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A CROSS-SECTIONAL ANALYTIC STUDY OF AGE-RELATED CHANGES IN WHITE MATTER IN DIFFUSION TENSOR IMAGING IN A SUBPOPULATION OF INDIA

Radiodiagnosis

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ABSTRACT

Ageing is the process of becoming older and it represents the accumulation of changes in a person over time .There are changes to the brain also: though neuron loss is minor after 20 years of age there is a 10% reduction each decade in the total length of the brain's myelinated axons. Cerebral white matter (WM) shows changes with aging. Diffusion tensor imaging (DTI) is an advanced MRI sequence used to calculate white matter changes. DTI in 76 adults were studied. Fractional anisotropy (FA) were calculated to determine whether any particular area of the brain was more susceptible to changes in WM. FA measures were studied from nine regions of interest (ROI) in each hemisphere and from the genu and splenium of the corpus callosum. The results showed significant age-related decline in FA in frontal WM and the genu of the Corpus Callosum. But, temporal and posterior WM was relatively preserved. Differences in FA in frontal white matter were consistent with the anterior–posterior gradient of age differences in white matter integrity.

KEYWORDS

FA-fractional anisotropy, DTI- Diffusion tensor imaging, WM-white matter, ROI-Region of interest

INTRODUCTION

Aging is process of maturing and knowledge along with structural changes in brain which, when captured by DTI-MRI and measured by FA value has been showing revolutionary ideas in recent times. Various studies on process of aging brain conclude that aging is associated with significant changes in white matter [28]. Evidence from humans [34] and non-human primates [32] suggests that changes are partly due to the degeneration of myelin in old age. There occurs decrease in density and number of myelinated fibres [1, 2]. Theories postulate that, association systems show greater age-related change compared to primary sensory and motor systems [7, 8]. Again, volumetric studies of old age subjects demonstrate that prefrontal WM and cortical change are greater than changes in the temporal lobes [9, 10, 11], indicating that age-related changes are different from those of neurodegenerative diseases, which involve mainly the temporal lobes.

Diffusion tensor is an advanced MRI technique which is based on the molecular diffusion of water. In this sequence 'Fractional anisotropy' (FA), is derived from the diffusion properties within a voxel and it gives a scalar idea of DTI. Fractional anisotropy has value between zero and one, that describes the degree of anisotropy of a diffusion process. A value of zero means that diffusion is isotropic, i.e. unrestricted or equally restricted in all directions. A value of 1 means that diffusion occurs only along one axis and is fully restricted along all other directions. FA signifies fibre density, axonal diameter, and myelination in white matter. It is high in regions of the brain with highly restricted diffusion, such as regions of the brain with highly organized myelinated structure (e.g. the corpus callosum-CC). [figure – 3]

It is assumed that the brain regions that mature last during development tend to decline first during aging [11]. Tensor imaging studies using ROI and VBM approaches have generally reported greater age effects in frontal compared to primary posterior cortices, though age-related decline in white matter volume and integrity occurs throughout the brain [33,34,21]

AIM OF STUDY

1. To test the 'last in- first out' theory i.e. the anterior posterior gradient of WM degeneration.
2. o examine if age-related WM changes are same throughout the brain.
3. To see whether changes in prefrontal WM are homogeneous throughout the lobe or are selective to particular regions.
4. To examine if WM associated with primary sensory or motor areas, such as occipital WM and internal capsule, was relatively preserved compared to WM in other areas.

MATERIAL AND METHOD

SOURCE OF DATA: 76 healthy volunteers were studied over a period of one year. Study was conducted at Dept of Radio-diagnosis ,S.C.B Medical college, Cuttack and subjects were recruited through general population of Cuttack, Odisha, India.

STUDY PERIOD: September 2014 to September 2015
STUDY DESIGN: Cross-sectional analytical study.

Tensor images were obtained from 76 participants aged 18–80 years and grouped as Old (O=60 years and older) ,Young (Y; 18–39 years) and middle-aged (M; 40–59 years) . All participants provided consent. EXCLUSION CRITERIA-Participants were excluded if they had a history of neurological or psychiatric disorder, or serious cardiovascular disease. Of the 76, 4 had high blood pressure. Four others had history of concussion. Data were analyzed without these participants.

DIFFUSION TENSOR IMAGING

MRI data were acquired on a 1.5 T General Electric Signa MRI scanner. images in the sagittal and axial planes were obtained at the region of interest (ROI); TR = 7389 m s, TE = 69 ms, slice thickness=2mm , acquisition matrix- 112mm×110mm (FOV= 224x224x120 mm),EPI factor 59, 5/8 partial Fourier, 6 averages, 6 non-collinear directions with *b*-value = 85 s/mm2, and 1 image, the T2 weighted 'low *b*' image, with *b*-value = 0 s/mm2). The effective diffusion gradient spacing was Δ=37ms and the bandwidth was 1783.7 Hz/pixel

Image processing was done using the software provided by GE to calculate the FA values.

ROIs were placed in nine regions of interest in each hemisphere, and in the genu and splenium of the corpus callosum (Fig. 1-a). Global FA evaluated by taking the low *b*, resulting in a measurement that was primarily comprised of the majority of brain WM.

The regions of interest are described in table no 2.

DIFFUSION TENSOR MAPS

Diffusion tensor maps give a qualitative examination of the WM fibre bundles most affected by aging. It is a three-dimensional rendering of the diffusion tensor data set, and provides information on the directional projection of large fibre bundles. The diffusion tensors are

coloured according the direction of the principal eigenvector using a red–green–blue scheme with red indicating medial–lateral projecting fibres, green representing anterior–poster projecting fibres, and blue representing superior–inferior projecting fibre.(fig-1;b)

STATISTICALANALYSIS

The obtained data were analyzed by using a software statistical package for the social science (SPSS version 20). ROI data analysed using Pearson's correlation among all participants and by analysis of variance among the Y, M, and O groups. Statistical values of $p \leq .01$ were considered statistically significant, and $p \leq .05$ were considered suggestive.

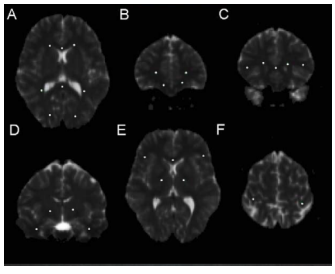
Table 1: Participant Age and Sex Distribution

GROUP	NO	MEAN AGE	MALE	FEMALE
Y=YOUNG	30	24.6	17	13
O=OLD	28	68.9	18	10
M=MIDDLE AGE	18	48.8	12	6

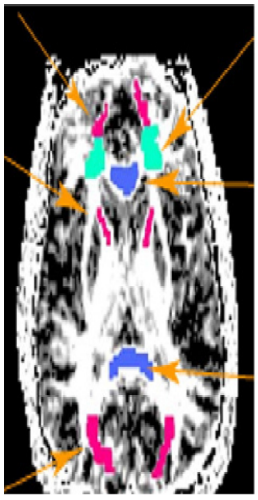
Table 2: Region of Interest [ROI]

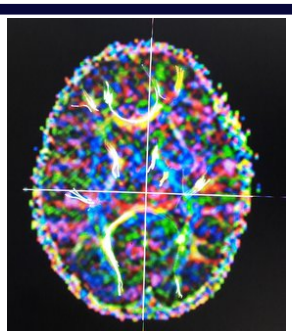
REGION	DESCRIPTION
Anterior CC	Centre of the genu of the corpus callosum
Posterior CC	Centre of the splenium of corpus the callosum
PLIC	In coronal section, directly dorsomedial to pallidum
Deep frontal	At the centre of deep frontal WM
Anterior PV	At the caps of anterior ventricular horn
Posterior PV	At the caps of posterior ventricular horn
Medial orbitofrontal	At just sub cortical to WM branching into the gyrus rectus
Inferior frontal	At WM sub cortical to WM branching into the inferior frontal gyrus
Deep temporal	At the centre of the temporal lobe WM
Post-central	At just posterior to the central sulcus
Occipital	At posterior portion of the WM within occipital gyrus

CC: corpus callosum.
PLIC: posterior limb of the internal capsule.
PV: periventricular.



Fig;1a; FA was sampled from nine ROIs in each hemisphere and the genu & splenium of the CC. The figure demonstrates the ROIs as described in table no 2





Fig;1b; Axial tensor images above showing orientation of fibres and representing colours accordingly where with red indicating medial–lateral projecting fibres, green represent anterior–poster projecting fibres, and blue represent superior–inferior projecting fibres.

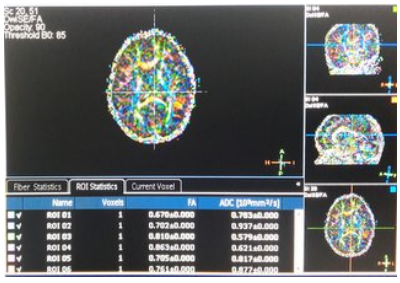


Fig-1-C: Different ROI with FA values and corresponding ADC Values. Voxel with high FA values show less ADC value in comparison.

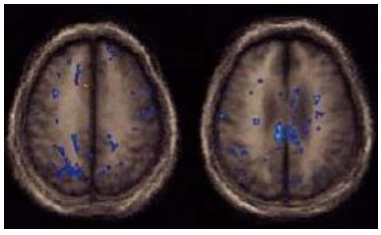


Fig-2a

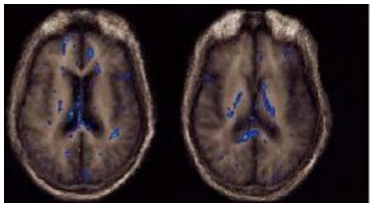


Fig-2b

Statistically significant regions of decreased anisotropy with increasing age. Areas with significant anisotropy decrease with age are shown in blue to blue-white and were identified in the frontal white matter, genu, and splenium of the corpus callosum and in the parietal and occipital periventricular white matter.

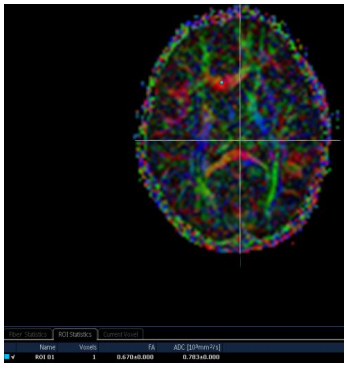


Fig-3: DTI image with single voxel and FA value.

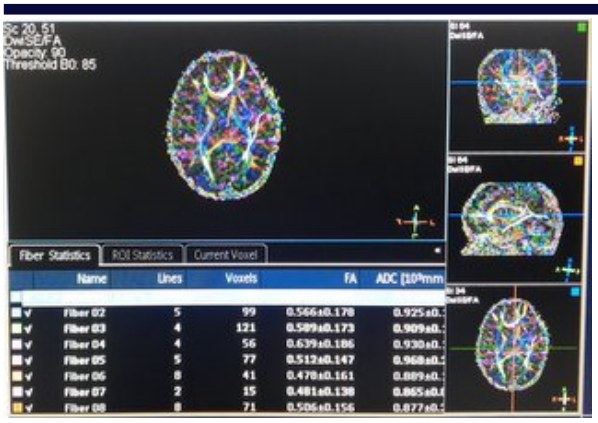


Fig-4: Different fibres with multi voxel FA & corresponding ADC Values

RESULTS

FA values of the Y, M, and O participant groups were regionally variable (Table 3). WM regions having higher myelination and structured orientation, such as the Corpus callosum and Internal Capsule had higher FA values, and less structured regions, such as the sub-cortical WM of the inferior frontal gyrus had lower FA values.

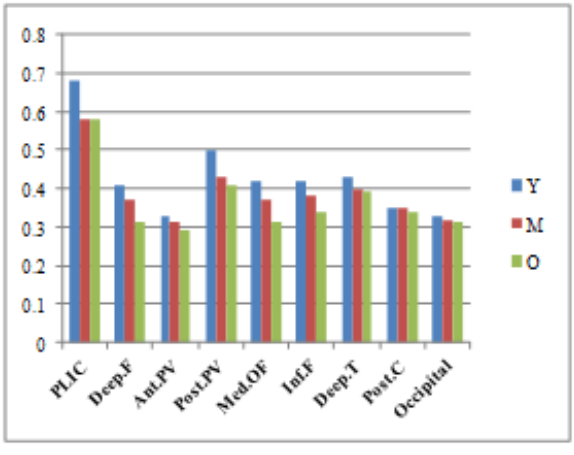
Scatter-plots for the correlations between age and FA are presented.

Analyses showed statistically significant reduction in FA with increasing age in the genu of the CC and bilaterally in the deep frontal, medial orbitofrontal, and anterior periventricular areas. There was a trend towards reduced FA in deep frontal WM of the left hemisphere. Middle-aged adults had greater deep frontal FA bilaterally compared to Old age group.

Greatest decline in anisotropy were in the deep frontal WM and anterior CC. In contrast, temporal and more posterior WM was relatively spared.

TABLE-3a
LEFTT HEMISPHERE: FA VALUES

REGION	YOUNG	MIDDLE AGE	OLD
PLIC	.68 (±.09)	.58 (±.08)	.58 (±.07)
Deep frontal	.41 (±.08)	.37 (±.07)	.31 (±.09)
Anterior PV	.50 (±.09)	.43(±.09)	.41 (±.04)
Posterior PV	.33 (±.07)	.31 (±.04)	.29 (±.09)
Medial orbitofrontal	.42 (±.09)	.37 (±.07)	.31 (±.06)
Inferior frontal	.42 (±.06)	.38 (±.09)	.34 (±.09)
Deep temporal	.43 (±.09)	.40 (±.08)	.39 (±.09)
Post-central	.35 (±.05)	.35 (±.09)	.34 (±.09)
Occipital	.33 (±.09)	.32(±.08)	.31(±.09)



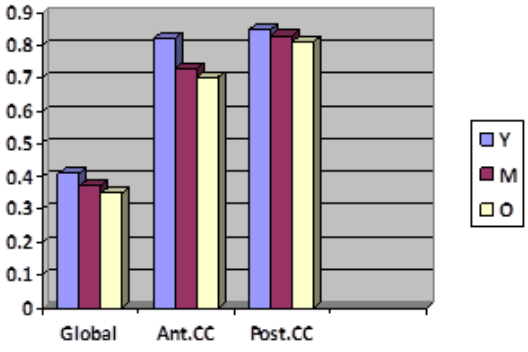
Bar diagram representing Table 3a.

TABLE -3b
RIGHT HEMISPHERE: FA VALUES

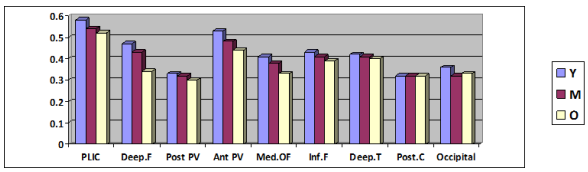
REGION	YOUNG	MIDDLE AGE	OLD
PLIC	.58 (±.08)	.54 (±.07)	.52 (±.06)
Deep frontal	.47 (±.07)	.37 (±.07)	.31 (±.09)
Posterior PV	.33 (±.06)	.32(±.04)	.30 (±.06)
Anterior PV	.53 (±.05)	.48 (±.05)	.44 (±.07)
Medial orbitofrontal	.41 (±.10)	.38 (±.05)	.33 (±.09)
Inferior frontal	.43 (±.08)	.41 (±.07)	.40 (±.07)
Deep temporal	.43 (±.09)	.40 (±.08)	.39 (±.09)
Post-central	.32 (±.05)	.32 (±.05)	.32 (±.07)
Occipital	.36 (±.04)	.32(±.06)	.33(±.07)

TABLE- 3c

REGION	YOUNG	MIDDLE AGE	OLD
GLOBAL	.41 (±.08)	.37 (±.09)	.35 (±.08)
Anterior CC	.82(±.06)	.73 (±.11)	.70 (±.07)
Posterior PV	.85 (±.07)	.83(±.07)	.81 (±.09)

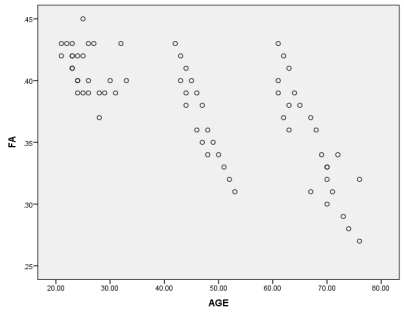


Bar diagram representing Table 3c

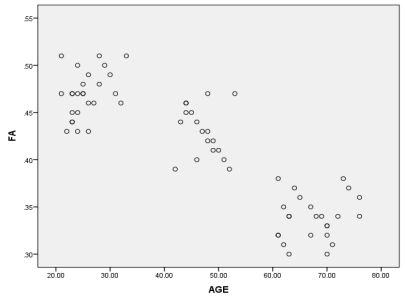


Bar diagram representing Table 3b.

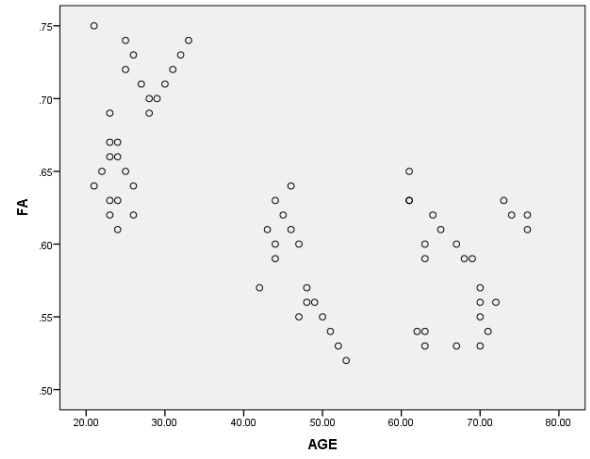
Scatter plot images are as below:



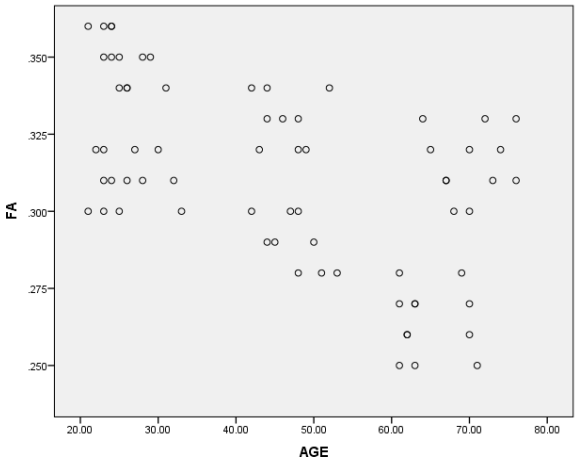
SP-1; GLOBAL



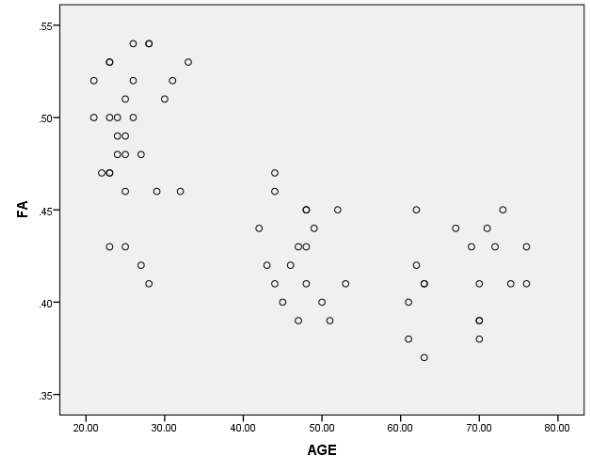
SP-2; LEFT DEEP FRONTAL



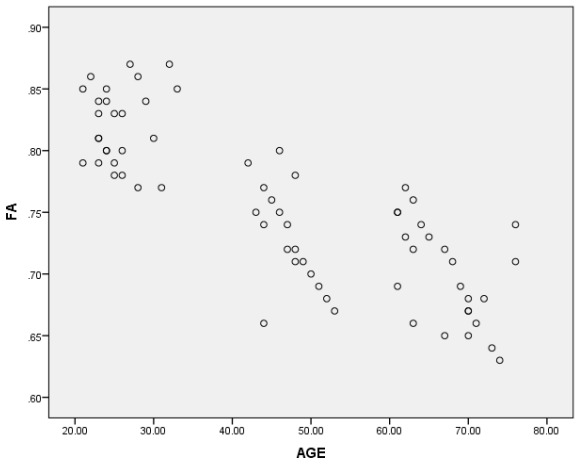
SP-3; Left PLIC



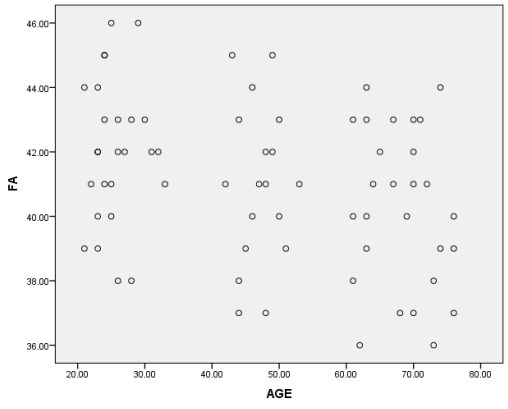
SP-7; LEFT POSTERIOR PERIVENTRICULAR



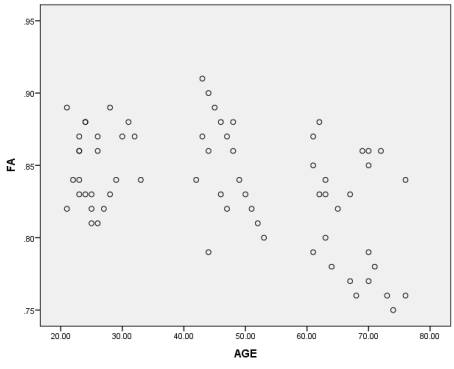
SP-4; LEFT ANTERIOR PERIVENTRICULAR



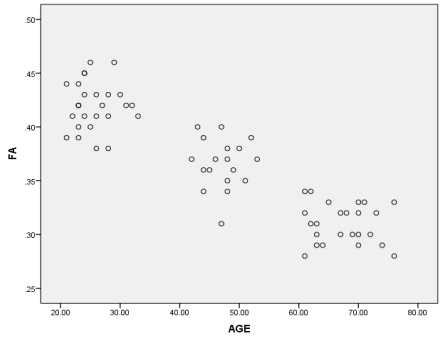
SP-8; ANTERIOR CORPUS CALLOSUM



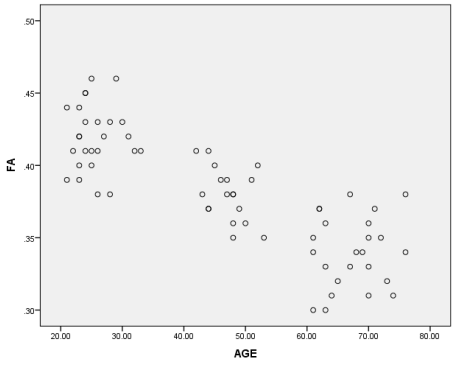
SP-5; DEEP TEMPORAL



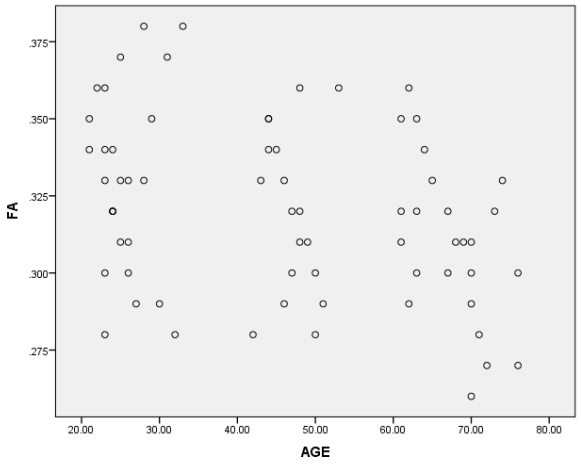
SP-9; POSTERIOR CORPUS CALLOSUM



SP-6; LEFT MEDIAL ORBITO FRONTAL



SP-10; INFERIOR FRONTAL



SP-11; OCCIPITAL

Decline in FA was variable across brain WM with significant changes in the deep frontal, PLIC & medial orbitofrontal and anterior periventricular ROIs. Relative preservation was found in a number of regions including temporal and occipital WM.

DISCUSSION

This study shows age related changes in WM as measured by FA in selected locations called as ROI. Though the change was noticed throughout brain, it was significant in prefrontal areas and was not significant in temporal and posterior regions of the brain. Thus it suggests regional progression of WM degeneration with aging.

Again, greater decline in FA has been seen in the PLIC than in particular regions of frontal WM which imply that WM changes are not specific to prefrontal WM.

Also changes within the WM showed an anterior to posterior gradient. WM changes seem to be conferred more to particular fibre bundles, fibre populations, and regional locations e.g., significant changes observed in corticospinal tracts.

The study shows that age-related white matter deficits increased gradually from posterior to anterior brain regions, as observed from FA values in different brain WM regions. Frontal WM were more affected as compared to occipital WM.

Similar to ours, In a study conducted by Salat D H, Kaye JA et al on 'Prefrontal gray and white matter volumes in healthy aging and Alzheimer disease' in 1999 demonstrated age-related atrophy of prefrontal WM.

In study conducted by Jernigan TL, Archibald SL, Berhow MT et al on 'Cerebral structure on MRI; localization of age related changes' in 1991 described greater frontal compared to temporal WM abnormalities.

The present data are also in agreement with prior studies as follows.

Study carried out by Head D, Buckner RL, Shimony JS, Williams LE et al. on 'Differential vulnerability of anterior white matter in non-demented aging with minimal acceleration in dementia of the Alzheimer type: evidence from diffusion tensor imaging. Cerebral Cortex' in 2004; and study by Nusbaum AO, Tang CY, Buchsbaum MS, Wei TC, Atlas SW. et al on 'Regional and global changes in cerebral diffusion with normal aging' on 2001 found that there occurs marked reduction of FA in prefrontal WM.

Similarly, the data are also consistent with prior studies showing greater volume [17,18,19] and FA [20,21] reduction in anterior compared to posterior CC, and relative preservation of occipital WM[22].

Neuro-imaging studies demonstrate that frontal WM of brain shows numerous age-related changes including accelerated cortical atrophy [25].

Prefrontal WM atrophy has also been reported with aging [25,26,27].

Additionally, studies have demonstrated significant age-related thinning of cortical tissue in the pre-central gyrus [24], where corticospinal fibres are expected to originate. The particular selection of regional WM ROIs in this study allows for more anatomically specific hypotheses about the fibre populations most susceptible to age related degeneration. For example, preservation of the anterior limb of the internal capsule with age-related reduction in FA in the genu of the corpus callosum suggests that the frontal lobe fibres most affected are those of the forceps minor (as opposed to the fronto thalamic or fronto pontine fibres). Thus, the current data support a selective vulnerability of specific fibre bundles.

Finally, age-related changes in WM, such as lacunar infarcts, likely do not contribute to the changes observed in the present study because these participants were free from such apparent lesions on their conventional MR images.

CONCLUSION

The present study suggests that prefrontal WM changes are significant, but regionally selective.

Older adults had significantly reduced FA in deep frontal and medial orbitofrontal WM, but not inferior frontal WM compared to young adults suggesting that there occurs variable changes even in the same lobe region.

Also the study shows that age-related white matter deficits increased gradually from posterior to anterior brain regions.

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