CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187

Avalable online at: http://www.iajps.com *Review Article*

AGEING BRAIN AND ITS EFFECT'S - REVIEW

B.Prashanthi*[1], Mr. Veermani[2], A.Madhukar[3]

[1]Assistant Professor, Department of Pharmacy Practice, KVK College of Pharmacy, Telangana, Surmaiguda (V) Lashkarguda (P) Near Ramoji Film City Hayathnagar(M) Rangareddy (Dist)-501512, India.

[2]Assistant Professor, Department of Pharmacy, Annamalai University, Annamalainagar-608002, Tamil Nadu, India.

[3]Associate Professor, Department of Pharmaceutical Analysis and Quality Assurance, MRM College of Pharmacy, Hyderabad, Telangana, 501505, India.

Article Received: December 2020 **Accepted:** January 2021 **Published:** February 2021

Abstract:

As our brains age , we tend to experience cognitive decline and are at greater risk of neurodegenerative disease and dementia. Aging of human brain is most incapacitating with its fallout on quality of life, general health and psychosocial implications.The aging of brain entails several structural biochemical and functional changes in brain as well as various cognitive changes . These changes that may affect on cognition behavior occur at molecular intracellular intercellular and neuronal tissue levels.

As we age, our brain shrink in volume particularly in frontal cortex, as our vasculature ages our BP rises the possibility of stroke and ischaemia increases and our white matter develop lesions, memory decline also occur with ageing and brain activation becomes more bilateral for memory task. While there is a strong evidence from cross sectional studies for a link between sensory acuity and cognitive performance in old age.

Therefore, the genetics, neurotransmitter, hormones all have a part to play in brain ageing the protective factor are healthy diet low moderate alcohol intake regular exercise. There are the most studies have focused on simple sensory measure (visual & auditory) perceptual activities show a link with cognition. The review evidence given the importance of fully accounting for perception deficits and investigating brain decreasing multiple factor including changes in cerebral vasculature , causes cognitive decline.

Keywords: *Alzheimer disease(AD), Mild cognitive impairment(MCI), cognition, perception.*

Corresponding author:

B.Prashanthi,

Assistant Professor,
Department of pharmacy practice,
KVK College of pharmacy,
Rangareddy (dist.)-501 512,Telangana India.
E-mail address: prashu13593@gmail.com

QR code

Please cite this article in press B.Prashanthi et al, ***Ageing Brain And Its Effect's-Review.,*** *Indo Am. J. P. Sci, 2021; 08(1).*

INTRODUCTION:

The aging of the brain is due to pathophysiological changes over the period of individual life span. The effect of ageing on brain and cognition are widespread, ageing has its effect on the molecules, cells, vasculature, morphology of brain and cognition.

As we age our brains shrink in volume in fontal cortex it has been found that the volume of brain and weight are declines with age at the rate of around 5%per decade after age 40(1) with the actual rate of decline possibly increasing with age particularly over age 70(2).The shrinking of grey matter is frequently reported to stem from neuronal cell death(3-4). Additional they may causes changes in dentritic, spines, synapse, dentritic sprouting may occur the maintaining a similar number of synapses(5).

The role of white matter in the ageing brain also need to be considered white matter may decline with age the myelin sheath deteriorating after the age of 40yrs and it has been suggest that myelinating regions of frontal lobes are more affected with white matter lesions(6).

THE AGEING OF BRAIN:

1. Aging is not genetically programmed
2. Aging: Results of cumulative insult over life time
3. The cellular and subcellular alterations due to oxidative stress.
4. Aging : Net result of inflammation, adaptation and neuronal degeneration.

CHANGES OCCUR IN AGEING BRAIN:

As a person gets older changes, occur in all parts of body including the brain. The brain controls many aspects of thinking, remembering, planning, and organizing, making decision, some changes in thinking are common as people get older.

1. Older adults may be slow to find the words and recall the names.
2. Find they have more problems with multitasking
3. Mild decreasing in ability to pay attention.

It may be occur due to certain parts of brain shrink those are important to learning and other mental activities, in certain brain region communication between neurons and blood flow in brain may decreased, brain inflammation which occur when body responds to an injury or diseased may progressed. These changes occur in the brain can affect mental function even in healthy older people.

Despite all the changes in cognition that may comes with age, older adults can still do many of things they have enjoyed their life by doing.

1. Learn new skills
2. Form new memories
3. Improve vocabulary &language skills.

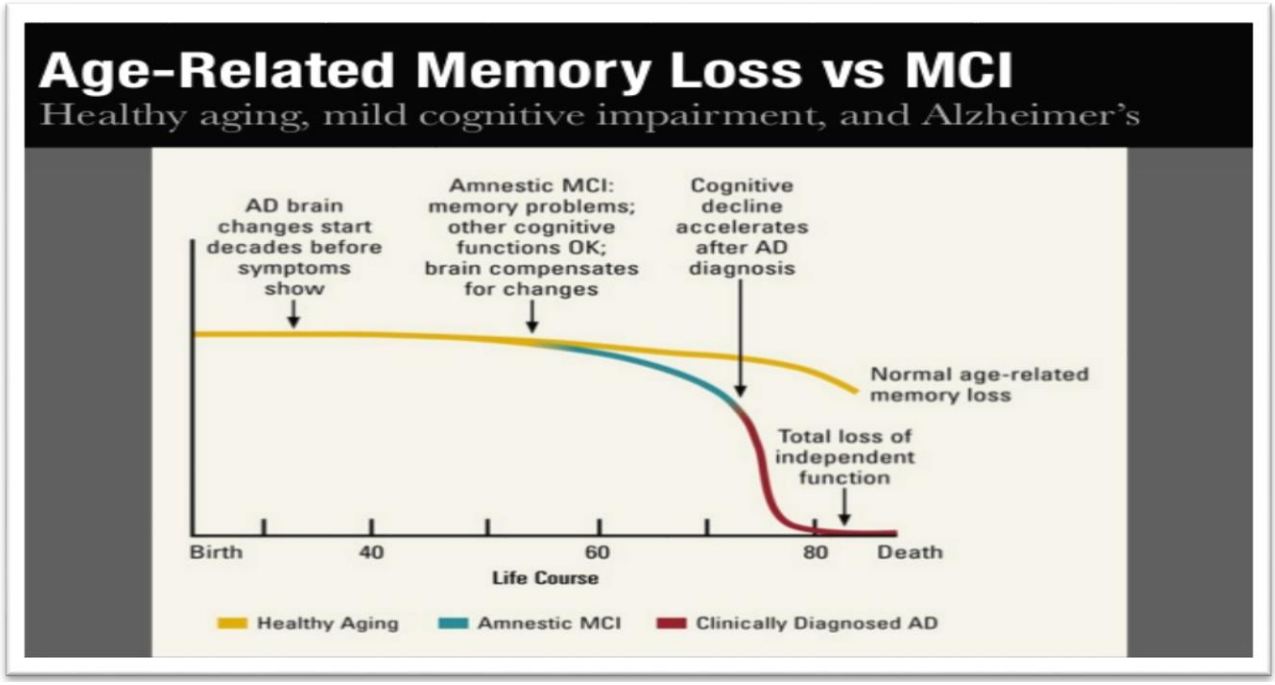
COGNITIVE CHANGES:

The most widely seen cognitive changes associated with ageing is that of memory.Memory function can be broadly divided into 4 sections episodic memory, semantic, procedural and working memory. The first two are most important with regard to aging. Episodic memory in which information is stored with 'mental tags'

For eg: memory would be first day at school, important meetings, lessons
Episodic memory performance is thought to decline from middle age onwards this is particularly true for recall in normal ageing and less so far recognition (7).It is also a characteristic of memory loss seen in Alzheimer's disease(AD)(8).

Semantic memory is defined as'memory of meaning' it increases gradually from middle age to young elderly but declines in very elderly. There have been studies investigating different types of memory in aging using neuro psychological testing and neuro imaging. However, methodological difficult to separate some of there function.
For eg: episodic memory encoding & semantic memory retrieval (9).

It can be focusing in area highlighted the changes in regional brain activation. Older brain tend to show more symmetrical activation, either they have increased activation in a hemisphere that is less activated than in younger adults. This has been shown for visual perception and in memory task. The observed changes in activation in left right prefrontal cortex and changes in memory performance it has been suggested that actual level of brain activation which shown in neuroimaging may be related to level of memory performance(10).



EFFECTS OF AGEING INFLUENCE BOTH PERCEPTION & COGNITION:

Healthy aging can lead to declines in both perceptual and cognitive function such as resulting from hearing loss or reduced visual tactile resolution, sensory system are subject to same molecular, cellular process age related changes willaffect both cognition and perceptual activities [11].

Therefore cognitive functions also decline in old age this means that perceptual impairment are exacerbated by cognitive decline.

For eg: making directions and routes easy to follow compensate for decline in navigation abilities [12].

Therefore common effects of ageing affect both perception and cognition directly impact on each other.(fig 1).

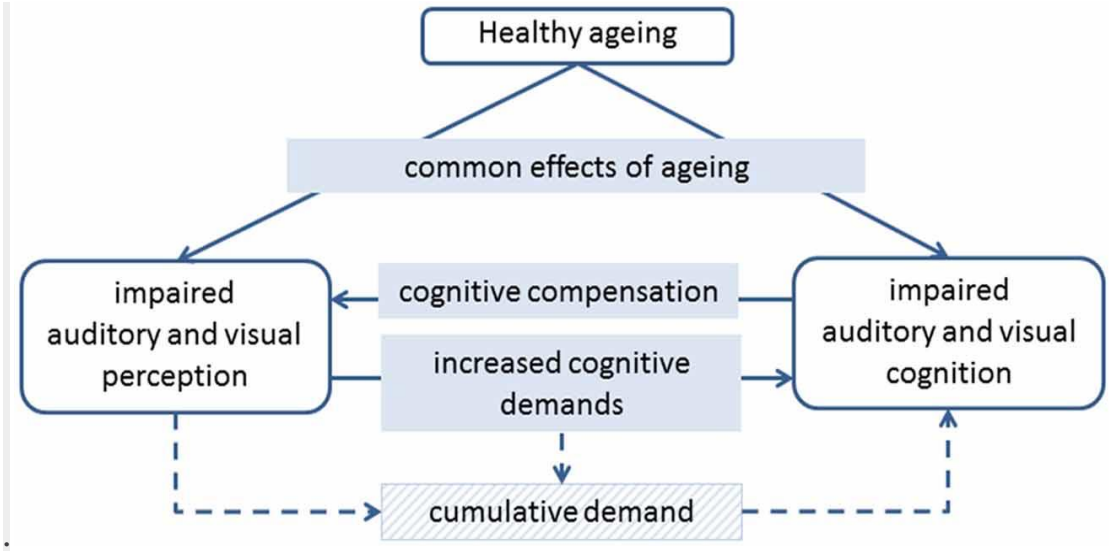


Fig 1: diagram of potential link between healthy ageing and auditory visual perception and auditory visual cognition.

POOR COGNITION AFFECTS ON PERCEPTUAL TASK:

Both perception and cognition are highly interrelated that can measure might be considered entirely sensory such as, audiogram of body is influenced by cognition. (13)

It seems poor cognition drives purely perceptual decline (14) reported that age related problems cause cognition poor perceptual task.

Some of the common signs and adverse effect of poor cognition are

1. Confusion
2. Poor motor co-ordination
3. Loss of short term and long-term memory
4. Identity confusion
5. Impaired judgment

SENSORY IMPAIRMENT WHICH LEADS TO COGNITIVE DECLINE AND MENTAL ILLNESS

The studies have shown that the impaired perception is associated with cognitive decline over a period of time. In old age acquired hearing impairment is known to be associated with psychotic illness (15), and acquired blindness with visual hallucination (Charles bonnet syndrome)

In general population there is an excess of behavioural and emotional difficulties in people with cognizable hearing loss (16).

In people with intellectual disability and sensory impairment studies have indicated an association between sensory impairment and challenging and self-injurious behavior.(17)

For eg: Women with impaired vision at baseline had a faster rate of cognitive decline over 4 yrs period than those without visual impairment (18). In additional found a poor hearing a baseline associated with higher rate of cognitive decline over a 6yrs period (19)

In contrast found a link between visual but not auditory, decline and cognition over a 2 yrs period. (20)

Several mechanisms have been proposed to explain how impaired perception could lead to worsening cognition over time (21) one possibility is that poor perception leads to social isolation found that while hearinf aid use with better cognition, this was not mediated by social isolation. (22)

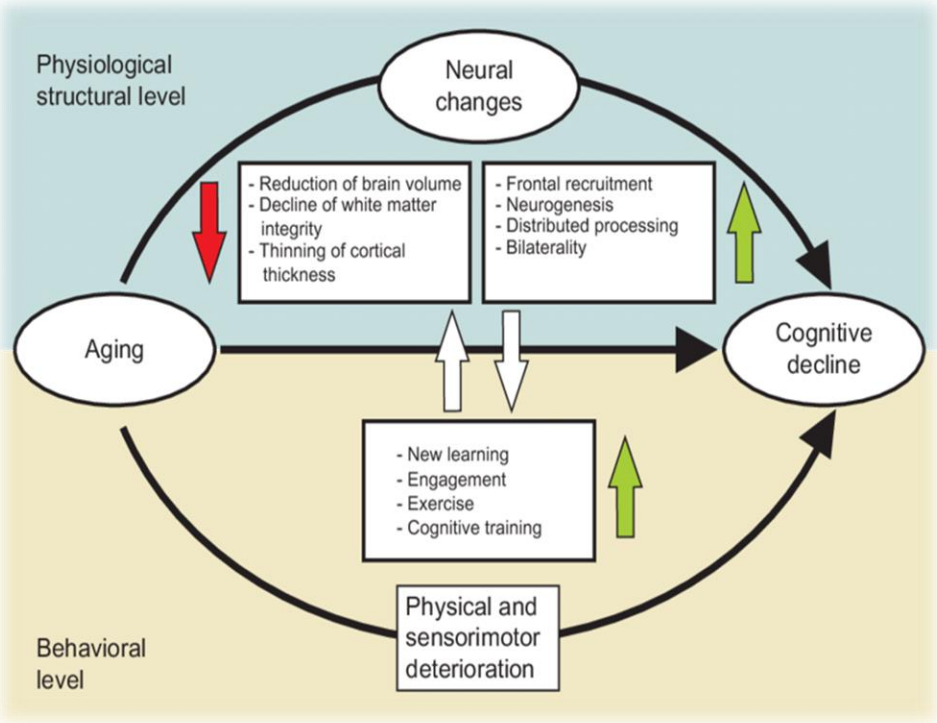


Fig 2: ageing causes neural changes which leads to cognitive decline.

ASSESSMENT:

People with intellectual disability may not be able to report visual and hearing because of difficulties with language and communication. As a result, changes in hearing or vision may present as changes in behavior carer may perceive a person to be non-co-operative when in reality they cannot hear or see properly. (23) Research also shows that 30% of people with intellectual disability and hearing impairment had never their hearing tested(24).

ASSESSMENT OF VISUAL IMPAIRMENT:

1. External appearance of the eyes
2. Abnormal eye movement
3. Head tilting
4. Finger flicking in front of eyes
5. Bringing objects very close to eyes
6. Not recognizing familiar faces
7. Bumping into things
8. Difficulty using steps
9. Not looking confident when walking

ASSESSMENT OF HEARING IMPAIRMENT:

1. Talking un usually loudly or in a whisper
2. Not taking notice of prolonged or loud noises (fire alms)
3. Prefer TV radio to be a louder than normal
4. Respond only to certain voices
5. Mis understanding instruction
6. Covering, pocking, slapping ears
7. Moving close to sound.

COGNITION CAN COMPENSATE FOR THE EFFECTS OF IMPROVISHED TO PERCEPTIONAL ACTIVITIES:

Older adults can engage compensatory cognitive processes in order to performance at a similar level to younger adults. This can be reflected to cortical activity (25) and is associated with better performance compared to older adults who shows less compensatory activation (26)

For eg: when listening to speech older adults showed reduced activation in auditory cortex, but increased in activation prefrontal region with working memory and attention (27). Increased activation in cognitive region was associated with better behavioral performance although older adults were still having dis advantage to younger adults.

At the higher task difficulty, the performance of older adults decline as their brain activation (28)

MECHANISM OF CHANGES IN AGEING BRAIN:

The neurotransmitters most often discussed with regard to ageing of brain are dopamine and serotonin. Dopamine level decline by around 10% from adult hood and have been associated with decline in cognitive and motor performance.

It may be dopamine pathway between frontal cortex and straitum decline with increasing age and other level of dopamine is also decreases.

Serotonin and brain derived neurotropic factor level also fall with age increasing and may be implicating in regulation of synaptic plasticity and neurogenesis in adult brain.(28)

A substance related to neurotransmitter levels, monoamine oxidase, increases with age and liberate free radicals from reaction (29) other factors which implicating in ageing brain include calcium dysfunction, mitochondrial dysfunction and production of reactive oxygen species (30,31).

Another factor to consider with regard to the ageing brain and its cognitive performance due to hormonal influences, it can be affected cognitive process in adult hood that changes in sex hormones occurring in women at menopause.
Women also have a higher incidence of AD even by failing memory and there has been a suggestion that estrogen therapy may increase dopaminergic responsivity (32).

It also suffers from impaired glucose metabolism and reduced glucose, oxygen as cerebro vascular efficiency falls, change in vasculature in elderly brains related to ischeamia and white matter lesion and stroke.

METHODS FOR ASSESING AGE RELATED NEURO-CHEMICAL CHANGES:

Non-Human research:

Non-human research that has used a variety of methods to extract and examine neurochemical data. In non-human research MRS has been to examine in vivo neurochemical changes. Many of these studies have used magnetic field strength to separate the metabolite peaks more effectively (33).The changes are associated with amyloid beta makers include reduced NAA & increased myo inositol (ml) and concentration.(34)

Human Research:

In this technique require brain tissue investigate of healthy human brain in vivo is not possible.
Proton (H1 MRS) magnetic resonance spectroscopy allow for non-invasive investigation which is used

signals emitted from hydrogen proton to measure neurometabolite concentration as there is a nature in high abundance hydrogen in human brain(35).

Mostly, studied resonance peak using H-MRS are (NAA) N-acetyl aspartate, (cho) choline, (cr) creatinine, (Glx) glutamate/ glutamine and myo-inositol. (36)

NAA is closely linked to ATP production also help to measure neuronal metabolic efficiency. (37).

Choline has been implicated as a changes in cell density fluctuating indicate changes in myelin sheath and inflammation occur. (38).

Creatinine is suggesting to play a key role in brain energy homeostasis important in brain osmolyte. Glutamate is major excitatory neurotransmitter involved in many aspects of functioning cognition, learning, and memory. (39)

This model research will now focus on examing how neurometabolites changes in healthy aging free neuro degenerative disorders other medical condition which can affect on cognitive ageing.

BRAIN AGEING DIRECTLY IMPLICATE ON COGNITIVE AGEING:

Neuroimaging and particularly magnetic resonance imaging (MRI), can provide varied and detailed information on living human brain. The applications of methods derived from the study of artificial intelligence particularly machine learning, has enabled researchers to use high dimensional MRI data sets to build predictive statistical model of brain ageing. (40)

The models, generally using data from T1-weighted MRI scans of brain structure, are informed by 'learning' the relationship between age and brain structure in large samples of healthy adults (41). Model performance, evaluated by predicting chronological age based on brain scans from new individuals, results in mean prediction errors of less than five years (42) .

These models can then be used to generate a biological age from neuroimaging data, a 'brain-predicted age'. Following the established biogerontological model of determining the discrepancy between the chronological and biological age of an organism (43) , if an individual's brain-predicted age is greater than their chronological age, this indicates that their brain structure more closely resembles a healthy person who is older than they are(44).

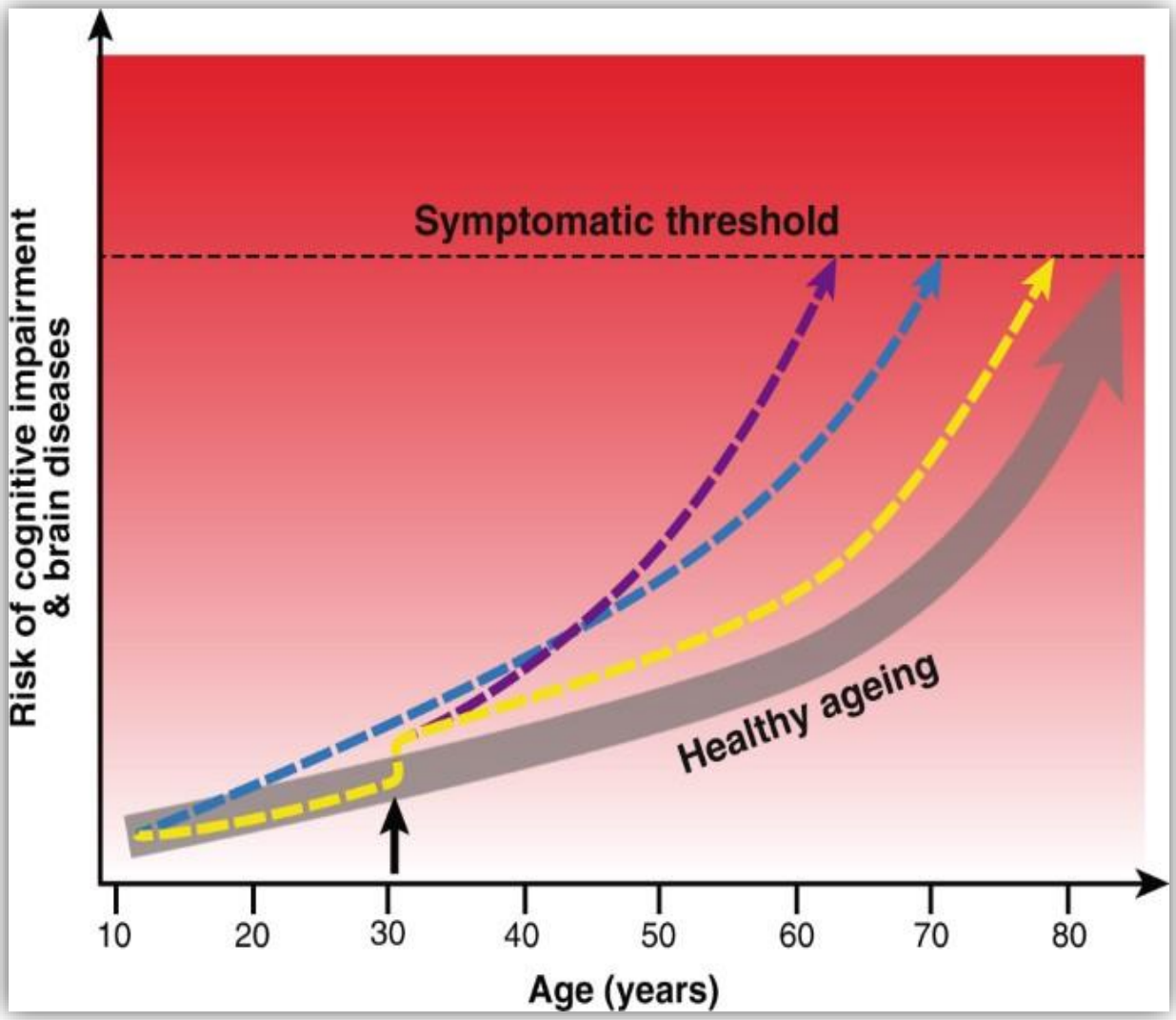


Fig 3: Illustrate that concepts of ageing trajectories, with increasing age even healthy people are at a higher risk of cognitive impairment and brain diseases, For example, a person may have genetic or developmental environmental factors that confer a higher rate of ageing throughout life (blue arrow). Someone may have traumatic injury or infection in adulthood (black arrow), which results in them following an accelerated (purple line) and people stable indicate (yellow line).

BRAIN AGEING AND DISEASES:

Ageing is a key risk factor for many major medical health problems, not least neurodegenerative diseases. Furthermore, even if ageing does not increase risk of a specific chronic disease, older age likely worsens disease symptoms and prognosis. This motivates research into how measures of biological ageing relate to disease risk or disease progression, and how diseases in turn can influence rates of biological ageing (45). In fact, a number of neurological and psychiatric diseases have been proposed to result in premature or accelerated ageing, based on clinical observations and behavioural or biological research (46). These include

1. Schizophrenia
2. Depression,
3. Epilepsy,
4. HIV infection, and traumatic brain injury.

therefore, models of brain ageing offer a possible window into the relationship between ageing and disease. If a disease can be shown to accelerate the ageing-related phenotype of brain structure, this provides information about the potential mechanisms involved and highlights possible commonalities across diagnostic categories (47). Importantly, it also

enables the measurement of individual differences in disease groups, with prognostic implications for future brain health.

A number of psychiatric disorders have been investigated using brain-predicted age metrics (Table 1). In schizophrenia, reports have suggested that not only is greater brain ageing observed, particularly in males (48), but that this accelerates over time.

TABLE 1: Studies of brain predicted age in disease

Study	Clinical group	*N*	Age (mean ± SD, or range)	MRI features	Algorithm	Brain-PAD (mean, years)
Psychiatric disorders						
Franke et al. [49]	Alzheimer's disease	102	76 ± 8	GM	RVR	10.0
	MCI—stable	36	77 ± 6	GM	RVR	BL: −0.5 FU (3 yrs): −0.4
Franke and Gaser [50]	MCI—progressive	112	74 ± 7	GM	RVR	BL: 6.2 FU (3 yrs): 9.0
	Alzheimer's disease	150	75 ± 8	GM		BL: 6.7 FU (2 yrs): 9.0
	High psychosis risk	89	25 ± 6	GM	SVR	1.7
Koutsouleris et al. [51]	Schizophrenia	141	28 ± 12	GM	SVR	5.5
	Major depression	104	42 ± 8	GM	SVR	4.0
Gaser et al. [52]	MCI—progressive (early/late)	58/75	74 ± 7/75 ± 7	GM	RVR	8.7/5.6
Schnack et al. [53]	Schizophrenia	341	34 ± 12	GM	SVR	BL: 3.4 FU (4 yrs): 4.3
	MCI—stable (APOE ε4 carriers/non-carriers)	14/22	77 ± 6/77 ± 6	GM	RVR	BL: −0.9/−0.9 FU(3 yrs): 0.0/−0.6
Löwe et al. [54]	MCI—progressive (APOE ε4 carriers/non-carriers)	78/34	74 ± 6/75 ± 9	GM	RVR	BL: 5.8/5.5 FU (3 yrs): 8.7/7.3
	Alzheimer's disease (APOE ε4 carriers/non-carriers)	101/49	74 ± 7/76 ± 9	GM	RVR	BL: 5.8/6.2 FU (2 yrs): 8.3/7.7
	Bipolar disorder	22	38 ± 11	GM	SVR	−1.3
Nenadic et al. [55]	Borderline personality disorder	57	26 ± 7	GM	SVR	3.1
	Schizophrenia	45	34 ± 10	GM	SVR	2.6
Li et al. [56]	Alzheimer's disease	411	75 ± 7	Hippocampal volume	SVR	7.0
Varikuti et al.	Alzheimer's disease	163	56–91	GM	LASSO	8.5; 10.7[a]

Study	Clinical group	*N*	Age (mean ± SD, or range)	MRI features	Algorithm	Brain-PAD (mean, years)
[57]	MCI	64	55–87	GM	LASSO	6.2; 5.4[a]
Kolenic et al. [58	Psychosis (first episode)	120	27 ± 4.9	GM	RVR	2.6
Guggenmos et al. [59]	Alcohol dependence	119	20–65	GM	MLRR	4.0
Neurological disorders						
Cole et al. [60]	Traumatic brain injury	99	38 ± 12	GM/WM	GPR	4.7/6.0
Cole et al. [61]	HIV	162	57 ± 8	Whole brain	GPR	2.2
Cole et al. [62]	HIV	131	56 ± 6	Whole brain	GPR	BL: 1.6 FU (2 yrs): 1.6
Cole et al. [63]	Down's syndrome	46	42 ± 9	Whole brain	GPR	2.5
Pardoe et al. [64]	Epilepsy (medically refractory/newly-diagnosed)	94/42	32 ± 14/31 ± 11	Whole brain	GPR	4.5/0.9
Liem et al. [65]	Objective cognitive impairment (mild/major)	632/251	58 ± 15/58 ± 16	Whole brain	SVR/RF	0.7/1.7
Physiological disorders						
Franke et al. [66]	Diabetes (type II)	98	65 ± 8	GM	RVR	4.6
	Diabetes (type II)—longitudinal	12	63 ± 7	GM	RVR	BL: 5.1 FU (4 yrs): 5.9
Ronan et al. [67]	Obesity	227	58 ± 17	WM	NLME	10.0
Franke et al. [68]	Gestational nutrient restriction (female/male)	22/19	67 ± 0.2/67 ± 0.1	GM	RVR	0.9/2.5

BL baseline, **FU** follow-up, **GM** grey matter, **GPR** Gaussian process regression, **LASSO** Least Absolute Shrinkage and Selection Operator, **MCI** mild cognitive impairment, **MLRR** multi-linear ridge regression, **NLME** non-linear mixed effects model, **RF** random forests, **RVR** relevance vector regression, **SVR** support vector regression, **WM** white matter.

PROTECTIVE FACTOR:

The diet may be a part to play in biological ageing and development of cognitive decline is raised by showing that diet higher in energy and lower antioxidant is a rise factor.

Increased consumption of fish and seafood, once a month may be protective or reduced stroke.

In addition to healthy diet low to moderate alcohol intake may reduce cardiovascular risk. Exercise is also beneficial studies have shown increasing executive functioning and reduction in ageing decline of white and grey tissue with increasing fitness.

1. Healthy diet intake
2. Exercise daily
3. Physical activity: This protective effect is related to several mechanisms, such as reduction of blood pressure, obesity and proinflammatory activity besides the improvement in lipid profile and endothelial function. In addition, adaptations that

occur in response to exercise can lead to a better cerebral blood flow and, consequently, better oxygenation of important areas for cognitive function.

CONCLUSION:

Over recent years, neuroimaging data have been increasingly used to model healthy brain ageing. These efforts have been conducted in parallel to, but rarely in combination with, research into ageing biomarkers derived from measures of blood chemistry, body composition, or physiological functioning. This neuroimaging research has shown that psychiatric and neurological diseases can influence the brain-ageing process, as can non-CNS conditions.

Alongside this, neuroimaging measures of brain-predicted age can provide prognostic information about the progression of individuals to cognitive decline, dementia, and subsequent death. In our view, this suggests that some of the long-term downstream sequele of different brain diseases may overlap with each other and with the changes to brain structure seen during ageing.

Potentially, a shift towards a greater emphasis in research on measuring individual differences, rather than group-average characteristics, will provide better predictions for long-term health outcomes in brain diseases and more generally. This should help us better understand whether fundamentally age-related processes are occurring, or whether the commonalities between disease and ageing are in fact epiphenomena. Epiphenomena or not, the brain-predicted age measure appears to meet all the same criteria for an ageing biomarker as other measures, such as the epigenetic clock. Telomere length, despite its long-standing popularity, appears, in fact, to be less appropriate than brain-predicted age, either at predicting chronological age or health outcomes. The long-term goal of bio gerontology should be to integrate the measurements of as many age-related epiphenomena as possible, using the growing array of biological measurement techniques available.

REFRENCES:

1. Sevennerholm L, Bostrom K, Jungbjer B changes in weight and composition of major membrane component of human brain during the span of adult human life (1997).
2. Scahill R, Frost C, Jenkins R, a longitudinal study of brain volume changes in normal ageing using serial register magnetic resonance imaging arch neural (2003).
3. Raz N: the ageing structural changes and their implication for cognition ageing (2004).
4. Anderton B ageing of brain mech ageing Dev (2002)
5. Kolb B brain plasticity and behavioural changes in geing persons (1998)
6. Artero S Timmeier H : neuroantomical localization and clinical correlates of white matter lesion in elderly persons (2004).
7. Nyberg L, Backman L, cognitive ageing a view from brain imaging in Dixon R, backman L, new frontier in cognitive ageing (2004)
8. Parkin A memory and amnesia oxford black wall (1997).
9. Cabeza R cognitive neuro science of ageing contributions of functional neuroimaging scand J (2001).
10. Rosen A, Prull M, Hara R, et al variable effects of ageing on frontal lobe contribution to memory (2002).
11. Pathai S, Sheild P.G lawn and Gilbert C the eye as a mosel of ageing in molecular research and clinical aspect (2013).
12. Humes L.E, Bussey T.A, and Kewley port D. age related changes in cognitive functions driven by age related changes in sensory processing (2013).
13. Zwislocki, J Maire, F Feldman, Rubin H on the affect of practice and motivation on audiobility (1958).
14. Schneider B, A & pichora fuller, implications of perceptional deterioration for cognitive ageing research.
15. Linn, F.R Gutierrer, P.R stone, K.L yaffe, H.A et al vision impairment and combined vision and hearing impairment fuction decline in older women(2004).
16. Vanden brock, Van ramshort T et al visual impairment in people with severe and profound multiple disability inventory of visual functioning (2006).
17. Carvill S, Marston G, people with intellectual disability sensory impairment and behavioral disorder
18. Lin, F.R, Ferrucci, L,Gutierrez, P.R, Stone K, L Yaffe et al (2004) vision impairment and combined vision and hearing impairment causes cognitive and functional decline in older womens.
19. Lin F,R Yaffe, K. xia , Harris, Helzner E, et al (2013) hearing loss and cognitive decline in older adults.
20. Valentinjn S, A.M Van Bocktel et al (2005) changes in sensory functioning predicts changes in cognitive functioning.
21. Linn, F.R, K Xia, hearing loss in cognitive decline in older adults (2013).

22. Strawbridge W, J Wallhagen M.L Shema, S.J and Kalpan negative consequence of hearing loss in old age.(2000)
23. Fellinger, J Holzinger, D Dirahrin A, et al (2009) fail to detect deaf blindness in population of people with intellectual disability.
24. Timehin C, Timehin E, prevalence of hearing impairment in community population of adults with learning disabilities and access to audiology and impact on behavior (2004).
25. Reuter- Lorenz P.A and Lustig brain ageing recognizing discoveries about ageing mind (2005).
26. Cabeza R, Anderson N.D Locantore J.K ageing gracefully compensatory brain ability in high performing older adults (2002).
27. Dhars and Wong PCM ageing and cortical mechanism of speech perception in noise (2009).
28. Schneider Garaces N, J Gordon B.A button et al working memory capacity and ageing of brain (2010).
29. Mattson M, Maudsley S, Martin B, dynamic duo in age- related neuronal plasticity and neurodenerative disorders.
30. Volchegorskii I, Turygin V, et al the age dynamic monoamine oxidase activity and level of lipid production in human brain.
31. Toescu E, Melov.S , regulation and gene expression and mitochondrial function in ageing neuron.
32. Craig M, Cutter W, Whickman H et al. effect of long term estrogen therapy on dopaminergic response in post menopausl women.
33. D.R Thal, L.T Ginberg attempt vascular dementia different form of vessel disorders occur in elderly brains.
34. R. A Cohen and X tong vascular oxidative stress, hypertensive diabetes, and other vascular diseases.
35. C, Iadecola and R.L davisson hypertension cerebro vascular dysfunction.
36. Hoyer C, N. Weber Farh challenges of small animal magnetic resonance (2014)
37. Chen, X Liang Y, Deng Y, Chen S. age associated reduction of asymmetric in human central auditory function.(2013)
38. Novontny, E J et al magnetic resonance spectroscopy neurotransmitter in brain (2003)
39. De graff Ding x, maudsley A, M Sheriff B, Schutze physiological neuronal decline in healthy ageing human brain in vivo study.
40. Cole JH, Poudel RPK, T sagkrasoulis D, Caan MWA, Steves C, Spector TD, et al. Predicting brain age with deep learning from raw imaging data results in a reliable and heritable biomarker. Neuroimage.(2017)
41. Franke K, Ziegler G, Klöppel S, Gaser C. Estimating the age of healthy subjects from T1-weighted MRI scans using kernel methods: exploring the influence of various parameters. Neuroimage. (2010)
42. Koutsouleris N, Davatzikos C, Borgwardt S, Gaser C, Bottlender R, Frodl T, et al. Accelerated brain aging in schizophrenia and beyond: a neuroanatomical marker of psychiatric disorders (2013)
43. Ludwig FC, Smoke ME. The measurement of biological age. (1980)
44. Schnack HG, Haren NEMv, Nieuwenhuis M, Pol HEH, Cahn W, Kahn RS. Accelerated brain aging in schizophrenia: a longitudinal pattern recognition study. Am J Psychiat. (2016)
45. Kirkpatrick B, Messias E, Harvey PD, Fernandez-Egea E, Bowie CR. Is schizophrenia a syndrome of accelerated aging (2008)
46. Moretti L, Cristofori I, Weaver SM, Chau A, Portelli JN, Grafman J. Cognitive decline in older adults with a history of traumatic brain injury. Lancet Neurol.(2012)
47. Pathai S, Bajillan H, Landay AL, High KP. Is HIV a model of accelerated or accentuated aging cognitive deterioration in adults (2008).
48. Nenadic I, Dietzek M, Langbein K, Sauer H, Gaser C. BrainAGE score indicates accelerated brain aging in schizophrenia, but not bipolar disorder.(2017)
49. Franke K, Ziegler G, Klöppel S, Gaser C. Estimating the age of healthy subjects from T1-weighted MRI scans using kernel methods: exploring the influence of various parameters.(2010)
50. Franke K, Gaser C. Longitudinal changes in individual BrainAGE in healthy aging, mild cognitive impairment, and Alzheimer's disease.(2012)
51. Koutsouleris N, Davatzikos C, Borgwardt S, Gaser C, Bottlender R, Frodl T, et al. Accelerated brain aging in schizophrenia and beyond: a neuroanatomical marker of psychiatric disorders. Schizophr. (2013)
52. Gaser C, Franke K, Klöppel S, Koutsouleris N, Sauer H. BrainAGE in mild cognitive impaired patients: predicting the conversion to Alzheimer's disease. (2013)
53. Schnack HG, Haren NEMv, Nieuwenhuis M, Pol HEH, Cahn W, Kahn RS. Accelerated brain aging in schizophrenia: a longitudinal pattern recognition study. Am J Psychiat. (2016)
54. Lowe LC, Gaser C, Franke K. The effect of the APOE genotype on individual BrainAGE in

normal aging, mild cognitive impairment, and Alzheimer's Disease.(2016)
55. Nenadic I, Dietzek M, Langbein K, Sauer H, Gaser C. BrainAGE score indicates accelerated brain aging in schizophrenia, but not bipolar disorder. Psychiatry Res.(2017)
56. Li Y, Liu Y, Wang P, Wang J, Xu S, Qiu M. Dependency criterion based brain pathological age estimation of Alzheimer's disease patients with MR scans. (2017)
57. Varikuti DP, Genon S, Sotiras A, Schwender H, Hoffstaedter F, Patil KR, et al. Evaluation of non-negative matrix factorization of grey matter in age prediction. (2018)
58. Kolenic M, Franke K, Hlinka J, Matejka M, Capkova , et al. Obesity, dyslipidemia and brain age in first-episode psychosis.(2018)
59. Guggenmos M, Schmack K, Sekutowicz M, Garbusow M, Sebold M, Sommer C, et al. Quantitative neurobiological evidence for accelerated brain aging in alcohol dependence.(2017)
60. Guggenmos M, Schmack K, Sekutowicz M, Garbusow M, Sebold M, Sommer C, et al. Quantitative neurobiological evidence for accelerated brain aging in alcohol dependence. Transl Psychiatry. (2017)
61. Cole J H, Underwood J, Caan MWA, De Francesco D, van Zoest RA, Leech R, et al. Increased brain-predicted aging in treated HIV disease. Neurology. (2017)
62. Cole JH, Caan MWA, Underwood J, De Francesco D, van Zoest RA, Wit FWNM, et al. No evidence for accelerated aging-related brain pathology in treated AIDS.
63. Cole JH, Annus T, Wilson LR, Remtulla R, Hong YT, Fryer TD, et al. Brain-predicted age in Down syndrome is associated with β-amyloid deposition and cognitive decline.(2017)
64. Pardoe HR, Cole JH, Blackmon K, Thesen T, Kuzniecky R. Structural brain changes in medically refractory focal epilepsy resemble premature brain aging. (2017)
65. Liem F, Varoquaux G, Kynast J, Beyer F, Kharabian Masouleh S, Huntenburg JM, et al. Predicting brain-age from multimodal imaging data captures cognitive impairment. (2017)
66. Franke K, Gaser C, Manor B, Novak V. Advanced brain age in older adults with type 2 diabetes mellitus. (2013)
67. Ronan L, Alexander-Bloch AF, Wagstyl K, Farooqi S, Brayne C, Tyler LK, et al. Obesity associated with increased brain age from midlife. Neurobiol Aging. (2016)
68. Franke K, Gaser C, de Rooij SR, Schwab M, Roseboom TJ. Premature brain aging in humans exposed to maternal nutrient restriction during early gestation. (2017).