Age - Associated Network Connectivity in Parkinson's Disease*

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Abstract—**Human brain structure changes with age and this has a great impact on memory, learning and other cognitive abilities. Earlier lifetime studies have demonstrated morphological changes in brain structure for both healthy individuals and Parkinson's disease (PD). However, age-associated alterations in brain network topology remain largely unexplored in PD. Several Parkinson's studies have confirmed decreasing grey matter (GM) in patients, but none about brain networks over age. This motivated us to study structural brain network variations with age in Parkinson's disease. The structural MRI of 180 PD patients (22-72 yrs) was acquired at National Institute of Mental Health and Neurosciences, India. The subjects were divided into different age groups - A: 22-32 years (N = 4), B: 33-42 years (N = 18), C: 43-52 years (N = 42), D: 53-62 years (N = 70) and E: 63-72 years (N = 46). The normalized grey matter map of each subject was partitioned into 56 regions of interest using LONI probabilistic brain atlas. Further, Pearson's correlation was computed between every pair of regional grey matter volume, separately for each age-group. Each of the weighted undirected correlation matrix was binarized using sparsity as the measure of threshold. Brain Connectivity toolbox-based MATLAB functions were employed to obtain the connectivity metrics. Mean clustering coefficient was observed to be reducing over sparsity for each age group. In addition, clustering coefficient was found to be significantly different between age group B and C (at sparsities 0.63, 0.66), C and E (at sparsities 0.66, 0.69), and A and every other group (at all sparsities). Our results indicate varying network connectivity pattern with age. Clustering coefficient reflects that the process of information integration and exchange differ between these groups. Limited patients at younger age is an obvious truth, particularly in the age-group of 22-23 years, however, it necessitates additional investigation on a larger dataset.**

Clinical Relevance— **The age-associated structural brain network analysis of Parkinson's patients may assist researchers and physicians in understanding the underlying connection across age. It provides evidence on brain network degeneration at older age as the brain shrinks.**

I. Introduction

Parkinson's disease (PD), is one of the most common neurological disorder that worsens over age. With a prevalence of 6.1 million people across the globe [1], it is commonly found in older people at 50-60 years [2]. Males are more likely to be affected with PD than females [3]. The associated pathological hallmark is loss of dopaminergic neurons of substantia nigra [4]. It leads to various classical motor and non-motor manifestations such as tremor, bradykinesia, rigidity, behavioral and cognitive dysfunctions. However, progression of neurodegeneration in PD begins and spreads throughout the nervous system long before these symptoms are expressed, termed as prodromal phase [5].

Our understanding of the brain regions and networks underlying the clinical manifestation of PD is constantly growing as a result of recent developments in neuroimaging [6]. The identification of structural changes in brain has been possible with the aid of structural Magnetic Resonance Imaging (sMRI). Parkinson's disease has been associated with grey matter (GM) atrophy which is detected as morphological changes by voxel-based morphometry [7], [8]. Hence, grey matter tissue contains important information to be deployed for further analysis and understanding of the disease.

Age is the largest risk factor influencing the clinical progression of PD. A faster development of motor disability, severe gait and postural impairment, often leads to dementia in PD patients with age [9]. Also, PD patients have been vastly observed with inability to understand, process information and other cognitive disabilities. We hypothesize such improper and inefficient information dissemination in PD patients may be due to aberrant brain connectivity.

Brain network states the pattern of connections between neuronal elements and explains information processing carried out inside the brain [8], [10]. A few connectivity studies using sMRI have analyzed brain network in PD compared to healthy control [10]–[12], compared across gender [13], and with different associated dysfunctions like tremor [14] and mild cognitive impairment [15]. Hence, there is a lack of structural brain connectivity studies in PD spanning the lifetime.

In our current research, we speculate disease progression with age may cause disruption of brain network, leading to cognitive decline in PD patients. Hence, we have analyzed the brain network pattern and evaluated the connectivity metrics in different age groups. To accomplish our objective, we deployed grey matter information from sMRI of brain. The weighted undirected matrix (or association matrix) was constructed using Pearson's correlation from which the binary undirected matrix (or adjacency matrix) was obtained by thresholding based on sparsity. The network metrics were extracted and brain network analysis was performed using MATLAB functions at different sparsity thresholds. We

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TABLE 1. DEMOGRAPHIC AND CLINICAL INFORMATION OF PARTICIPANTS

Age-Group (Age range)	Count	Gender (Male : Female)	UPDRS Off (Mean ± SD)	UPDRS On (Mean ± SD)	H&Y (Median)	Age at Onset (Mean ± SD)
A (<32)	4	3:1	31.69 ± 2.71	16.75 ± 9.91	2	16.83 ± 10.67
B (33-42)	18	11:7	32.94 ± 7.13	16.67 ± 6.16	2	35.19 ± 4.69
C (43-52)	42	28:14	32.33 ± 11.11	17.78 ± 8.15	2	42.83 ± 4.29
D (53-62)	69	56:13	32.79 ± 8.76	17.70 ± 5.37	2	47.47 ± 6.26
E (63-72)	46	36:10	35.17 ± 6.97	19.30 ± 4.78	2	51.54 ± 9.88
p-value			0.58	0.54		3.08×10^{-22} **

*A,B,C,D,E: Age based groups as per the age range mentioned in brackets; H & Y: Hoehn and Yahr scale; p-value: from ANOVA test; SD: Standard Deviation; UPDRS: Unified Parkinson's Disease Rating Scale; **: Significant at 99% confidence interval; Data are expressed as Mean ± SD; Since H&Y is a categorical value, it's expressed as median.*

assume our investigation may play a new role in assisting researches in understanding the underlying connection across age.

II. Materials and Methods

A. Participants

The data considered for our current investigation included 180 PD patients as in Table.1 (135 males and 45 females; age: 54.84 ± 9.78 years, age range 22-72 years). The subject characteristics are: mean Unified Parkinson's Disease Rating Scale at off state (UPDRS Off): 33.26 ± 8.92, mean Unified Parkinson's Disease Rating Scale at on state (UPDRS On): 17.85 ± 6.27, Hoehn and Yahr scale (H&Y): 2.07 ± 1.46, and Age at onset: 48.27 ± 9.14. The subjects were recruited at the Department of Neurology, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India. Every individual had provided a written informed consent in compliance with NIMHANS Institutional Ethics Committee. The participants were categorized into five age groups (age group A: < 32 years, B: 33-42 years, C: 43-52 years, D: 53-62 years, and E: 63-72 years) with group size of N1 = 4; N2 = 18; N3 = 42; N4 = 70; and N5 = 46, respectively.

B. MRI scanning and Image processing

A 3 Tesla Philips Achieva scanner with a 32-channel head coil was used to scan the participants. A high resolution T1-weighted structural MRI scan was obtained with a magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence (repetition time (TR) = 8.2 ms, echo time (TE) = 3.7 ms, flip angle = 8, field of view (FOV) = 256 x 256 x 165 mm^3, 165 sagittal slices, voxel size = 1 x 1 x 1 mm^3). The original scans were obtained in DICOM format, which were converted into NIfTI by using MRIcron's dcm2nii tool (http://www.nitrc.org/projects/mricron). The pre-processing steps are explained elsewhere [10]. This involved MATLAB-based Computational Anatomy Toolbox (CAT12, http://www.neuro.uni-jena.de/cat/) within Statistical Parametric Mapping (SPM12). Recent study [16] has inferred better age prediction using this pipeline and hence we used it for brain network analysis. The scans were segmented and GM map was taken for further study.

C. Structural Graph Construction

The GM map of every individual was parcellated using LONI Probabilistic Brain Atlas, LPBA40 (https://resource.loni.usc.edu/resources/atlases-downloads/) into 56 regions [17]. The regions are illustrated in the Appendix of [10]. Brain parcellation for one subject in age group D was unsuccessful, due to which it was excluded from the study. Each region of the brain indicated a node in the network and the region- specific grey matter volume (rGMV) were obtained using CAT12. Thus, it resulted into a subject x regions matrix for each age group, where subject size varied with age-group with a constant number (56) of regions. A

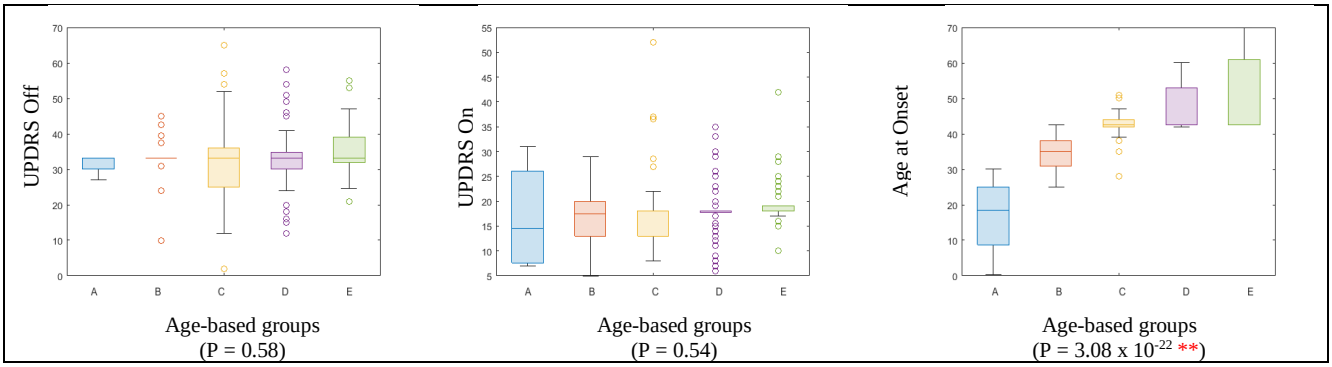


Figure 1. Plotted are ANOVA of clinical features across the groups

UPDRS: Unified Parkinson's Disease Rating Scale; Notches indicate the median; Top, bottom edges of the box indicate the 25th and 75th percentiles; **: Significant at 99% confidence interval

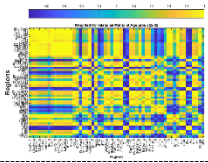
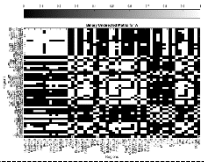
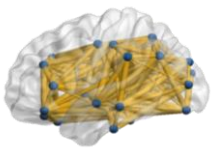
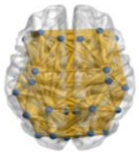
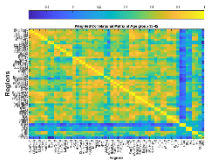
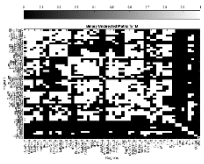
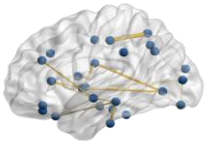
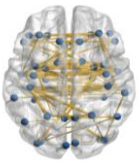
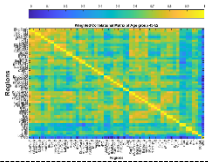
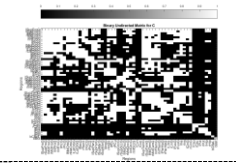
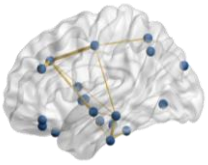
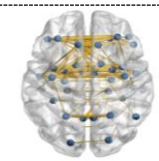
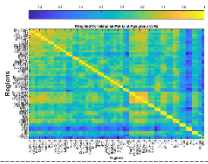
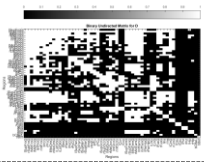
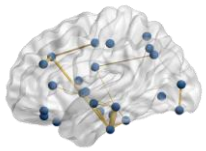
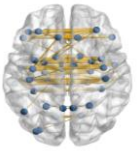
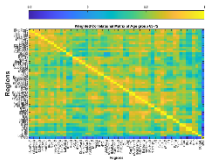
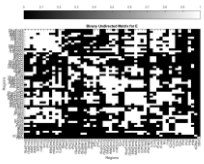
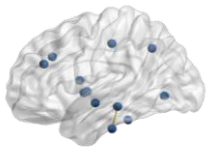
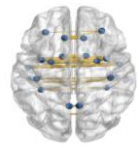
Age Group (N)	Weighted Undirected Matrix	Binary Undirected Matrix	Weighted Undirected Network	
			Sagittal View	Axial view
22-32 (4)				
33-42 (18)				
43-52 (42)				
53-62 (69)				
63-72 (46)				

Figure 2. Age-based Weighted Undirected Matrix, Binary Undirected Matrix and Weighted Undirected Network

Color-bar shows the strength of the connections. A correlation value, r =1 (yellow in Weighted Undirected and white in Binary Undirected matrix) indicates a full positive correlation, while r =0 (deep blue in Weighted Undirected and black in Binary Undirected matrix) indicates the lack of correlation between the regions. N is the number of subjects in the specified age range. The x- and y-axes of weighted and binary matrices are brain regions in order according to [17]

linear regression analysis was performed to remove the effect of age and gender. As described in our previous work [10], an weighted undirected matrix was constructed using Pearson's correlation between every pair of nodes, MATLAB (MathWorks R2020a). For instance, value r_{78} indicates the correlation of region 7 with region 8.

D. Network metrics and analysis

To facilitate simplified network analysis, weighted undirected matrix of each age-group was binarized across an optimized range of sparsities [10], [18], [19] using average of 1000 random networks. A complex brain network is often measured and analysed in terms of clustering coefficient. Nodal clustering coefficient is defined as the fraction of directly linked neighbours which are interconnected among themselves [19]. These nodal clustering coefficient was estimated using Brain Connectivity Toolbox-derived MATLAB functions [19] and averaged over the network to obtain mean clustering coefficient. Structural brain network is the pattern containing edges between two nodes where the interregional correlation exists. The networks for each age-group was visualized using BrainNet Viewer [20].

E. Statistical Analysis

Analysis of Variance (ANOVA) was performed between the age groups to find the differences in clinical variables, such as UPDRS Off, UPDRS On and age at onset. A P-value < 0.05 was concluded to be significant. The inter-group differences in clustering coefficient were examined using a nonparametric permutation test [10], [12] with 1000 iterations to determine their statistical significance. While preserving the number of subjects in each group, clustering coefficients were randomly assigned to either of the groups. The computed randomised group differences were used to determine the permutation distribution of the difference. Following that, actual between-group differences were compared using a 95% confidence interval. We tested the statistical significance of inter-group differences using a self-developed MATLAB code.

III. Results and Discussions

A. Participants

A significant difference was found in age at onset (P = 3.08 x 10-22) between the age-based groups of PD at 99% confidence interval (Table 1). However, no intergroup significant difference was observed in UPDRS at Off (P =

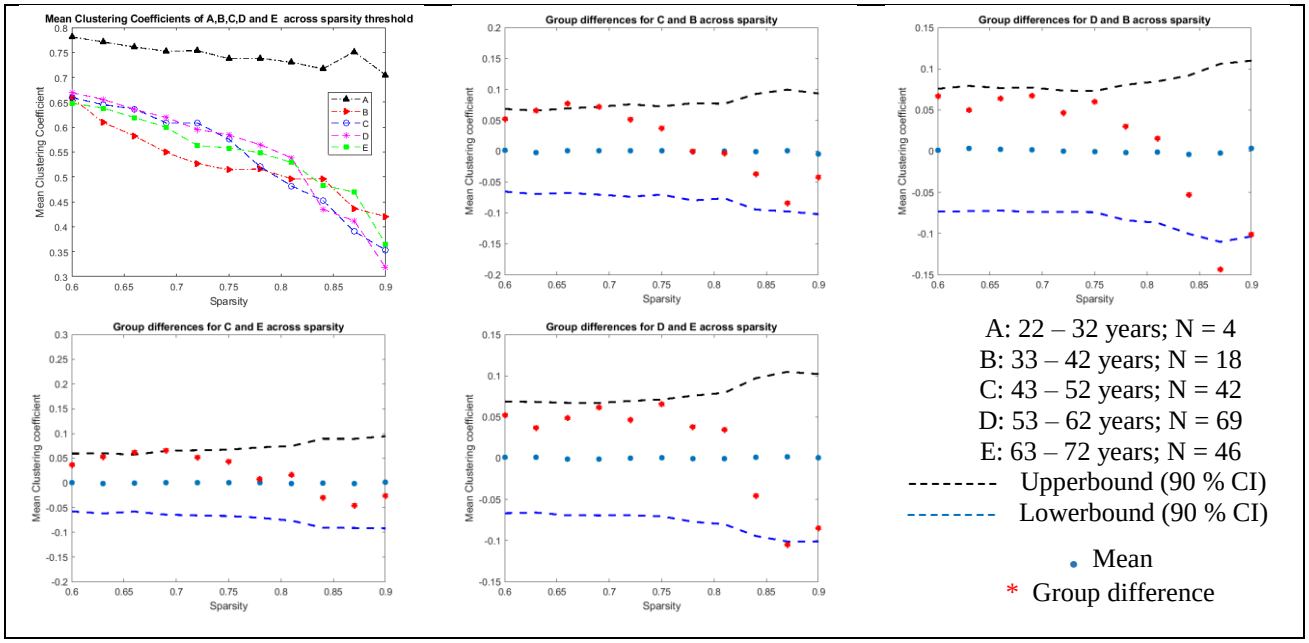


Figure 2. Distribution and intergroup differences in mean clustering coefficient for age-based groups

0.58) and On (P = 0.54) state (Table 1). The detailed demographic and clinical information of the age groups are in Table 1 and the multiple group comparison is plotted in Fig.1.

B. Structural graph

Pearson correlation was performed to detect relationship between the regions. The weighted undirected matrix, hence formed, contained 56 nodes and 1540 (= 56x55/2) edges. All the groups showed varied positive and negative interregional correlations (2nd column of Fig.2). The strengths of the connections in weighted undirected correlation matrix are indicated by the color-bar. The binary undirected correlation matrix is shown in 3rd column of Fig.2. The sagittal and axial view of weighted undirected networks of each age group, at the same sparsity, are respectively shown in the fourth and fifth columns of Fig.2. The intra-hemispheric connections are seen in sagittal view, while the inter-hemispheric connections in axial view. Although standard parcellation method has been employed in our study, use of connectivity based parcellation is encouraged in PD [21]. Our results (from 4th and 5th column of Fig.2) accentuates progressive decline in structural connectivity with increase in age which indirectly affects the functional characteristics, which corroborates with normal aging in the earlier findings [22].

C. Network metrics and analysis

The sparsity threshold was estimated from the data and a range from 0.6 to 0.9 with a step size of 0.03 was considered for analysis for every age group. The small-world property exceeded 1 for every threshold level. The clustering coefficient of our network was higher and at the same time the mean shortest path length was equivalent to that of the random network within 0.6 to 0.9 sparsity levels. Fig.3 illustrates the distribution of mean clustering coefficient and the significant comparison of the age groups as obtained from the binary undirected matrix. The mean clustering coefficient declined over sparsity except for group A at 0.87 sparsity. The blue circles are the mean differences in clustering coefficient obtained from averaging 1000 permutations. The mean clustering coefficient of group A was observed to be significantly higher than that of B, C, D and E age groups.

We obtained significantly higher mean clustering coefficient in group A than other groups. This suggests higher information integration in young adults i.e., up to 32 years old. This is in agreement with a previous study [23] on healthy individuals from electroencephalogram (EEG) signals. The functional connectivity network from the beta-band working memory task evoked a significant increase in clustering coefficient for younger adults (19-29 years) than that of older participants (58-70 years) [23]. However, due to limited sample size in group A, we suggest additional investigation with larger sample size. Since, clustering coefficient measures the functional segregation [24], functional connectivity studies have shown it decreasing with age [25], which corroborates with our result. The clustering coefficient of group C (between 43 and 52 years) is significantly different from that of group B (33-42 years) at 0.66 sparsity level. However, we can observe that it is overall, though not significant, higher in group C than B at lower sparsities up to 0.75, and lower at higher sparsities from 0.84 onwards. The clustering coefficient of group C (between 43 and 52 years) is significantly different from that of group E (63-72 years) at 0.66 and 0.69 sparsity. It is overall higher in group C than E at lower sparsities up to 0.75, but lower at higher sparsities from 0.84 onwards. Also, the clustering coefficient of group D (53 – 62 years) is significantly different from that of group B (33-42 years) at higher sparsity levels of 0.87 and 0.9. It is higher in group D than B till 0.81 sparsity, but afterwards it is lower. The clustering coefficient in group D is significantly different from that of group E (63-72 years) at 0.87 sparsity. Group D has a larger clustering coefficient than group E up to 0.81 sparsity, but after that it decreases. However, other group comparison

showed no difference between group B (33-42 years) with E (63-72 years), and group C (43-52 years) with D (53-62 years).

IV. Conclusion

To our knowledge, this is the first study in Parkinson's disease comparing the age-based network pattern and performing connectivity analysis. Our investigation on sMRI- based structural network demonstrated varying clustering coefficient at different age in PD. Since prodromal stage is a crucial time in PD and is not explored yet, more research is required in this direction. Also, longitudinal study may help understand the underlying change in brain network over time due to the disease. Although PD is uncommon at younger age and the immensely dense connectivity at younger age (<32 years) is an obvious truth, the connectivity could be analysed in detail with large sample size of younger patients. As clustering coefficient reveals statistically significant group difference, it could be treated as a biomarker to understand the information communication at different age. Our study could be taken as a base work to analyse other connectivity metrics so as to perform a comprehensive connectivity analysis. Employing connectivity information from other imaging modalities (like diffusion tensor imaging, functional MRI) may help draw more firm conclusions about aging in Parkinson's disease as evident from loss of connections and differences in network metric.

AUTHOR CONTRIBUTIONS

TS proposed this idea to CNG and JS. The entire study and the first draft of the paper was done by TS. CNG, JS and TS then discussed and refined the paper to arrive at final submitted version

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