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Regions and Sub-regions Dysfunctions in Alzheimer's during Rest

K. C. Usha[1*] and Dr. H. N. Suma[2]

[1]Department of Electronics and Communication Engineering, BMS College of Engineering, Karnataka, India.
[2]Department of Medical Electronics, BMS College of Engineering, Karnataka, India.

Authors' contributions

This work was carried out in collaboration among both authors. Preparation of the data acquired from ADNI. Author KCU did the data analysis, components extraction, statistical analysis, interpreting the results and drafting the manuscript. Author HNS did the revision of the manuscript and technical guidance throughout the analysis. Both authors read and approved the final manuscript.

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ABSTRACT

Aims: Alterations in the cerebrum structurally and functionally are triggered largely due to an increase in neuro depressive brain disorders like Alzheimer's. This study aims is to determine these alterations in the regions of the cerebrum which are significant and distinguishing in Alzheimer's disease subjects compared to healthy. We employ the most potential resting-state functional Magnetic Resonance Imaging (rs-fMRI) modality for this analysis.
Methodology: 24 Alzheimer's disease (AD) and 25 Healthy Controlled (HC) subjects were evaluated with rs-fMRI which is more efficient in anticipating neuronal activity changes. Thus, obtained data of all subjects were preprocessed and components of larger networks to smaller regions were extracted by independent component analysis (ICA) method. Differences in resting-state connectivity were examined for 6 networks of interest viz., Auditory network, Central Executive network, Default mode network, Silence mode network, Sensory-motor network and Visual network and their regions, which are affected due to the common symptoms of Alzheimer's

**Corresponding author: E-mail: ushagautamsk@gmail.com;*

disease-like memory, thinking and behavioral changes. Statistical analysis was done with one sample t-test to check the functional connectivity activations in Resting-State Networks (RSNs) and regions of both AD & HC groups at a threshold of T>2. Finally, to obtain the abnormal sub-regions in each of the RSNs of AD a two-sample t-test was carried out at a threshold of P < .03.

Results: Our method potentially identifies the functional connectivity alterations and core regions dysfunction amongst the major 6 RSNs in AD compared to HC subjects. The results also showed decreased connectivity in regions of sensory-motor and default mode networks increased connectivity in regions of central executive and silence mode network along with some of the sub-regions dysfunctions in AD.

Conclusion: Modifications in functional connectivity within the major RSNs and regions have been detected which serves as a capability to determine an early biomarker and examining the disease progression.

Keywords: Functional Magnetic Resonance Imaging (fMRI); resting-state fMRI; functional connectivity; Alzheimer's disease; independent component analysis; resting state networks; auditory network; central executive network; default mode network; salience network; sensory-motor network; visual network.

ABBREVIATIONS

AD : Alzheimer's disease;
ADNI : Alzheimer's disease Neuroimaging Initiative;
BOLD : Blood oxygen level dependent;
fALfFF : Fractional amplitude of low frequency fluctuations
fMRI : Functional magnetic resonance imaging;
RS-fMRI : Resting state fMRI;
RSN : Resting state networks;
ICA : Independent components analysis;
GIFT : Group ICA fMRI toolbox;
DPARSF : Data processing assistance for resting-state fMRI toolbox;

1. INTRODUCTION

The chronic Alzheimer's disease (AD) gradually increases with episodic cognitive decline and progress towards irreparable memory loss, executive functions, language, visuospatial functions, and other behavioral domains. Neuronal dysfunction in AD is mainly due to the role of b-amyloid and neurofibrillary tangles which not only contribute to the structural changes but also functional connectivity deterioration in the brain. Evaluation of these reductions in functional neuronal activity is a sensitive biomarker for AD [1].

Functional magnetic resonance imaging (fMRI) has become increasingly prominent in understanding neuronal activity, which would be significantly widened to explore the functional neuronal network alterations of AD in comparison with Healthy controlled (HC) subjects. Resting-state functional magnetic resonance imaging (rs-fMRI) is more effective over task-based fMRI. In rs-fMRI the subjects are not given any task, thus excluding the cofounds of task difficulties and allow a review of neural activity when the subjects are at rest and offer valuable functional mapping measure that synchronizes activations between regions that are spatially distinct. Even during the resting period, it has been observed that some of the brain networks are functionally active [2,3], and thus using rs-fMRI modality it has been effective in identifying altered neural connectivity in AD [4].

The neural connectivity in the cortical brain is studied using methods such as Voxel-based [5], the region of interest (ROI) or seed-based analysis [6], graph theory [7], Independent component analysis (ICA) [8] and machine learning methods [9,10]. Independent component analysis (ICA), is the most popular and effective data-driven approach in the analysis of fMRI data. ICA is powerful to disintegrate heterogeneous magnetic resonance signal patterns and identify the resting-state networks (RSNs) from rs-fMRI [11,12]. It is also advantageous compared to other methods since it does not require prior and outside knowledge like ROI or seed-based analysis [13] or parameter and measure selections as in graph theory analysis and it can be used in complementary with machine-learning [14].

The challenging issue faced in ICA analysis is the number of components selection, previous studies have used lower-order components

extraction between 20 to 40 which would lead to the overlapping of the resting-state networks regions and high order components between 70 to 90 and more would lead to over splitting of components [15,16]. In this current work, we set the components to be extracted from a lower-order ranging from 20 components to a higher-order component of 60 in steps of 10, Hence the major network and their regions are addressed. Another major issue is the separation of resting-state components and the artifacts components. Most of the previous studies have explored on an automated method for identification of only language network component [17], hand classification of noise components in single subject [18], SVM classifier [19] and Naive-Bayes algorithm [20] for noise components classification and some have used predefined spatial masks provided by Dante Mantini from Leuven Medical School [8] for classification. In this study we use a simple and efficient method in the identification of valid components by creating the masks with specific regions of interest so, that redundant regions are eliminated. The obtained resting-state components are the measure of functional connectivity within specific brain networks and show optimistic biomarkers in AD studies and helps in exploring abnormal regions in diseased [11].

2. METHODOLOGY

2.1 Participant's

The experimental data is obtained by the publically available dataset ADNI "Alzheimer's Disease Neuroimaging Initiative". It is a non-profitable organization since 2003 which consists of structural and functional magnetic resonance imaging along with positron emission tomography data of Alzheimer's, Mild Cognitive Impairment and normal subjects with detailed basic and clinical information [21].

In this analysis, we make use of the functional MRI and structural MRI data of 49 subjects including 24 AD patients and 25 HC in the database of ADNI-2.AD subjects had MMSE (Mini-Mental State Examination) score between 20-25; CDR (Clinical Dementia Rate) equal to 0.5 or 1and HC had an MMSE score between 27-30; CDR equal to 0.We excluding the subjects with their head translation exceeding ±1.5 mm and rotation exceeding ±1.5 mm. Finally remained with 45 subjects and their details are as shown in Table 1.

Table 1. The participants information

Project	AD	HC
No of subjects	23	22
Gender (male/female)	10/13	7/15
Age	69.3±6	70.3±3
MMSE	20-25	27-30
CDR	0.5 or 1	0

2.2 Resting-state Data Collection

The images were obtained from a 3.0 Tesla Philips MRI scanner. Acquisition parameter includes 140 time points, TR=3000 ms, TE=30 ms, flip angle=80°, 48 slices with a thickness of 3.3 mm and spatial resolution of 3×3×3 mm^3 and matrix 64×64 as obtained from the database.

2.3 Data Preprocessing

The preprocessing was carried out with DPARSF "Data Processing Assistance for Resting-State fMRI" software tool [22], based on SPM "Statistical Parameter Mapping" in MATLAB and further statistical analysis was done with REST Resting-state fMRI toolkit. The raw data obtained from the ADNI-2 was processed by DPARSF with following steps,

1. Conversion from Digital Imaging and Communications in Medicine (DICOM) format to NIfTI format.
2. Reorientation of both functional and structural data for an alignment check.
3. To reduce the error caused by the subject's adaptation to the circumstances initial 10-time points of the functional images were discarded.
4. Slice timing correction was performed with reference to the last slice.
5. For head movement compensation the images were realigned using a six-parameter rigid-body spatial transformation since excessive head motion may induce large artifacts in fMRI time series.
6. T1 structural images were co-registered to the mean rsfMRI images.
7. Normalization of the images to Standard EPI temple in SPM.
8. Spatial smoothing of functional images with Gaussian kernel 6 mm full width at half maximum filter to reduce white noise and residual effect.
9. Finally, linear drifts are removed and temporal filtering (0.01 Hz~0.08 Hz) were performed.

2.4 Independent Component Analysis

The independent component analysis (ICA) is accomplished using GIFT "Group ICA for fMRI toolbox". After the initial preprocessing ICA separates the fMRI signal into different sources of variance and extracts the spatially independent components. The ICA process includes reduction of subject's functional data dimension using principle component analysis PCA along with INFOMAX algorithm, stable components were obtained by running the analysis 100 times using ICASSO toolbox [23] [24]. The number of components to be extracted is evaluated using Minimum Distance Length (MDL) [25] principle from all participants, the optimal number of components obtained were 60 components; it always varies on the dataset selected. We repeat the ICA, by setting the number of components (ICs) to be extracted from a lower order of 20 signifying larger networks to higher order 60 components signifying smaller regions in steps of 10. Once all the components are extracted next we have to classify the valid components and artifacts. With the sole purpose to examine all the resting-state networks and their regions contributing to the differences in AD progression compared to HC. The subsequent components extracted from both AD and HC include time courses and their respective spatial maps, where the time courses of components representing the brain activity and spatial maps indicating their intensity.

2.5 Identification of RSNs

The extracted components are the combination of resting-state networks with valid brain signals and artifact components due to several causes such as white matter, blood vessels and cerebral fluid. Classification was performed by sorting of components using spatial correlation method. The sorting was carried out using masks created by WFU Pick Atlas [26] software by manually including specific region of interest in the grey matter. The masks with six major resting-state networks and the sub-masks with of all the regions were created. This method of mask creation helped eliminate all the redundant regions resulted from overlap of white matter, cerebrospinal fluid or brain boundaries. After sorting the components with largest correlation values were selected and examined for adequate dynamic range i.e. difference between the peak power and minimum power at frequencies to the right of the peak, fALFF (fractional amplitude of low frequency fluctuations) the integral of spectral power below 0.10 Hz to the integral of power between 0.15 and 0.25 Hz and finally visually inspected [27]. Hence the components extracted range from lower order comprising of larger networks and higher-order comparing of smaller regions of the networks. The six resting-state network and their region representing the components are auditory network (AN) which includes right and left superior temporal lobe [28], the central executive network (CEN) including right and left regions of dorsolateral prefrontal cortex and posterior parietal cortex, Default mode network (DMN) is consists of medial pre-frontal cortex, inferior parietal lobe, posterior cingulated cortex, precuneus and hippocampus, Salience mode network (SN) includes anterior cingulated cortex and anterior insular [29], sensory-motor network (SMN) which includes precentral and post-central gyrus [30], and visual network (VN) including high and prim visual regions which are the part of the occipital cortex [31].

2.6 Statistical Analysis

The six RSNs and their region components of AD and HC are evaluated for one sample t-test to know the activated brain network regions in each group and to obtain the significant group differences, with results displayed at the threshold of $T > 2$. Finally, the *Z*-shift was performed. Then two-sample t-tests were accomplished using REST toolbox on the specific region of interest. The masks with region of interest were obtained by the union of activated brain regions of both groups. This estimates the alterations in the functional connectivity of all the networks and regions. Finally results obtained were z transformed and represented with $P < 0.03$ (AlphaSim correction) [8].

3. RESULTS

3.1 Spatial Distribution in RSNs

One-sample t-test ($T>2$) results depict the resting-state network in two groups have typical spatial distribution patterns. The differences in spatial pattern distribution of auditory, central executive, default, salience, sensory-motor and visual networks along with their regions are as shown in Figs. 1-4 below. The auditory, sensory-motor and visual being sensory networks show decreased functional connectivity in AD; executive and salience network part of the attention networks show increased

connectivity and default mode network which are active when the subjects are at rest, shows reduced connectivity in AD as compared to HC [32,33].

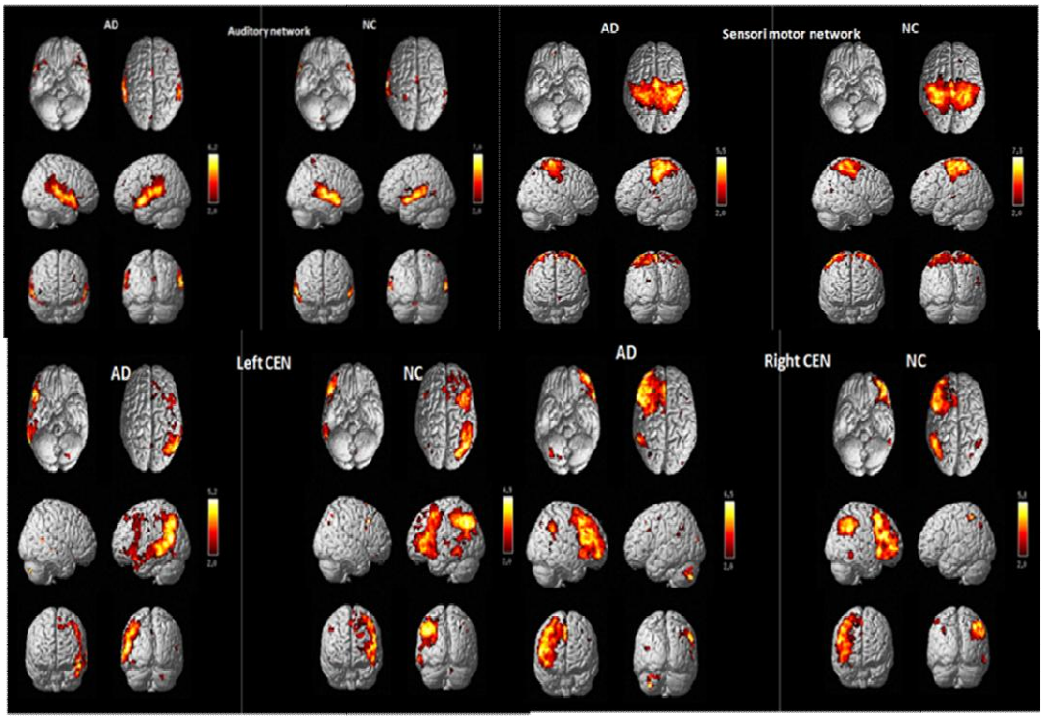

Fig. 1. Auditory, sensory-motor and executive network functional activations differences in AD and HC

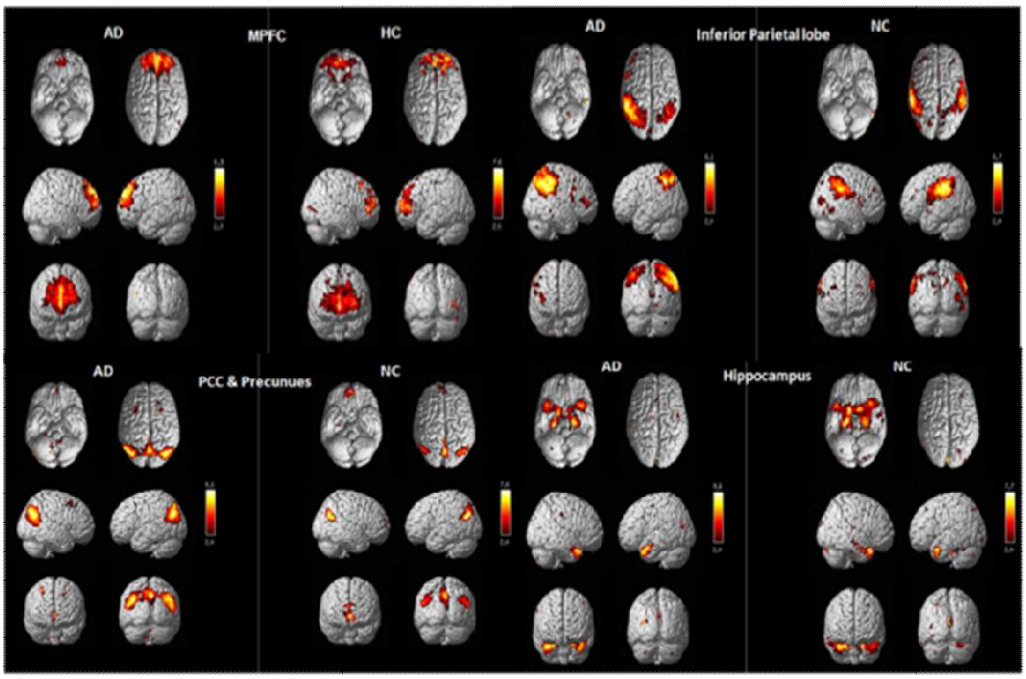

Fig. 2. Default mode network functional activation differences in AD and HC

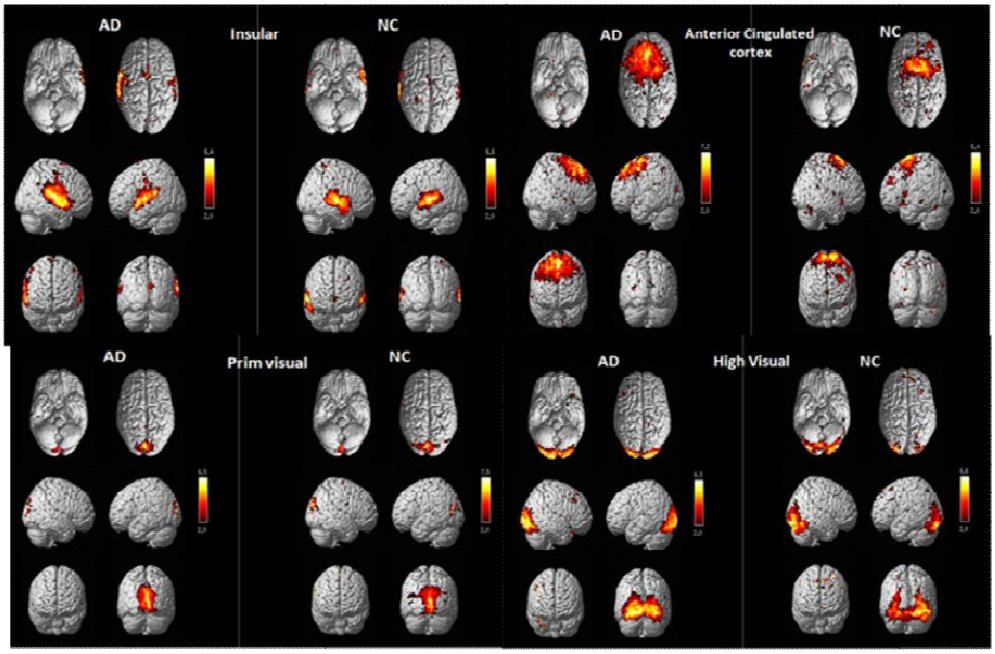

Fig. 3. Salience network and visual network functional activation differences in AD and HC

3.2 Abnormal RSNs in AD Patients

The functional connectivity alterations in abnormal resting-state networks and their brain regions of AD compared to HC are obtained from two -ample t-test (P >.03) is as shown in Figs. 4-5, Table 2 depicts the list of altered functional connectivity sub regions in AD.

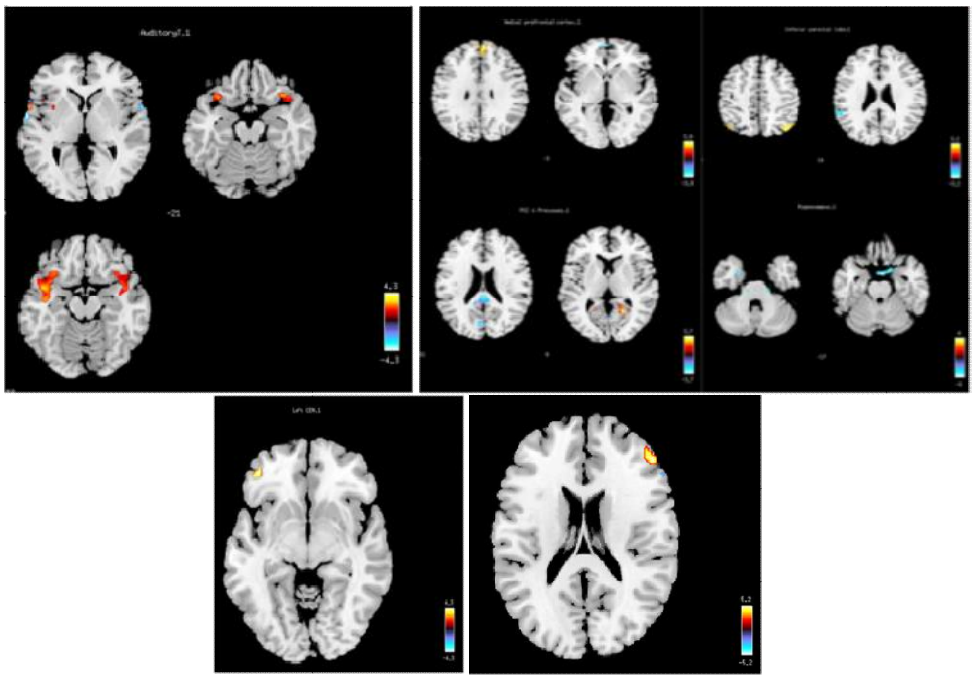

Fig. 4. Abnormal sub-regions in auditory network, default mode network and left & right executive network

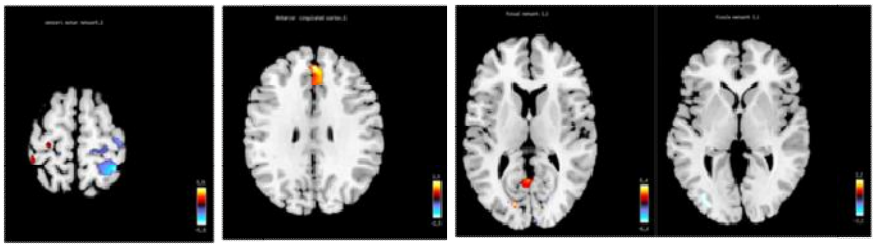

Fig. 5. Abnormal sub-regions in sensory-motor, anterior cingulated cortex & visual network

Table 2. Altered functional connectivity sub regions of AD compared to HC

RSNs	Regions	Sign	Abnormal brain regions	No of Voxels	Peak coordinate
AN	L. Superior temporal gyrus	positive	L middle temporal gyrus	97	-45,-12,-18
	R superior temporal gyrus	positive	R IFG (P Orbitalis)	48	39,24,-21
		negative	L Superior temporal gyrus	50	-63,-3,0
DMN	Medial prefrontal gyrus	positive	R superior medial gyrus	53	6,60,30
		negative	L mid orbital gyrus	10	-6, 60,-3
	Inferior parietal lobe	positive	L angular gyrus	87	-39,-57,63
			R angular gyrus	115	45,-72,63
		negative	L Superior temporal gyrus	21	-63,-45,24
	PCC & Precunues	positive	R Lingual gyrus	51	24,-57,6
		negative	L Calcarine gyrus	45	0,-78,21
	Hippocampus	positive	L temporal pole	78	
		negative	L medial temporal pole	78	-27,6,-36
CEN	left	positive	L IFG (P Orbitalis)	24	-42,45,-9
	Right	positive	R IFG (P Triangularis)	66	54,39,18
SN	Anterior cingulated cortex	positive	L Superior medial gyrus	99	3,48,30
	Insular	NC			
SMN		negative	R Superior parietal lobule	51	39,-48,66
VN	High VN	Positive	L Calcarine gyrus	62	-15,-81,9
	Prim VN	negative	Inferior occipital gyrus	62	-33,-87,0

4. DISCUSSION

Resting-state fMRI data of AD vs HC were analyzed using ICA methods in which the decomposition of mixed components represents the actual brain activity and this will be very helpful in clinical treatment. By implementing this method of lower to higher order components extraction, all resting-state network components with both minor and major regions grouping was found. These extracted components were identified and classified using masks with manually specified region of interest. Thus enabling to explore and compare all the regions of the six resting-states networks in both AD and HC revealing the significant group difference. This analysis proved that RSNs of AD patients are having abnormalities compared to HC. Demonstrating reduced connectivity in RSNs such as in DMN, AN, SMN, and VN which represents the cognitive and sensory networks and increased connectivity in attention networks such as central executive and salience network [34,35].

AN, Auditory network is the part of the temporal lobe that processes auditory information. As suggested the basic auditory capacities in AD should be normal, whereas more significant level of sound-related function should be increasingly damaged [36]. The auditory network includes superior temporal gyrus. Our results shows that increased FC in the left middle temporal gyrus and right inferior frontal gyrus P Orbitalis (IFG P Orbilatis).

Default, salience and central executive networks are highly explored networks in AD. Results of salience and central networks appear to be unstable. Our results is consistent with earlier results, DMN showed decreased connectivity, whereas mean increased connectivity in the central network and in the regions of the salience network of AD [30]. This study shows decreased connectivity in posterior cingulated cortex, precuneus, inferior parietal lobe, medial prefrontal cortex and high functional connectivity in the hippocampus correlating with the previous results [37]. In the sub-regions DMN we observed increased connectivity in the right part of superior medial gyrus, parts of angular gyrus, right lingual gyrus and decreased connectivity in left parts of mid orbital gyrus, superior temporal gyrus and calcarine, the sub-region of hippocampus exhibits increased connectivity in left temporal pole and decreased connectivity in left medial temporal pole.

Default mode networks and salience networks being the part of largest networks are stated to be the early signature in cognitive decline in the AD; the most recent work examined the alterations in AD at two slow frequency bands i.e 0.073-0.198 and 0.01-0.027 [38] and had similar results with displaying decreased connectivity in DMN and increased connectivity in SN along the spectrum too are not variant thus consisting of the strong abnormal regions.

CEN, the central executive network consists of the right and left parts of the dorsolateral prefrontal cortex (DLPFC) and the posterior parietal cortex (PPC).It plays an important role in the maintenance of information in working memory. Our results show increased connectivity in a mean central executive network of AD as reported [30], whereas sub-regions such as left IFG (P orbitalis) and right IFG (P triangularis) exhibits increased connectivity in AD compared to HC.

SN, salience network as suggested by previous studies dynamically controls the default and executive networks; hence we can say that these three networks are functionally correlated [30], SN consists of anterior cingulated cortex and anterior insular, shows increased connectivity and their sub regions of left superior medial gyrus [39,40].

VN, Visual network consists of high and prim visual shows decrease connectivity in AD is allied with visual memory and visuospatial network [41]. High visual also called as extra striate visual network includes inferior occipital gyrus and prim visual lingual gyrus, calcarine gyrus, and parts of the cerebellum [42]. Our results show reduced functional connectivity in left inferior occipital gyrus and higher connectivity in left calcarine gyrus.

Our study explores on major resting-state network regions, but there are other regions affected due to the disease progression. Distinguishing of these regions by examining the whole brain would result in more significant regions responsible for AD. Second main concern is about the subject's count more number of data would lead to more significant abnormal regions.

5. CONCLUSION

The resting-state fMRI has provided a better understanding of the resting-state networks in AD and normal's. Major RSNs or group of regions that exhibit alterations in spontaneous BOLD fluctuations i.e functional connectivity differences have been identified in AD compared to normals. Parts of temporal gyrus and inferior frontal gyrus along with lingual gyrus, calcarine gyrus, angular gyrus, and temporal pole appear to be abnormal in Alzheimer's during rest. From this study we were able to locate the core regions that would play a major role in the cerebrum damage due to the disease and further these regions would be targeted in performing the classification Alzheimer's with controls.

CONSENT

As per international standard or university standard written participants consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per the ADNI protocol, all procedure performed is this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with 1964 Helsinki declaration and its later amendments or comparable ethical standards. More details can be found at adni.loni.usc.edu.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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