with a reduction in the amyloid and lipofuscin deposits (Matsubara E., *et al.*, 2003 and Abd El Mohsen MM., *et al.*, 2005).

B.3. Specific Action on Age-Related Neurological Pathologies:

Animal models investigating several age-related neurologic diseases, such as Parkinson's and Alzheimer diseases, have reported the favorable effects of melatonin in these diseases. These effects are more significant after chronic administrations of exogenous melatonin, starting prior to the overt symptoms of the disease. For example, to correctly prevent Alzheimer's disease, melatonin-therapy should start long before the apparition of characteristic amyloid plaques (Quinn J., *et al.*, 2005). In Parkinson's disease, melatonin action results in the preservation of dopaminergic neurons by reducing lipid peroxidation and free oxygen radicals; and also the inhibition of auto-oxidation of L-DOPA (Mayo JC., *et al.*, 2005 and Rocchitta G., *et al.*, 2006).

In addition, ischemic brain diseases and their functional and anatomical outcomes are also improvement by melatonin, through its antioxidant action that counteracts the

oxidative reaction following the ischemia/reperfusion event. Some studies of brain ischemic episodes report a reduction in neuronal necrosis and in neurologic deficits, with melatonin (Cervantes M., *et al.,* 2008)], even administered 24 hours after the ischemia (Kilic E., *et al.,* 2008).

In sum, we could say that melatonin has three big target actions:

a) Reducing oxidative damage to macromolecules,
b) Regulating adverse inflammation,
c) Improving adverse hyperexcitation.

All of these targets are important and common features of age-related changes and neurologic diseases.

A. ***Mechanisms of Action of Melatonin in Cerebral Aging***:

C.1. Antioxidant Action:

All multi-cellular organisms are fitted with melatonin, as well as bacteria and fungi. It is hypothesized that the first function of melatonin in primal organisms was anti-oxidation (Hardeland R., Poeggeler B., 2003). This propriety is observed at the tissue level (in-vitro) as well as at the organism level.

There are two possible anti-oxidant effects of melatonin: direct and indirect effects. The direct effect implies direct scavenging of free oxygen radicals and was actually observed in isolated cell-free models (Beyer CE., *et al.,* 1998 and Tan DX., *et al.,* 2002). The indirect effect suggests a pro-oxidant action of melatonin (Bondy SC., *et al.,* 2002 and Buyukavci M., *et al.,* 2006). However, the relatively low concentrations of melatonin in the brain, as compared with other leading antioxidants such as glutathione and α-tocopherol, suggest that the direct anti-oxidant effect of melatonin on free oxygen radicals is accessory (Lahiri DK., *et al.,* 2004 and Ferrari E., *et al.,* 2008).

2- Cognition, Emotion and Memory:

A.Cognition:

Cognitive disorders are probably the biggest concern of authorities and medical societies regarding the issue of population aging. These disorders constitute big handicaps, with multi-dimensional repercussions on the individual, family, heath care providers and economy. Therefore, several studies aim to find solutions for successful cognitive aging, a non-consensual concept characterized by a beam of genetic and bio-cellular markers. Moreover, neuro-imaging has brought precious indications on cognitive aging (Yaffe K., *et al.,* 2010).

On the therapeutic side, cognitive stimulation, along with dietetic, environmental and lifestyle measures reveal efficient to prevent major age-related disorders and to grant a successful cognitive aging.

However, beyond the absence of cognitive disorders, successful cognitive aging (SCA) was defined as "the development and preservation of the multi-dimensional cognitive structure that allows the older adult to maintain social connectedness, and ongoing sense of purpose, and the abilities to function independently, to permit functional recovery from illness and injury, and to cope with residual cognitive deficits.'' (Cognitive and Emotional Health Project. National Institutes of Health., US. 2006). Even if there is no consensus regarding this definition yet, what is irrefutable is that an accurate assessment of SCA takes a multi-parameter investigation, including as many parameters as the respective factors of each dimension concerned with cognition (Colin A., *et al.,* 2012).Operationally, the multi-parameter assessment of SCA should refer each elementary result to either a respective predefined threshold, a normative scale, or to the anterior individual results. This implies the designation of cut-off measures, age-related scales and variance and rate curves, as per the studied parameter.

As an example, the Mini-Mental Status Examination test was among the parameters relative to cognitive skills and was proposed with a cut-off of 24 for diagnosing SCA. Other neurocognitive tests are proposed with comparison to healthy population median scores, which constitutes a more relevant approach, with respect to limitations in generalizing the "normality" scores.

Comparison to anterior individual results may also be a relevant approach as

maintaining personal performances with aging is the key objective in SCA, which constitutes the very concern of the subject. Yaffe et.al. reported that the maintain of cognitive performance at the ages of 80 and 90 years is associated with less disability and death (Yaffe K., *et al.,* 2010). However, the main limitation of the latter approach is the difficulty to acquire longitudinal data for the whole population; as cognitive tests are rarely requested outside a suspicion of a cognitive decline, in which case the comparison would be biased.

1.Genetic Determinants of SCA:

Several studies have investigated the effect of genetic factors on the cognitive outcome of cerebral aging. In 1998, Finkel and his collaborators demonstrated that more than 50% of age-related cognitive decline is explained by genetic background and that this proportion is augmented to up to 80% in premature cognitive decline (Gurland BJ., *et al.,* 2004). In opposition to genetic factors, authors suggested that the involvement of environmental factors in cognitive decline increases with age and becomes more important than genetic factors (Finkel D., *et al.,*1998). In 2004, in a study comparing two groups of monozygotic and dizygotic twins (n= 1,384 and 1,337 respectively), Gurland's team concluded to up to 25% of aging-related brain functional deficiencies were attributed to genetic factors (Glatt SJ., *et al.,* 2007).

Further, besides the cognition-specific phenotype, genetics may also indirectly involve cognition, engaging genes related to cardiovascular risk factors, genes related to inflammatory activity, or genes involved in cellular growth and signaling (Glatt SJ., *et al.,* 2007).

A recent study from Zubenko (2007) using a genome-wide association identified about 16 markers associated with SCA, though the model was not gender consistent (Zubenko GS., *et al.,* 2007).

Further genetic explorations of successful cognitive aging have exposed the role of mitochondrial DNA and epigenetic, such as DNA methylation. The epigenetic model has the advantage to enable intricate processes between both environmental and genetic factors and the interaction between them. One of the epigenetic mechanisms involved in cognitive aging is the regulation of the telomere, which is likely to be associated with cellular aging. Indeed, short telomeres are associated with accelerated aging and correlate with higher levels of environmental stress (Aviv A., *et al.,* 2003). On the other hand, longer telomeres have been associated with better scores on Mini-Mental Status Examination (Atzmon G., *et al.,* 2010).

2.Stress Factor:

Stressful events are more frequent and long-lasting in adulthood than in youth, due to the life circumstances. However, there is notable variability in individual response to stressors and their psychological impact, whose further consequence on cognition has been investigated for decades.

Chronic stress has the potential of impacting several physiological processes which can trigger sub-pathological status resulting in neuronal injury. Stress is an important stimulator of cortisol secretion, through the Hypothalamic-Pituitary-Adrenal axis; and consequent hypercortisolism is responsible for several lesions in disposed cerebral regions, such as the hippocampus. Moreover, stress can stimulate the secretion of inflammatory cytokines and suppress the immune response, which represents an additional risk factor for brain damage (McEwen BS., 2000).

Inter-individual variability in vulnerability to stress could be partially explained by some genetic factors, such as the carrying of the 5HTT short allele, which is associated with higher levels of cortisol and increased reactivity to stress (O'Hara R., Hallmayer JF., 2007). This may be a relevant pathophysiological ground for the association between anxiety and depression with age-related cognitive decline.

On the other hand, resilience faculties, also different across individuals, could be very helpful against the cognitive impact of stress and might represent a very optimistic therapeutic perspective.

3.Brain Reserve and Cognitive Reserve:

Brain reserve is characterized by the aptitude of the brain to maintain optimal functionality after age-related damage, such as physiological aging shrinkage of some cerebral structures and also white matter tract disorganization. A good brain reserve implies a reduced cognitive impact of neuronal damage and the necessity of consequent damage to affect the cognitive functions of the brain. This concept was mostly suggested to explain the absence of Alzheimer's disease in some individuals whose brains revealed all the traits of the disease, in post-mortem examination, including characteristic amyloid deposits and neurofibrillary tangles (Snowdon DA., 2003). Anatomically, brain reserve may correspond to a larger brain volume, with a bigger amount of neurons and extended synapses. It has been demonstrated that a larger cranial circumference is associated with a reduced impact of cerebral atrophy on cognition in Alzheimer's patients (Perneczky R., *et al.,* 2010).

Conversely, cognitive reserve is characterized by active compensatory functions of the brain that aim to palliate a certain structural deficit. Functional neuro-imaging has revealed some of these spectacular activities, by showing reduced lateralization of brain signaling in the prefrontal lobe of old subjects, while performing an intellectual task. These observations suggest the solicitation of more neuronal resources by aging brains, in comparison to younger controls, in order to appropriately perform the assigned task. Moreover, supporting the previous observation, the Scaffolding Theory of Aging Cognition (STAC) suggests the development, with age, of alternative neuronal connections that aim to uphold or reinforce some specific cognitive functions (Park DC., Reuter-Lorenz P.,2009).

4.Wisdom:

Unlike memory and processing faculties, wisdom is a cognitive faculty that is generally enhanced with age. Although it lakes of neurobiological characterization, wisdom attracts scientific curiosity as it was correlated to superior cognitive outcomes in old age. In 2010, Jeste surveyed several experts on wisdom, in an attempt to end a consensual conceptualization of wisdom and concluded that wisdom is a form of sophisticated cognitive and emotional skills, specific for humans, enhances with age and could be acquired through life experience and learning (Jeste DV., *et al.,* 2010). In further collaborative works, Jeste has attempted to put forward a neurobiological definition of wisdom and suggested the following criteria: 1) sociability and pro-social behavior; 2) pragmatism and social decision-making; 3) emotional stability; 4) meditation and self-understanding; 5) tolerance and relativism and 6) recognition of uncertain and ambiguous situations and efficient coping with them.Consequent neuro-biochemical theories have been suggested by authors, including the congruent actions of multiple neurotransmitters, such as dopamine in self-control, serotonin in sociability, norepinephrine in stress management and decision making and oxytocin in social cognition.

Furthermore, with the help of neuro-imaging, authors attempted to localize the brain region involved in the wisdom process; and suggest the interaction between the dorsal Anterior Cingulate Cortex (ACC), Orbitofrontal Cortex (OFC) and Medial Prefrontal Cortex (MPFC) with the lateral prefrontal cortex (PFC). All of these three brain regions are involved in pro-social attitudes and behaviors; and their cooperation has a remarked role in inhibiting many brain regions, such as the amygdala, and ventral striatum, linked to emotive reactions and immediate reward dependence (Colin A., *et al.,* 2012).

5.Lifestyle Factor:

Lifestyle and life conditions have an important role in aging, in general, and in cerebral aging. Regular physical exercise, a healthy diet and appropriate cognitive stimulation are all assets that allow successful cognitive aging.

a) Regular physical activity:

Physical activity has many known

positive effects on health, such as a reduction in mortality and cardiovascular events and motor disabilities. Besides these effects that can indirectly influence cerebral aging, physical activity is associated with a reduced incidence of senile dementia (Larson EB, Wang L.,2004), and increased cognitive performance (Kramer AF., *et al.,* 2006). Other studies showed an increase in cerebral white and gray matter after only one year of regular aerobic exercise even initiated at late age (Colcombe SJ., *et al.,* 2006). Such observations could be explained by the decrease in oxidative stress and inflammatory activity (Fontana L., *et al.,* 2010), which are remarkably reduced by physical activity.

b) Healthy Diet:

Dietary restriction is recognized to expand longevity and has caught a huge scientific and popular interest. A limitation of only a third of the usual food ration could increase life span, as it was associated with up to 40% increase in rodents' life span (Fontana L., *et al.,* 2010). Moreover, food restriction is also associated with improvement in cognitive faculties, including memory (Witte AV., *et al.,* 2009). One of the supposed mechanisms to explain the effect of food restriction effect on cognitive performance is the reduced oxidative stress resulting from a decreased metabolism. Besides food restrictions, no further evidence has been presented for the supposed beneficial effect of some particular nutriments, such as Ginko Bilboa or fish oil, despite the popular ideology. Conversely, a diet with poor vitamins, especially vitamins D, K and B12, is associated with an increased risk of cognitive decline (Colin A., *et al.,* 2012).

c) Cognitive stimulation:

The effect of cognitive stimulation on the maintenance of cognitive performances with age has been demonstrated in several studies. However, bigger investment in activities with less cognitive stimulation is associated with an increased risk of dementia. There emerged the concept of "use it or lose it". Nevertheless, it is not objectively possible to quantitatively measure the cognitive stimulation for each activity; whereas, for the same activity stimulation level may differ from one individual to another (Colin A., *et al.,* 2012).

In 2006, Willis and his team accomplished one of the largest retrospective trials assessing the effect of cognitive training, called "ACTIVE", and concluded a significant improvement in cognitive performance (Willis SL., *et al.,* 2006). Some of these observed improvements were maintained up to 5 years after the study.

A.Emotion:

In physiological conditions, emotional aging, including emotional expression, is characterized by stability; regardless of some impaired perception of emotional stimuli. However, some studies report a particular reduced stimulation of the autonomic nervous system (ANS) in reply to negative emotions, in aging, along with a modified response of the CNS to the same stimuli (Alfred W., *et al.,* 2012). The latter modifications are characterized by a hyper-activation of the prefrontal cortex and a hypo-activation of the amygdale. Investigation of emotion-related memory and attention in aging concludes with a weakened negativity effect in old subjects (i.e.processing of negative emotional stimuli); and, on the other hand, an improved positivity effect (processing of positive emotional stimuli). These physiological changes have been explained within a socio-emotional theory, as the consequence of a tendency of the aging individual to invest more in steady relationships, providing such an emotional "security" and bringing positive social experiences. Nevertheless, these characteristics of physiological emotional aging are accompanied by structural modifications in the brain region involved in emotion.Observational studies agree that aged individuals present less emotional distress than younger controls, in both terms of frequency and severity. However, this diminution of emotional response seems not linked to a diminished consciousness regarding emotional stimuli.

a) Emotional Perception:

Some past studies reported rather a

diminished perception of visual and auditory emotional stimuli in old persons (Malatesta CZ, *et al.*, 1987 and Oscar-Berman M., *et al.*, 1990). More recent studies suggest a relative difficulty in older adults to discriminate between emotion-related facial and body expressions and tones of voice (Rufman T,, *et al.*, 2008 and Ryan M,, *et al.*, 2010). However, these modifications may be related to the use of larger neocortical networks, by older adults, in the processing of emotional faces (Tessitore A, *et al.*, 2005), and do not forcibly imply a diminished emotional experience.

Furthermore, it was noted that these observations concerned mostly negative emotions, such as sad, fear and anger facial expression (Mathersul D., *et al.*, 2009 and Slessor G., *et al.*, 2010). This may converge with the previously mentioned positivity effect observed in older persons, versus the younger adults who, on the opposite, show a predilection for negative emotional stimuli (Murphy NA., Isaacowitz DM., 2008).

However, it is to note that most of these studies use for the assessment a selection of emotional images, such as those provided by the International Affective Picture System (Lang PJ., *et al.*, 2005) or the POMS (Profile of Mood State) questionnaire (McNair DM, *et al.*, 1992), which are scaled according to the young adult perception.

b) Emotional Expression:

There are differences between emotional expressions in older versus younger adults pointed out by several studies. These studies used different assessment criteria, such as the facial expressions or the electric recording of facial muscles activity, by EMG, in response to emotional stimuli. The authors agree to draw the conclusion that, similarly to emotional experience, emotional expression is likely not affected by aging.

c) ANS, CNS and age-related emotional change:

ANS reactivity to emotion is likely to be reduced in older adults, in comparison with younger ones. A study by Levenson et.al. showed, in parallel with a reduced facial expression, a significant decrease in ANS activity indices (heart rate and finger temperature), in response to emotional stimuli, in comparison with the younger group (Levenson RW., *et al.*, 1991). Moreover, the emotion-related change in cardiovascular activity (as reflected in ANS activity) was also diminished in older persons, regardless of the negativity or positivity of the emotional stimuli, including the recall of negative memories and conflict situations (Tsai JL., *et al.* 2000 and Levenson RW., *et al.*, 1994). These findings suggest a greater ability of older persons to regulate emotion. However, an increase in systolic blood pressure was reported by Uchino in similar conditions (Uchino BN., *et al.*, 2010).

Comparative studies in functional MRI have also shown significant age-related differences in the activation of CNS regions in response to emotional stimuli. Reduced activation of the amygdala region and greater activation of the prefrontal cortex were reported (Gunning-Dixon FM., *et al.*, 2003). This is likely to contrast with the structural alterations, predominating in the frontal region and sparing more the amygdala (Raz N.,2000 and Grieve SM., *et al.*, 2005). To elucidate this intriguing contradiction, Mather suggested a greater regulating activity of the prefrontal brain, to suppress the emotion-related activation of the amygdala. Other researchers have used electroencephalograms to examine the brain's electric potential changes in response to neutral, negative, or positive emotional stimuli (Wood S., Kisley MA.,2006). These observations found decreased potentials in older adults for both positive and negative emotional stimuli (IAPS images for this study), as compared to younger controls, still with the absence of the negativity effect in the older group.

Comparable findings were reported in other functional MRI studies examining connectivity, emphasizing this reduced negativity effect in older individuals without an analogous reduction in amygdala activation (St Jacques P., *et al.*, 2010). Furthermore, analysis of the functional connectivity of the right amygdala, which is the structure of the brain implicated in threat

vigilance, with the rest of the brain structures has shown greater connectivity between this structure and the ventral cingulated cortex, in older adults in comparison with the younger. The authors explained this greater connectivity with the anterior structures as the probable reflect of the emotional regulation increasing with age. On the other hand, the connectivity of the right amygdala with the posterior regions of the brain was diminished in the older group, suggesting a weaker emotional perception.

Altogether, these observations support the aging-related physiological resistance against negative emotion experiences.

B-Memory:

Memory disorders constitute a major health problem in aging, as well as in several neuropsychiatric diseases, such as Alzheimer's disease. Therefore, the elucidation of the neurobiological processes of memory defects related to aging is essential to develop appropriate and efficient therapeutic or preventive measures.

Because of the existence of different types of memory, results from animal models could not be always generalized to humans.

The first type of memory touched by aging-related disorders is short-term memory (STM), which constitutes a capital ability of the brain that interacts with several cognitive skills. The thorough conceptualization of STM in humans is not applicable to animals, which represents an obstacle to the progression of research in this specific field (Aline Marighetto, *et al.,* 2012).

Conversely, a declarative component of long-term memory (D-LTM) is subjected to more deterioration in normal aging and early stages of Alzheimer's disease. D-LTM is involved in conscious events, their verbal formulation and their location in time and space (Squire LR., Zola SM.,1996 and Cohen NJ., *et al.,* 1997).

However, unfortunately, the cellular and bio-molecular mechanisms involved in each concerned brain region or in inter-region connectivity related to memory are not elucidated enough (Aline Marighetto, *et al.,* 2012). Therefore, it is still difficult to comprehend the pathological mechanisms of aging-related memory disorders and to draw relevant therapeutic perspectives.

2- Mobility:

Walking ability disorders constitute an important public health issue, with high prevalence in old ages that my reach 35% in individuals over 70 years and more than half of individuals over 85 years old (Rosso AL., *et al.,* 2013). These disorders result in limitations of mobility and dependence, which may considerably affect the quality of life or lead to frequent hospitalizations. Moreover, walking disabilities and their consequent repercussions are associated with a high risk of falls and premature death (Guralnik JM., *et al.,* 2000 and Segev-Jacubovski O., *et al.,* 2011).

Despite the demographic, economic and medical importance of the issue of walking disabilities, the underlying mechanisms are still not elucidated sufficiently to provide evidence-based management guidelines (Rosso AL., *et al.,* 2013).

Research on walking disabilities has primarily focused on locomotive system determinants or further components of certain specific neurologic diseases. However, recent studies have thrown light on the role of cerebral processes involved in walking; and consequently, in aging-related walking disabilities. Brain control of mobility is discovered to be interrelated with cognition, as demonstrated in old individuals with no neurological disorder explaining the walking disability and related cerebral changes (Holtzer R., *et al.*, 2006 and Annweiler C., *et al.,* 2012). These observations suggest that aging-related cerebral changes may constitute the main substratum of walking disabilities of the old person, by the alteration of motor regions. Indeed, these disabilities are associated with several cumulative and diffuse alterations of the CNS.

It is to note also that prior studies focusing on peripheral systems, have investigated the consequent effects on CNS plasticity and adaptability, and respective

correlations with other risk factors (Segev-Jacubovski O., *et al.*, 2011; Steffener J., *et al.*, 2012 and Nithianantharajah J., *et al.*, 2009). On the other hand, most of these researches have specifically studied the gait, specifically, though it is not the only aspect of ability; and at the same time, the involvement of the CNS was not explored (Rosso AL., *et al.*, 2013).

Subsequent work has turned to multidisciplinary approaches, such as the initiative of the Gerontological Society of America, in collaboration with the National Institute on Aging and the University of Pittsburgh, who proposed three axes of research:

a) Providing consistent evidence of the role and interactions of CNS with mobility,

b) Investigating neuro-biological and biomechanical mechanisms involved in mobility limitations related to aging,

c) Exploring therapeutic and preventive options, under the light of the previous discoveries.

4- Sensorial Changes and Aging:

A. Audition:

Auditory impairments are frequent in the old population, with up to 50% of hearing loss diagnosed in subjects over 65 years old.The two most common hearing disorders found in older subjects, often associated, are:

1) Irreversible bilateral sensorineural disorders, concerning high-tones; mostly resulting from alteration of the auditory nerve.

2) Conduction-deafness, in relation to deterioration in the structures of the outer and or the middle ears.

The clinical manifestation of these abnormalities is difficulty to hear and distinguishing the high-pitched sounds and discriminating speech, especially in low and normal volumes. However, this specific impairment of the high tones usually progresses to a general auditory loss, touching all tones (Nettina, S. M., *et al.*, 2010).

B. Vision:

Aging is characterized by impairment of both central and peripheral visions, respectively related to macular degeneration and a decrease in visual fields.

Similarly, a diminution of the dark adaptation is observed, along with an elevation in the minimal light perception threshold and in the color discrimination.

Moreover, structural changes are observed in the lens, such as cataracts and loss in elasticity, resulting in blurred and double vision, sensitivity to light and impairment in visual accommodation leading to presbyopia.

Other physiological changes of the eye structures and functionality include dry eye by decreased tear production, glaucoma and arcus senilis (lipid deposits around the eye) (Nettina, S. M., *et al.*, 2010).

C. Smell and Taste:

In aging, there is a decrease in olfactory sensitivity and differentiation, due either to sinus disorders or olfactive nerve degeneration. Among the preserved sensitivity are the odors of the fruits. Moreover, women are likely less affected by these modifications than men (Jeste DV., *et al.*, 2010).

Regarding aging-related taste changes, a decrease in taste buds is observed, with mal predominance, reaching up to 80% of loss by age 80.

Factors Accelerating Cerebral Aging:

Age-related changes and subsequent physiological and functional alterations may be influenced by many factors: some accelerating and some delaying, whose recognition could lead to precious therapeutic approaches. Some of these factors are:

1-Hypertension:

Chronic high blood pressure is known to affect the vascular system, notably in the cerebral circulation, resulting in aggravated age-related changes. Indeed, both structural changes, such as hippocampal shrinkage, and cognitive alterations are more prevalent and occur earlier in subjects with uncontrolled hypertension, in comparison with those with controlled hypertension or with normal blood pressure. Moreover, brain regions that are usually spared by age-related changes, such as the primary visual cortex and parietal areas, may present alterations in subjects with

hypertension. It is interesting to note that the expansion rate of these alterations is linearly correlated with systolic blood pressure.

Although there are scarce animal studies to explore neuroanatomical age-related changes correlated to hypertension, naturally hypertensive rats showed elective alterations in their prefrontal areas preventable by antihypertensive treatments (Raz N.,Rodrigue KM.,2006).

2-Stress and Depression:

Age-related cerebral alterations may also involve the stress level, which is conditioned by individual characteristics, either genetic variances in the stress system or differences in exposure to stressors during life. Stress occurring in early life is associated with memory and learning impairment; but develops emotional memory.

It was recently reported that chronic exposure to stress as well as recurrent depression are accelerating factors for cerebral aging.

With aging, telomeres are subjected to shortening, which was proved to be aggravated by inflammation and oxidative stress. Moreover, a measure of telomere length was proposed as a biological marker of aging and assimilated as an indicator of age-related conditions, lifestyle quality and longevity.

A more recent study reports a correlation between recurrent depression and high cortisol levels (standing for chronic stress), with telomere shortness (Wikgren M., *et al.,* 2012).

Cerebral Aging: From Normal to Pathological:

Healthy cerebral aging implies efficient adaptation from neural cells to the changing environment, in addition to competent protective and healing processes to repair consequent damages (Fig.1). Otherwise, degenerative anomalies develop cumulatively, resulting in pathological aging disorders, such as Alzheimer's and Parkinson's diseases.

Among the healing mechanisms are protein chaperones, cytokines, neurotrophic factors and cell survival-promoting proteins, such as antioxidant enzymes, Bck-2 and apoptotic protein inhibitors. Moreover, the integrity of the neuronal genome involves telomerase and DNA repair proteins. Another repair mechanism involves neural stem cell recruitment for the replacement of injured neurons or glial cells.

Pathological aging begins when alterations overpass these protective and restorative mechanisms; an equation that puts in competition other factors like hypoxemia; as well as different genetic and other environmental conditions. Among unfavorable genetic conditions are the mutations in genes of amyloid precursor protein and presenilins, genes of α-synuclein and parkin and genes of huntingtin, androgen receptor and ataxin; respectively responsible for inherited forms of Alzheimer's disease, Parkinson's disease and trinucleotide repeat disorders.

On the other hand, dietetic control, antioxidant supplementation, herbal therapies and physical and intellectual activities seem to boost the neuroprotective mechanisms. Moreover, healthy cerebral aging is also promoted by the hyperproduction of neurotrophic factors and stress proteins, in addition to steroid hormones that support the regulation of neurotransmission, myelination, cell viability and cognitive faculties. The protective role of neurosteroids has been demonstrated in a case-control study involving Alzheimer patients and healthy controls, showing an inverse relation between the level of neurosteroids and Alzheimer biomarkers, such as phosphorylated tau and beta-amyloid peptides (Schumacher M., *et al.,* 2003). Other hormones with a neuroprotective role are estrogen and melatonin.

Finally, we should remark on the regenerative role of the stem cells in replacing the degenerated neurons and glial cells, in the adult brain as well as during cerebral aging.

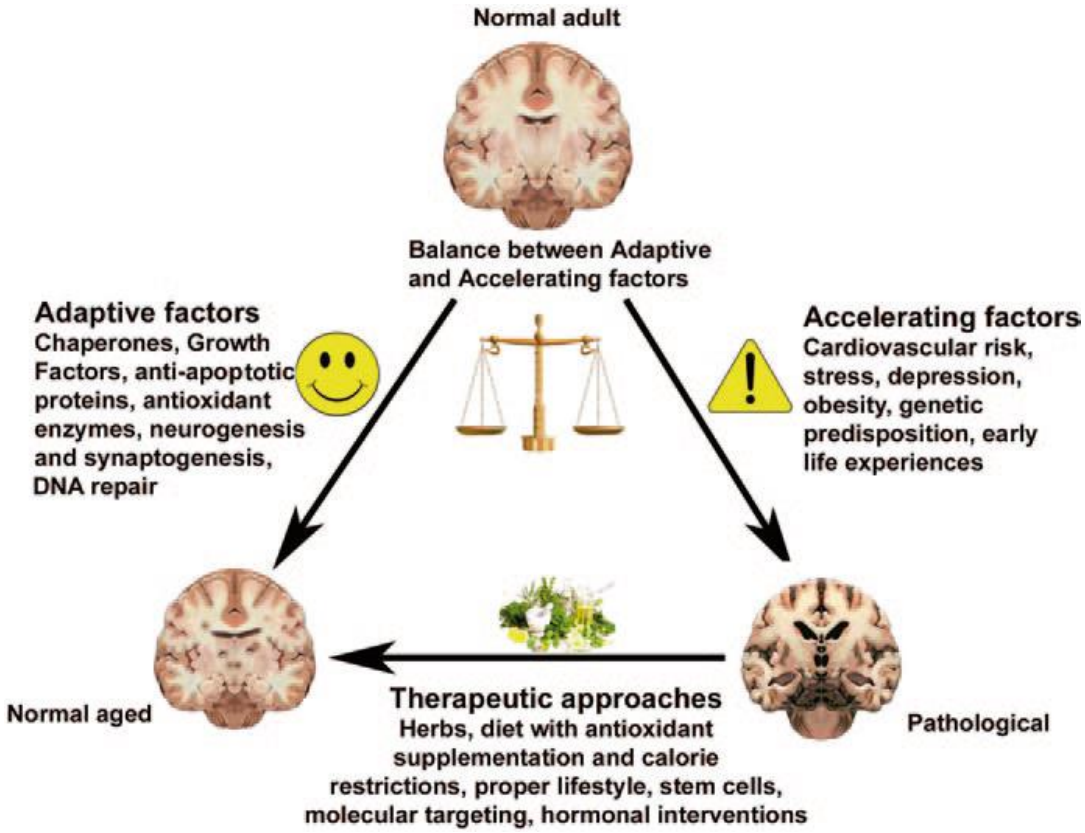

Fig 1: Schematic representation of transition from normal aging brain to pathological brain.

REFERENCES

Abd El Mohsen MM, Iravani MM, Spencer JP, Rose S, Fahim AT, Motawi TM, Ismail NA, Jenner P. 2005.Age-associated changes in protein oxidation and proteasome activities in rat brain: modulation by antioxidants. *Biochemical and Biophysical Research Communications;* 36:386–391.

Akbulut KG, Gonul B, Akbulut H. 2001.The effects of melatonin on humoral immune responses of young and aged rats. *Immunological Investigations,*30:17–20.

Akbulut KG, Gonül B, Akbulut H. Exogenous melatonin decreases age-induced lipid peroxidation in the brain. Brain Res. 2008; 1238:31–35.

Albert MA, Funkenstein HH. 1992. The effects of age: normal variation and its relation to disease. In: Asbury AD, McKhann GM, McDonald WI, editors. Diseases of the Nervous System-Clinical Neurobiology. 2nd ed. Philadelphia: WB Saunders; p.598-611.

Alfred W. Kaszniak and Marisa Menchola. 2012. Behavioral Neuroscience of Emotion in Aging. Behavioral Neurobiology of Aging. Ed. Marie-Christine Pardon, Mark W. Bondi.

Aline Marighetto, Laurent Brayda-Bruno and Nicole Etchamendy. 2012.Studying the Impact of Aging on Memory Systems: Contribution of Two Behavioral Models in the Mouse. Behavioral Neurobiology of Aging. Ed. Marie-Christine Pardon, Mark W. Bondi.

Ames BN, Shigenaga MK, Hagen TM. 1993.Oxidants, antioxidants, and the degenerative diseases of aging. *Proceedings of the National Academy of Sciences (PNAS)* USA,90:7915–7922.

Anisimov SV, Popovic N. 2004.Genetic aspects of melatonin biology. *Reviews in the Neurosciences*; 15:209–230.

Annweiler C, Montero-Odasso M. 2012.Vascular burden as a substrate for higher-level gait disorders in older adults. A review of brain mapping literature. *Panminerva Medica*, 54:189–204.

Atzmon G, Cho M et al. 2010. Genetic variation in human telomerase is associated with telomere length in Ashkenazi centenarians. *Proceedings of the National Academy of Sciences (**PNAS**)* U S A 107:1710–1717

Aujard F, Dkhissi-Benyahya O, Fournier I, Claustrat B, Schilling A, Cooper HM, Perret M. 2001.Artificially accelerated aging by shortened photoperiod alters early gene expression (Fos) in the suprachiasmatic nucleus and sulfatoxymelatonin excretion in a small primate, Microcebus murinus. *Neuroscience;* 105:403–412.

Aviv A, Levy D et al. 2003. Growth, telomere dynamics and successful and unsuccessful human aging. *Mechanisms of Ageing and Development*, 124(7):829–837

Balaban RS, Nemoto S, Finkel T. 2005. Mitochondria, oxidants and aging. *Cell;* 120:483-95.

Barnes CA. 2011.Seerets of aging:what does a normally aging brain look like? *F1000 Biology Reports*, 3:22

Beason-Held LL,Kraut MA,Resnick SM. 2008. Temporal patterns of longitudinal change in aging brain function.*Neurobiology Aging*, 29: 497-513

Beckman KB, Ames BN. 1998.The free radical theory of aging matures. *Physiological Reviews*, 78:547–581. [PubMed]

Bender A, Schwarzkopf RM, McMillan A, Krishnan KJ, Rieder G, Neumann M, Elstner M, 2008.Turnbull DM, Klopstock T. Dopaminergic midbrain neurons are the prime target for mitochondrial DNA deletions. *Journal of Neurology*, 255:1231–1235.

Bernadett M. 2013.Motor imagery training facilitates neural adaptations associated with muscle strengthening in aging. A dissertation submitted to Kent State University in partial fulfillment of the requirements for the degree of Doctor of Philosophy. August, 2013.

Berti V,Mosconi L,Glodzik L,Li Y,Murray J,De Santi S,Pupi A,Tsui W,De Leon MJ. 2011. Structural brain hanges in normal individuals with a maternal history of Alzheimer's. *Neurobiology Aging*, 32:2325e17-2325.e26

Beyer CE, Steketee JD, Saphier D. 1998.Antioxidant properties of melatonin – an emerging mystery. *Biochemical Pharmacology*, 56: 1265–1272.

Bishop NA,Lu T, Yankner BA. 2010.Neural mechanisms of aging and cognitive decline:*Nature*, 464:529-535

Bohr VA, Anson RM. 1995. DNA damage, mutation and fine structure DNA repair in aging. *Mutation Research*, 338:25-34.

Bondy SC, Lahiri DK, Perreau VM, Sharman KZ, Campbell A, Zhou J, Sharman EH. 2004. Retardation of brain aging by chronic treatment with melatonin. *Annals of the New York Academy of Sciences*,1035:197–215.

Bondy SC, Sharman EH. Melatonin and the aging brain. Neurochem Int. 2007;50: 571–580.

Bondy SC, Yang YE, Walsh TJ, Gie YW, Lahiri DK. 2002. Dietary modulation of age-related changes in cerebral pro-oxidant status. *Neurochemistry International*, 40: 123–130.

Bonilla E, Medina-Leendertz S, Diaz S. 2002.Extension of life span and stress resistance of Drosophila melanogaster by long-term supplementation with melatonin.

Experimental Gerontology, 37:629–638.

Boveris A, Chance B. 1973The mitochondrial generation of hydrogen peroxide. General properties and effect of hyperbaric oxygen. *Biochemical Journal*, 134:707–716.

Bowling AC, Beal MF. 1995.Bioenergetic and oxidative stress in neurodegenerative diseases. *Life Sciences*, 56:1151–1171.

Butterfield DA, Martin L, Carney JM, Hensley K. 1996.A beta (25-35) peptide displays H2O2-like reactivity towards aqueous Fe2+, nitroxide spin probes, and synaptosomal membrane proteins. *Life Sciences*, 58:217–228.

Buyukavci M, Ozdemir O, Buck S, Stout M, Ravindranath Y, Savasan S. 2006.Melatonin cytotoxicity in human leukemia cells: relation with its pro-oxidant effect. *Fundamental & Clinical Pharmacology*, 20:73–79.

Caballero B, Vega-Naredo I, Sierra V, Huidobro-Fernández C, Soria-Valles C, De Gonzalo-Calvo D, Tolivia D, Pallás M, Camins A, Rodríguez-Colunga MJ, Coto-Montes A. 2009.Melatonin alters cell death processes in response to age-related oxidative stress in the brain of senescence-accelerated mice. *Journal of Pineal Research*, 46:106–114.

Calabrese V, Bates TE, Stella AM. 2000.NO synthase and NO-dependent signal pathways in brain aging and neurodegenerative disorders: the role of oxidant/antioxidant balance. *Neurochemical Research*, 25:1315–1341.

Cayetanot F, Van Someren EJ, Perret M, Aujard F. 2005.Shortened seasonal photoperiodic cycles accelerate aging of the diurnal and circadian locomotor activity rhythms in a primate. *Journal of Biological Rhythms*, 20:461–469.

Cervantes M, Moralí G, Letechipía-Vallejo G. 2008.Melatonin and ischemia-reperfusion injury of the brain. *Journal of Pineal Research*, 45:1–7.

Chang L,Jiang CS,Ernst T. 2009.Effects of age and sex on brain glutamate and other metabolites. *Journal of Magnetic Resonance Imaging (JMRI)*, 27:142-145.

Clapp-Lilly KL, Smith MA, Perry G, Duffy LK. Melatonin reduces interleukin secretion in amyloid-beta stressed mouse brain slices. Chem Biol Interact. 2001; 134:101–107.

Cohen E,Dillin A.2008.The insulin paradox: aging, proteotoxicity and neurodegeneration. *Nature Reviews Neurosciences* ,9:759-767.

Cohen NJ, Poldrack RA, Eichenbaum H.1997. Memory for items and memory for relations in the procedural/declarative memory framework. *Memory*, 5:131–178

Colcombe SJ, Erickson KI et al. 2006. Aerobic exercise training increases brain volume in aging humans. Journals of Gerontology Series A: Biological sciences and medical sciences, 61(11):1166–1170

Colin A. Depp, Alexandria Harmell, Ipsit V. Vahia. 2012.Successive Cognitive Aging. Behavioral Neurobiology of Aging. Ed. Marie-Christine Pardon • Mark W. Bondi.

Corral-Debrinski M, Horton T, Lott MT, Shoffner JM, McKee AC, Beal MF, Graham BH, Wallace DC. 1994.Marked changes in mitochondrial DNA deletion levels in Alzheimer brains. *Genomics;* 23:471–476.

Croteau DL, Bohr VA. 1997.Repair of oxidative damage to nuclear and mitochondrial DNA in mammalian cells. *Journal of Biological Chemistry (JBC)*, 272:25409–25412.

Cuzzocrea S, Costantino G, Gitto E, Mazzon E, Fulia F, Serraino I, Cordaro S, Barberi I, De Sarro A, Caputi AP.

2000.Protective effects of melatonin in ischemic brain injury. *Journal of Pineal Research*, 29:217–227.

Davies MJ. 2005.The oxidative environment and protein damage. *Biochimica et Biophysica Acta*, 1703:93–109.

Deelen J, Beekman M, Uh H-W, et al. 2011.Genome-wide association study identifies a single major locus contributing to survival into old age; the APOE locus revisited. *Aging Cell*;10(4):686-698.

Diaz E, Pazo D, Esquifino AI, Diaz B. 2000.Effects of ageing and exogenous melatonin on pituitary responsiveness to GnRH in rats. *Journal of reproduction and fertility*,119:151–156.

Dickstein DL,Kabaso D,Rocher AB,LuebkeJI,WearneSL,Hof PR(2007) Changes in the structural complexity of the aged brain,*Aging Cell*, 6:275-284.

Dupuis F, Regrigny O, Atkinson J, Liminana P, Delagrange P, Scalbert E, Chillon JM. 2004.Impact of treatment with melatonin on cerebral circulation in old rats. British Journal of Pharmacology, 141:399–406.

Dupuis K, Pichora-Fuller MK. 2010. Use of affective prosody by young and older adults. *Psychology and Aging*, 25:16–29

Esiri MM. 2007. Aging and the Brain Pathology. The journal of Pathology, 211:181-187. https://doi.org/10.1002/path.2089

Farrall AJ,Wardlaw JM. 2007. Blood brain barrier:aging and microvascular disease-systemic review and meta-analysis. *Neurobiology Aging*, 30;337-352.

Ferrari E, Cravello L, Falvo F, Barili L, Solerte SB, Fioravanti M, Magri F. 2008.Centenarians have good diurnal flux of melatonin: neuroendocrine features in extreme longevity. *Experimental Gerontology*,43:88–94.

Filadelfi AM, Castrucci AM. 1996. Comparative aspects of the pineal/melatonin system of poikilothermic vertebrates. *Journal of Pineal Research*, 20:175–186.

Finkel D, Pedersen NL et al.1998. Longitudinal and cross-sectional twin data on cognitive abilities in adulthood: the Swedish adoption/twin study of aging. *Developmental Psychology*, 34(6): 1400–1413

Floyd RA. 2006.Nitrones as therapeutics in age-related diseases. *Aging Cell;* 1:51–57.

Fontana L, Partridge L *et al*.2010.Extending healthy life span—from yeast to humans. *Science*, 328(5976):321–326

Fraga CG, Shigenaga MK, Park JW, Degan P, Ames BN. 1990. Oxidative damage to DNA during aging: 8-hydroxy-2"-deoxyguanosine in rat organ DNA and urine. *Proceedings of the National Academy of Sciences (**PNAS**)* USA.;87:4533–4537.

Fukui H, Moraes CT. 2009.Mechanisms of formation and accumulation of mitochondrial DNA deletions in aging neurons. *Human Molecular Genetics*,18:1028–1036.

Garthwaite, S., Cheng, H., Bryan, J., Craig, B., & Holloszy, J. 1986. Aging, exercise and food restriction: effect on body composition. *Aging Development*, 36, 187-196.

Glatt SJ, Chayavichitsilp P. *et al.* 2007. Successful aging: from phenotype to genotype. *Biological Psychiatry*, 62(4):282–293

Grieve SM, Clark CR, Williams LM, Peduto AJ, Gordon E. 2005. Preservation of limbic and paralimbic structures in aging. *Human Brain Mapping*, 25:391–401

Gunning-Dixon FM, Gur RC, Perkins AC, Schroeder L, Turner T, Turetsky BI. 2003. Age-related differences in brain activation during emotional

face processing. *Neurobiology Aging*, 24:285–295

Guralnik JM, Ferrucci L, Pieper CF, et al. 2000.Lower extremity function and subsequent disability: consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. Journals of Gerontology Series A: Biological sciences and medical sciences, 55:M221–M231.

Gurland BJ, Page WF et al.2004. A twin study of the genetic contribution to age-related functional impairment. Journals of Gerontology Series A: Biological sciences and medical sciences, 59(8):859–863

Hardeland R, Poeggeler B. 2003.Non-vertebrate melatonin. *Journal of Pineal Research*, 34:233–234.

Harman D. 1981.The agong process. *Proceedings of the National Academy of Sciences (**PNAS**)* U S A; 78:7124-8.

Harman D. 2002.Alzheimer's disease: role of aging in pathogenesis. *Annals of the New York Academy of Sciences; 959:384*–395.

Hausdorff JM, Yogev G, Springer S, Simon ES, Giladi N. 2005.Walking is more like catching than tapping: gait in the elderly as a complex cognitive task. *Experimental Brain Research*, 164:541–548.

Holtzer R, Verghese J, Xue X, Lipton RB. 2006.Cognitive processes related to gait velocity: results from the Einstein Aging Study. *Neuropsychology*.;20:215–223.

Jeste DV, Ardelt M et al. 2010. Expert consensus on characteristics of wisdom: a Delphi method study. *Gerontologist,* 50(5):668–680

Kilic E, Kilic U, Bacigaluppi M, Guo Z, Abdallah NB, Wolfer DP, Reiter RJ, Hermann DM, Bassetti CL. 2008.Delayed melatonin administration promotes neuronal survival, neurogenesis and motor recovery, and attenuates hyperactivity and anxiety after mild focal cerebral ischemia in mice. *Journal of Pineal Research*, 45:142–148.

Kim R, Emi M, Tanabe K. 2006. Role of mitochondria as the gardens of cell death. *Cancer Chemotherapy and Pharmacology;* 57:545–553.

Kokoszka JE, Coskun P, Esposito LA, Wallace DC. 2001.Increased mitochondrial oxidative stress in the Sod2 (+/-) mouse results in the age-related decline of mitochondrial function culminating in increased apoptosis. *Proceedings of the National Academy of Sciences (**PNAS**)* USA.;98:2278–2283.

Korkmaz A, Reiter RJ, Topal T, Manchester LC, Oter S, Tan DX. 2009.Melatonin: an established antioxidant worthy of use in clinical trials. *Molecular Medicine,* 15:43–50.

Kotler M, Rodriguez C, Sainz RM, Antolin I, Menendez-Pelaez A. 1998.Melatonin increases gene expression for antioxidant enzymes in rat brain cortex. *Journal of Pineal Research*, 24:83–89.

Kramer AF, Erickson KI et al. 2006. Exercise, cognition, and the aging brain. *Journal of Applied Physiology*, 101(4):1237–1242

Kumar V, Abbas AK, Fausto N. 2005. Robbins and Cotran: pathologic basis of disease, 7th ed. W.B. Saunders, St. Louis.

Labouvie-Vief G, LumleyMA, Jain E,Heinze H.2003.Age and gender differences in cardiac reactivity and subjective emotion responses to emotional autobiographical memories. *Emotion*, 3:115–126

Lahiri DK, Chen DM, Lahiri P, Bondy S, Greig NH. 2005. Amyloid, cholinesterase, melatonin, and metals and their roles in aging and neurodegenerative diseases. *Annals*

of the New York Academy of Sciences; 1056:430–449.

Lahiri DK, Ge YW, Sharman EH, Bondy SC. 2004.Age-related changes in serum melatonin in mice: higher levels of combined melatonin and 6-hydroxymelatonin sulfate in the cerebral cortex than serum, heart, liver and kidney tissues. *Journal of Pineal Research*, 36:217–223.

Lang PJ, Bradley, MM, Cuthbert, BN. 2005. International affective picture system (IAPS): affective ratings of pictures and instruction manual. Technical report A-6, University of Florida, Gainesville

Larson EB, Wang L. 2004. Exercise, aging, and Alzheimer disease. *Alzheimer Disease & Associated Disorders*, 18(2):54–56

Lass A, Sohal BH, Weindruch R, Forster MJ, Sohal RS. 1998. Caloric restriction prevents ageassociated accrual of oxidative damage to mouse skeletal muscle mitochondria. *Free Radical Biology and Medicine*, 25:1089–1097.

LeBel CP, Bondy SC. 1992.Oxidative damage and cerebral aging. *Progress in Neurobiology*,38: 601–609.

Levenson RW, Carstensen LL, Friesen WV, Ekman P.1991. Emotion, physiology, and expression in old age. *Psychology and Aging,* 6:28–35

Levenson RW, Carstensen LL, Gottman J. 1994. The influence of age and gender on affect, physiology and their interrelations: a study of long-term marriages. *Journal of Personality and Social Psychology,* 67:56–68

Lezoualch F, SparapaniM, Behl C. 1998.N-acetyl-serotonin (normelatonin) and melatonin protect neurons against oxidative challenges and suppress the activity of the transcription factor NF-kappaB. *Journal of Pineal Research*, 24:168–178.

Liu J, Ames BN. 2005.Reducing mitochondrial decay with mitochondrial nutrients to delay and treat cognitive dysfunction, Alzheimer's disease, and Parkinson's disease. *Nutritional Neuroscience,* 8:67–89.

Loerch PM,LuT,Dakin KA,Vann JM,Isaacs A,Geula C,Jianbin W,Pan Y,Gabuzda DH,LiC, Prolla TA,Y ankner BA.2008.Evolution of the aging brain transcriptome and synaptic regulation.*PLoS One*, 3:e3329.

Lupien SJ,McEwen BS,Gunnar MR,Heim C.2009. Effects of stress throughout the lifespan on the brain,behaviour and cognition.Nat Rev Neurosci10: 434-445.

Mailliet F, Ferry G, Vella F, Thiam K, Delagrange P, Boutin JA. Organs from mice deleted for NRH:quinone oxidoreductase 2 are deprived of the melatonin binding site MT3. *FEBS Letters*, 2004;578:116–120.

Malatesta CZ, Izard CE, Culver C, Nicolich M. 1987. Emotion communication skills in young, middle-aged, and older women. *Psychology and Aging,* 2:193–203

Manda K, Bhatia AL. 2003. Melatonin-induced reduction in age-related accumulation of oxidative damage in mice. *Biogerontology*; 4:133–139.

Masilamoni JG, Jesudason EP, Dhandayuthapani S, Ashok BS, Vignesh S, Jebaraj WC, Paul SF, Jayakumar R. 2008.The neuroprotective role of melatonin against amyloid beta peptide injected mice. *Free Radical Research*, 42:661–673.

Mathersul D, Palmer DM, Gur RC, Gur RE, Cooper N, Gordon E, Williams LM.2009. Explicit identification and implicit recognition of facial emotions: IICore domains and relationships with general cognition. *Journal of Clinical and Experimental Neuropsychology* ,31:278–291

Matsubara E, Bryant-Thomas T, Pacheco Quinto J, Henry TL, Poeggeler B, Herbert D, Cruz-Sanchez F, Chyan YJ, Smith MA, Perry G, Shoji M, Abe K, Leone A, Grundke-Ikbal I, Wilson GL, Ghiso J, Williams C, Refolo LM, Pappolla MA, Chain DG, Neria E. 2003.Melatonin increases survival and inhibits oxidative and amyloid pathology in a transgenic model of Alzheimer's disease. *Journal of Neurochemistry*, 85:1101–1108.

Mayo JC, Sainz RM, Tan DX, Antolin I, Rodriguez C, Reiter RJ. 2005.Melatonin and Parkinson's disease. *Endocrine; 27:169*–178.

McEwen BS. 2000. Allostasis, allostatic load, and the aging nervous system: role of excitatory amino acids and excitotoxicity. *Neurochemical Research,* 25(9–10):1219–1231

McEwen BS. 2003. Interacting mediators of allostasis and allostatic load: towards an understanding of resilience in aging. *Metabolism*, 52(10):10–16.

McGeer PL, McGeer EG. 2007.NSAIDs and Alzheimer disease: epidemiological, animal model and clinical studies. *Neurobiology Aging,* 28:639–647.

McNair DM, Lorr M, Droppleman L.1992. EdITS manual for the profile of mood states. San Diego (revised) 64 A. W. Kaszniak and M. Menchola.

Mecocci P, Beal MF, Cecchetti R, Polidori MC, Cherubini A, Chionne F, Avellini L, Romano G, Senin U. 1997. Mitochondrial membrane fluidity and oxidative damage to mitochondrial DNA in aged and AD human brain. *Molecular and chemical neuropathology*, 31:53–64.

Mecocci P, MacGarvey U, Kaufman AE, Koontz D, Shoffner JM, Wallace DC, Beal MF. 1993.Oxidative damage to mitochondrial DNA shows marked age-dependent increases in human brain. *Annals of Neurology*, 34:609–616.

Melov S, Schneider JA, Coskun PE, Bennett DA, Wallace DC. 1999.Mitochondrial DNA rearrangements in aging human brain and in situ PCR of mtDNA. *Neurobiology Aging*,20:565–571.

Mitchell RLC.2007. Age-related decline in the ability to decode emotional prosody: primary or secondary phenomenon? *Cognition and Emotion,* 21:1435–1454

Morioka N, Okatani Y, Wakatsuki A. 1999. Melatonin protects against age-related DNA damage in the brains of female senescence-accelerated mice. *Journal of Pineal Research,* 27:202–209.

Murphy NA, Isaacowitz DM. 2008. Preferences for emotional information in older and younger adults: a meta-analysis of memory and attention tasks. *Psychology and Aging,* 23:263–286

Nava F, Carta G. Melatonin reduces anxiety induced by lipopolysaccharide in the rat. Neurosci Lett. 2001; 307:57–60.

Nettina, S. M., & Lippincott Williams & Wilkins. 2010. Lippincott manual of nursing practice. Philadelphia: Wolters Kluwer Health.

Nithianantharajah J, Barkus C, Vijiaratnam N, Clement O, Hannan AJ. 2009.Modeling brain reserve : experience-dependent neuronal plasticity in healthy and Huntington's disease transgenic mice. *American Journal of Geriatric Psychiatry,* 17:196–209.

O'Hara R, Hallmayer JF.2007. Serotonin transporter polymorphism and stress: a view across the lifespan. *Current Psychiatry Reports*, 9(3): 173–175

Oaknin-Bendahan S, Anis Y, Nir I, Zisapel N. Effects of long-term administration of melatonin and a putative antagonist on the ageing rat. Neuroreport. 1995; 6:785–788.

Ortega V, Phillips LH .2008. Effects of age and emotional intensity on the

recognition of facial emotion. *Experimental Aging Research,* 34:63–79

Oscar-Berman M, Hancock M, Mildworf B, Hunter N, Weber DA.1990. Emotional perception and memory in alcoholism and aging. *Alcohol: Clinical and Experimental Research,* 14:383–393

Ota M,YasunoF,Ito H,SekiC,Kozaki S,Asada T, SuharaT.2006. Age-related deeline o dopamine synthesis in the living human brain measured by positron emission tomography with L-IB-11CJDOPA. *Life Sciences*, I 79:730-736.

Paramanik V,Thakure MK.2012.Estrogen receptor β and its domains interact with casein kinase 2,phosphokinase C and N-myristoylation sites of mitochondrial and nuclear proteins in mouse brain. *Journal of Biological Chemistry (JBC)* ,287; 22305-22316.

Park DC, Reuter-Lorenz P.2009. The adaptive brain: aging and neurocognitive scaffolding. *Annual Review of Psychology,* 60:173–196

Park DC, Yeo SG. 2013. Aging. Korean Journal of Audiology,17(2):39-44. doi:10.7874/kja.2013.17.2.39. Epub 2013 Sep 24. Review.

Payao SL, de Carvalho CV, da Silva ER, Lopes C, Markus RP, Winter LM, Smith MA. 2001.Pinealectomy-associated decrease in ribosomal gene activity in rats. *Biogerontology*; 2:105–108.

Perneczky R, Wagenpfeil S et al. 2010. Head circumference, atrophy, and cognition: implications for brain reserve in Alzheimer disease. *Neurology*, 75(2):137–142

Perret M. 1997.Change in photoperiodic cycle affects life span in a prosimian primate (Microcebus murinus). *Journal of Biological Rhythms, 12*:136–145.

Perry VH, Matyszak MK, Fearn S. 1993.Altered antigen expression of microglia in the aged rodent CNS. Glia; 7:60–67.

Pitchumoni SS, Doraiswamy PM. 1998.Current status of antioxidant therapy for Alzheimer's disease. *Journal of the American Geriatrics Society (JAGS)*, 46:1566–1572.

Poon HF, Calabrese V, Scapagnini G, Butterfield DA. 2004Free radicals and brain aging. *Clinics in Geriatric Medicine*, 20:329–359.

Price JL, Davis PB, Morris JC, White DL. 1991.The distribution of tangles, plaques and related immunohistochemical markers in healthy aging and Alzheimer's disease. *Neurobiology of Aging,* 12:295–312.

Provinciali M, Di Stefano G, Bulian D, Tibaldi A, Fabris N. 1996.Effect of melatonin and pineal grafting on thymocyte apoptosis in aging mice. *Mechanisms of Ageing and Development*, 90:1–19.

Quinn J, Kulhanek D, Nowlin J, Jones R, Pratico D, Rokach J, Stackman R. 2005.Chronic melatonin therapy fails to alter amyloid burden or oxidative damage in old Tg2576 mice: implications for clinical trials. *Brain Research;* 1037:209–213.

Raz N,Rodrigue KM.2006. Differential aging of the brain:patterns,cognitive correlates and modifiers. *Neuroscience & Biobehavioral Reviews,* 30:730-748.

Raz N. 2000. Aging of the brain and its impact on cognitive performance: Integration of structural and functional findings. In: Craik FIM, Salthouse TA (eds) The handbook of aging and cognition, 2nd edn. Erlbaum, Mahwah, pp 1–90

Reiter RJ, Acuna-Castroviejo D, Tan DX, Burkhardt S. 2001.Free radical-mediated molecular damage. Mechanisms for the protective actions of melatonin in the central nervous system. *Annals of the New*

York Academy of Sciences,939:200–215.

Reiter RJ, Tan D, Kim SJ, Manchester LC, Qi W, Garcia JJ, Cabrera JC, El-Sokkary G, Rouvier-Garay V. 1999Augmentation of indices of oxidative damage in life-long melatonindeficient rats. *Mechanisms of Ageing and Development*, 110: 157–173.

Reiter RJ, Tan DX, Manchester LC, Tamura H. 2007.Melatonin defeats neurally-derived free radicals and reduces the associated neuromorphological and neurobehavioral damage. *Journal of Physiology and Pharmacology*, 58 (Suppl 6):5–22.

Roberts LJ II, Reckelhoff JF. 2001.Measurement of F2-isoprostanes unveils profound oxidative stress in aged rats. *Biochemical and Biophysical Research Communications;* 287: 254–256.

Rocchitta G, Migheli R, Esposito G, Marchetti B, Desole MS, Miele E, Serra PA. 2006.Endogenous melatonin protects L-DOPA from autoxidation in the striatal extracellular compartment of the freely moving rat: potential implication for long-term L-DOPA therapy in Parkinson's disease. *Journal of Pineal Research*, 40:204–213.

Ross JM,Oberg J,Brene S,Coppotelli G,Terzioglu M,Pernold K,Goiny M,Sitnikov R,Kehr J,Trifunovie A,Larsson NG,Hoff BJ,Olson L.2010. High brain lactate is a hallmark of aging and caused by a shift in the lactate dehydrogenase A/B ratio. *Proceedings of the National Academy of Sciences (**PNAS**)* USA 107;20087-20092.

Rosso AL, Studenski SA, Chen WG, Aizenstein HJ, Alexander NB, Bennett DA, Black SE, Camicioli R, Carlson MC, Ferrucci L, Guralnik JM, Hausdorff JM, Kaye J, Launer LJ, Lipsitz LA, Verghese J, Rosano C. 2013.Aging, the central nervous system, and mobility. *Journal of Gerontology: Biological Sciences and Gerontology: Medical Sciences,* **Nov**;68(11):1379-86. doi:10.1093/gerona/glt089. Epub 2013 Jul 10.

Rufman T, Henry JD, Livingstone V, Phillips LH. 2008. A meta-analytic review of emotion recognition and aging: implications for neuropsychological models of aging. *Neuroscience & Biobehavioral Reviews,* 32:863–881

Ryan M, Murray J, Ruffman T.2010. Aging and the perception of emotion: processing vocal expressions alone and with faces. *Experimental Aging Research,* 36:1–22

Sack CA, Socci DJ, Crandall BM, Arendash GW. 1996.Antioxidant treatment with phenyl-alphatert-butyl nitrone (PBN) improves the cognitive performance and survival of aging rats. *Neuroscience Letters*, 205:181–184.

Sasaki T, Unno K, Tahara S, Shimada A, Chiba Y, Hoshino M, Kaneko T. 2008.Age-related increase of superoxide generation in the brains of mammals and birds. *Aging Cell*; 7:459–469.

Schumacher M,Weill-Engerer S.Liere P,Robert F,Franklin RJM,Garcia-Segura LM,Lambert JJ.Mayoe W,Melcangi RC,Parducz A,Suter U,CarelliC,Baulieu EE,Akwa Y(2003)Steroid hormones and neurosteroids in normal and pathological aging of the nervous system. *Progress in Neurobiology*,71:3-29.

Sebastià J, Cristòfol R, Martín M, Rodríguez-Farré E, Sanfeliu C. 2003.Evaluation of fluorescent dyes for measuring intracellular glutathione content in primary cultures of human neurons and neuroblastoma SH-SY5Y. *Cytometry Part A*.;51A:16–25.

Sebastiani P, Perls TT. 2012.The Genetics of Extreme Longevity: Lessons from

the New England Centenarian Study. *Frontiers in Genetics.*;3:277.

Segev-Jacubovski O, Herman T, Yogev-Seligmann G, Mirelman A, Giladi N, Hausdorff JM. 2011.The interplay between gait, falls and cognition: can cognitive therapy reduce fall risk? *Expert Rev Neurother*.;11:1057–1075.

Sehmidt R,Schmidt H,Haybaeck J,Loitfelder M,Weis S,Cavalieri M,Seiler S,Enzinger C.Ropele S,Erkinjuntti T,Pantoni L,Scheltens P,Fazekas F,Jellinger K(2011)Heterogeneity in age-related white matter changes, *Aeta Neuropathol* ,122:171-185.

Sewerynek E, Abe M, Reiter RJ, Barlow-Walden LR, Chen L,McCabe TJ, Roman LJ, Diaz- Lopez B. 1995.Melatonin administration prevents lipopolysaccharide-induced oxidative damage in phenobarbital-treated animals. *Journal of Cellular Biochemistry*, 58:436–444.

Sharman E, Sharman KG, Lahiri DK, Bondy SC. 2004.Age-related changes in murine CNS mRNA gene expression are modulated by dietary melatonin. *Journal of Pineal Research*, 36: 165–170.

Sharman EH, Vaziri ND, Ni Z, Sharman KG, Bondy SC. 2002.Reversal of biochemical and behavioral parameters of brain aging by melatonin and acetyl L-carnitine. *Brain Research;* 95:223–230.

Sharman KG, Sharman E, Bondy SC. 2002.Dietary melatonin selectively reverses age-related changes in cortical basal cytokine mRNA levels, and their responses to an inflammatory stimulus. *Neurobiology Aging*, 23:633–638.

Sivanandam TM,Thakur MK.2011. Amyloid precursor protein (APP)mRNA level is higher in the old mouse cerebral cortex and is regulated by sex steroids. *Journal of Molecular Neuroscience*, 43:235-240.

Skulachev VP. 2006.Bioenergetic aspects of apoptosis, necrosis and mitoptosis. *Apoptosis;* 11:473–485.

Slessor G, Miles LK, Bull R, Phillips LH.2010. Age-related changes in detecting happiness: discriminating between enjoyment and nonenjoyment smiles. *Psychology and Aging*, 25:246–250

Sloane JA, Hollander W, Moss MB, Rosene DL, Abraham CR. 1999. Increased microglial activation and protein nitration in white matter of the aging monkey. *Neurobiology Aging*, 20:395–405.

Smith DP, Hillman CH, Duley AR. 2005. Influences of age on emotional reactivity during picture processing. *Journal of the Gerontological Series B, Psychological sciences and social sciences*, 60: P49–P56

Snowdon DA (2003) Healthy aging and dementia: findings from the nun study. Ann Intern Med 139(2):450–454

Sobreira C, Davidson M, King MP, Miranda AF. 1996.Dihydrorhodamine 123 identifies impaired mitochondrial respiratory chain function in cultured cells harboring mitochondrial DNA mutations. *Journal of Histochemistry and Cytochemistry*, 44:571–579.

Sohal RS, Agarwal S, Dubey A, Orr WC. 1993.Protein oxidative damage is associated with life expectancy of houseflies. *Proceedings of the National Academy of Sciences (**PNAS**)* USA.;90:7255–7259.

SonntagWE,Lynch C,Thornton P,Khan A,Bennett S,IngramR.2000. The effects of growth hormone and IGF-1 deficiency on cerebrovascular and brain aging. *Journal of Anatomy, 197*:575-585.

Squire LR, Zola SM.1996. Structure and function of declarative and nondeclarative memory systems. *Proceedings of the National*

*Academy of Sciences (**PNAS**)* U S A 93:13515–13522

St Jacques P, Dolcos F, Cabeza R.2010. Effects of aging on functional connectivity of the amygdala during negative evaluation: a network analysis of fMRI data. *Neurobiology Aging,* 31:315–327

Steffener J, Stern Y. 2012.Exploring the neural basis of cognitive reserve in aging. *Biochim Biophys Acta*.;1822:467–473.

Studenski S, Perera S, Patel K, et al. 2011.Gait speed and survival in older adults. *JAMA*.;305:50–58.

Sullivan S, Ruffman T.2003.Emotion recognition deficits in the elderly. *International Journal of Neuroscience,* 114:403–432

Taki Y, Thyreau B, Kinomura S, SatoK, GotoR,KawashimaR,Fukuda H. 2011.Correlations among brain gray matter volume,age,gender and hemisphere in healthy individuals. *PLos One,* 6:e22734.

Tan DX, Reiter RJ, Manchester LC, Yan MT, El-Sawi M, Sainz RM, Mayo JC, Kohen R, 2002.AllegraM, Hardeland R. Chemical and physical properties and potential mechanisms: melatonin as a broad-spectrum antioxidant and free radical scavenger. *Current Topics in Medicinal Chemistry*, 2:181–197.

Tatar M, Bartke A, Antebi A. 2003.The endocrine regulation of aging by insulin-like signals. Science; 299:1346-51.

Terrazzino S, Perego C, De Luigi A, De Simoni MG. 1997.Interleukin-6, tumor necrosis factor and corticosterone induction by central lipopolysaccharide in aged rats. *Life Sciences*, 61:695–701.

Tessitore A, Hariri AR, Fera F, Smith WG, Das S, Weinberger DR, Mattay VS.2005. Functional changes in the activity of brain regions underlying emotion processing in the elderly. *Psychiatry Research: Neuroimaging,*139:9–18

Thakur MK, Sharma PK. 2006.Aging of brain:role of estrgn. *Neurochemical Research* ,31:1389-1398.

Thakure MK,Ghosh S.2007. Age and sex dependent alteration inpresenilin expression in mouse cerebral cortex. *Cellular and Molecular Neurobiology,* 27:1059-1067.

Tian L, Cai Q, Wei H. 1998.Alterations of antioxidant enzymes and oxidative damage to macromolecules in different organs of rats during aging. *Free Radical Biology and Medicine*, 24:1477–1484.

Trifunovic A, Wredenberg A, Falkenberg M, Spelbrink JN, Rovio AT, Bruder CE, et al. 2004.Premature ageing in mice expressing defective mitochondrial DNA polymerase. *Nature,* 429:417-23.

Troen BR.2003. The biology of aging. *Mount Sinai Journal of Medicine* ,70(1): 3–22

Tsai JL, Levenson RW, Carstensen LL.2000. Autonomic, expressive, and subjective responses to emotional films in older and younger Chinese American and European American adults. *Psychology and Aging,* 15: 684–693 Behavioral Neuroscience of Emotion in Aging 65

Uchino BN, Birmingham W, Berg C.2010. Are older adults less or more physiologically reactive? A meta-analysis of age-related differences in cardiovascular reactivity to laboratory tasks. *Journal of Gerontology:Psychological Sciencs* , 65B:154–162

Veiga S,Melcangib RC,DonCarlosc LL,Garcia-Seguraa LM,Azcoitial I.2004. Sex hormones and brain aging. *Experimental Gerontology*, 39:1623-1631.

Verghese J, Lipton RB, Hall CB, Kuslansky G, Katz MJ, Buschke H. 2002.Abnormality of gait as a

predictor of non-Alzheimer's dementia. *New England Journal of Medicine (NEJM),* 347:1761–1768.

Vermulst M, Wanagat J, Kujoth GC, Bielas JH, Rabinovitch PS, Prolla TA, Loeb LA. 2008.DNA deletions and clonal mutations drive premature aging in mitochondrial mutator mice. *Nature Genetics*, 40:392–394.

Wang E, Wong A, Cortopassi G. 1997.The rate of mitochondrial mutagenesis is faster in mice than humans. *Mutation Research;* 377:157–166.

Wei YH, Lee HC. 2002.Oxidative stress, mitochondrial DNA mutation, and impairment of antioxidant enzymes in aging. *Experimental Biology and Medicine*, 227:671–682.

Weinert BT, Timiras PS. 2003.Invited review: theories of aging. *Journal of Applied Physiology*, 95:1706-16.

Weinert D. 2000.Age-dependent changes of the circadian system. *Chronobiology International*, 17: 261–283.

WikgrenM,Maripuu M,Karlsson T,Nordfjall K,Bergdahl j,Hultdin J,Del-favero J,Roos G,Nilsson LG,Adolfsson R,Norrback KF.2012. Short telomerase in depression and the general population are associated with a hypocortisolemic state. *Biological Psychiatry* ,71:294-300

Willis SL, Tennstedt SL et al.2006. Long-term effects of cognitive training on everyday functional outcomes in older adults. *JAMA*, 296(23):2805–2814

Witte AV, Fobker M et al.2009. Caloric restriction improves memory in elderly humans. *Proceedings of the National Academy of Sciences (**PNAS**) USA*, 106(4):1255–1260

Wong JM, Collins K. 2003.Telomere maintenance and disease. *Lancet*; 362:983-8.

Wood S, Kisley MA.2006. The negativity bias is eliminated in older adults: age-related reduction in event-related brain potentials associated with evaluative categorization. *Psychology and Aging*, 21:815–820

Woodard JL,Sugarman MA.2012.Functional magnetic resonance imaging in aging and dementia:detection of age-related cognitive changes and prediction of cognitive decline. *Current Topics in Behavioral Neurosciences*, 10:113-136.

Wu DC, Jackson-Lewis V, Vila M, Tieu K, Teismann P, Vadseth C, Choi DK, Ischiropoulos H, Przedborski S. 2002.Blockade of microglial activation is neuroprotective in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model of Parkinson disease. *Journal of Neuroscience*, 22:1763–1771.

Xie Z, Morgan TE, Rozovsky I, Finch CE. 2003.Aging and glial responses to lipopolysaccharide in vitro: greater induction of IL-1 and IL-6, but smaller induction of neurotoxicity. *Experimental Neurology*, 182:135–141.

Yaffe K, Lindquist K et al. 2010. The effect of maintaining cognition on risk of disability and death. *Journal of the American Geriatrics Society (JAGS)* ,58(5):889–894

Yamamoto M.2001. Depression in Parkinson's disease: its prevalence, diagnosis, and neurochemica background. *Journal of Neurology*, 248: III5-III11.

Yankner A, LuT, BruceLP.2008. The aging brain. *Annual Review of Pathology: Mechanisms of Disease* ,3:41-66.

Yogev-Seligmann G, Hausdorff JM, Giladi N. 2008.The role of executive function and attention in gait. *Movement Disorders,* 23:329–342; quiz 472.

Zeier Z, Madorsky I, Xu Y, Ogle WO, Notterpek L, Foster TC.2001. Gene expression in the hippocampus; regionally specific effects og aging and caloric restriction. *Mech Angel Development*, 132:8-19.

Zeng Y, Tan M,Kohyama J,Sneddon M,Watson JB,Sun YE,Xie CW.2011. Epigenetic enhancement of BDNF signaling rescues synaptic plasticity in aging. *Journal of Neuroscience*, 31:17800-17810.

Zheng JJ, Delbaere K, Close JC, Sachdev PS, Lord SR. 2011.Impact of white matter lesions on physical functioning and fall risk in older people: a systematic review. *Stroke*.;42:2086–2090.

Zubenko GS, Hughes HB III et al.2007. Genome survey for loci that influence successful aging: results at 10-cM resolution. *American Journal of Geriatric Psychiatry,* 15(3):184–193