

# Evaluation of Default Mode Network In Mild Cognitive Impairment and Alzheimer's Disease Individuals

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## Abstract

Although progressive functional brain network disorders has been one of the indication of Alzheimer's disease, The current research on aging and dementia focus on diagnostics of the cognitive changes of normal aging and Alzheimer Disease (AD), these changes known as Mild Cognitive Impairment (MCI). The default mode network (DMN) is a network of interacting brain regions known to have activity highly correlated with each other and distinct from other networks in the brain, the default mode network is active during passive rest and consists of a set of brain areas that are tightly functionally connected and distinct from other systems within the brain. Anatomically, the DMN includes the posterior cingulate cortex (PCC), dorsal and ventral medial prefrontal cortex, the lateral parietal cortex, and the medial temporal lobes. DMN involves multiple anatomical networks that converge on cortical hubs, such as the PCC, ventral medial prefrontal, and inferior parietal cortices. The aim of this study was to evaluate the default mode network functional connectivity in MCI patients. While no treatments are recommended for MCI currently, Mild Cognitive Impairment is becoming a very important subject for researchers and deserves more recognition and further study, In order to increase the ability to recognize earlier symptoms of Alzheimer's disease.

**Keywords:** Alzheimer's Disease, Mild Cognitive Impairment, Functional Magnetic Resonance Imaging, Independent Component Analysis, Default Mode Network.

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## 1. INTRODUCTION

The concept of MCI originally was defined in 1999. The field of aging and dementia is focusing on the characterization of the earliest stages of cognitive impairment. Recent research had

identified a transitional state between the cognitive changes of normal aging and Alzheimer's disease, known as Mild Cognitive Impairment (MCI). People diagnosed with MCI may have different patterns of symptoms and many possible underlying causes. However, only 5 to 10% of people with MCI will progress to dementia each year. Typically, Mild cognitive impairment is believed to be a high risk condition for the development of clinically probable AD.

In conjunction with increased attention to the early stages of development of Alzheimer disease (AD), Most of these studies examined the amnesic subtype of MCI, in which memory impairment is a key feature. However, other studies, often encompassing a broader definition of MCI, have demonstrated a reversion to normal in some subjects, implying of stability for the construct over time. Currently, several approaches and techniques have been used to quantify the different types of brain connectivity. In this work, we focused on those connectivity derived from functional Magnetic Resonance Imaging (fMRI): structural connectivity, functional connectivity, and effective connectivity, Functional MRI has been used to investigate abnormalities in patterns of regional brain activation during a variety of cognitive tasks in patients diagnosed. It is important to keep in mind that the abnormalities found in fMRI study of AD or other patient groups are heavily dependent on the type of behavioral task used in the study.

The nature of functional abnormalities may depend on whether the activated brain regions are directly affected by the disease, are indirectly affected via connectivity. Analytic and visualization software tools are now available to directly investigate the overlap of disease-related alterations in brain structure and task-related functional activity, but further efforts in computational and visualization software development are essential. It should also be kept in mind that even brain regions not usually thought to be affected by Alzheimer's disease have been shown to exhibit abnormal function in AD patients. Using fMRI, many studies have extensively investigated functioning and anatomical correlates of the Default mode network (DMN), Default mode network has received the greatest attention because it contains several regions that support cognitive functions as well as in neurodegenerative diseases including AD.

Independent component analysis (ICA) is an important signal separation technique. It considered one of the multivariate techniques that enable the analysis of MRI data in order to extract useful information about the relationships among the brain substructures for the diagnosis or classification of Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI) patients. In the current study, we have applied Independent component analysis (ICA) based method. The ICA-based method has three steps. First, all data scans are normalized by statistical parametric mapping (SPM). Second, ICA is applied to the images for extracting specific neuroimaging components as potential classifying features. Finally, the separated independent component among AD, MCI, and control subjects (HC). Our results indicate that the proposed method is able to classify AD and MCI patients and normal control subjects with certain accuracy.

## **2. MATERIALS AND METHODS**

### **2.1 Experiment Materials**

The data of this study was approved by Alzheimer's disease Neuroimaging Initiative (ADNI) <http://adni.loni.usc.edu>, University of Southern California. One hundred and five individuals participated in this study: Twenty (20) elderly healthy controls (HC) and Thirty five (35) Mild Cognitive Impairment (MCI) and Fifty (50) subjects with Alzheimer's disease (AD). The healthy control (HC) subjects ranged in age from 65 to 80 (mean age 72.2). The Mild Cognitive Impairment (MCI) subjects ranged in age from 68 to 85 (mean age 76.7). The Alzheimer's disease (AD) subjects ranged in age from 68 to 88 (mean age 77.6). According to the Clinical Dementia Rating (CDR), Twenty-five (25) of the AD had the rate of 0.7 placing them in (very mild); the other half of AD had a CDR of 1, classing them to (mild) subjects. The MCI subjects all had an overall CDR of 0.5. Moreover, All CN subjects received CDR of (0). The three groups showed significant differences ( $p < 0.01$ ) in the age, education scores, and MMSE evaluation. Subjects were evaluated with Mini Mental State Examination (MMSE).

	Gender (M/F) ( $p = 0.11$ ) <sup>a</sup>	Age ( $p < 0.01$ ) <sup>b</sup>	MMSE ( $p < 0.01$ ) <sup>b</sup>	Education ( $p < 0.01$ ) <sup>b</sup>
HC 20	25	70.20 (4.20)	30.37 (0.75)	2.20 (1.01)
MCI 35	35	75.80 (5.10)	25.50 (1.50)	2.16 (1.35)
AD 50	70	88.80 (7.20)	38.50 (3.00)	5.60 (3.25)

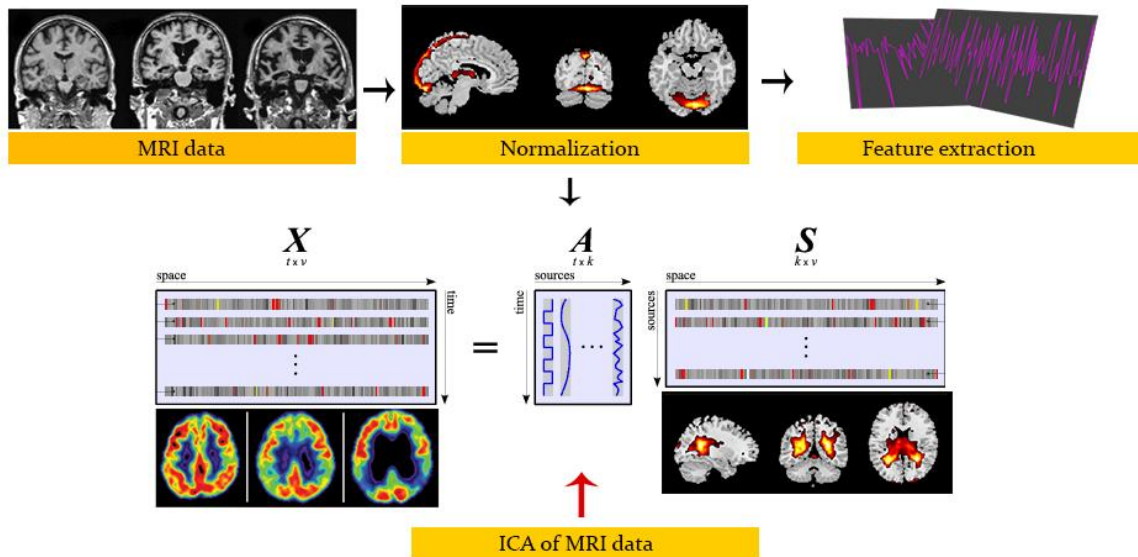
**TABLE 1:** Group1, HC (Healthy control), Group2, MCI (Mild Cognitive Impairment), Group3: AD (Alzheimer’s disease). MMSE: Mini Mental State Examination. Education background: from Elementary school to High Education. (A/p): Tests values.

### 2.2 Data Analysis

ICA is a probabilistic and multivariate method for learning a linear transform of random vectors. The basic goal of ICA is to search for the components which are maximally as independent and non-Gaussian as possible. It is fundamental difference to classical multivariate statistical methods such as PCA and linear discriminate analysis (LDA), which ensures the identification of original components, in comparison with these classical methods. ICA can be mathematically modeled as

$$X = A \times S$$

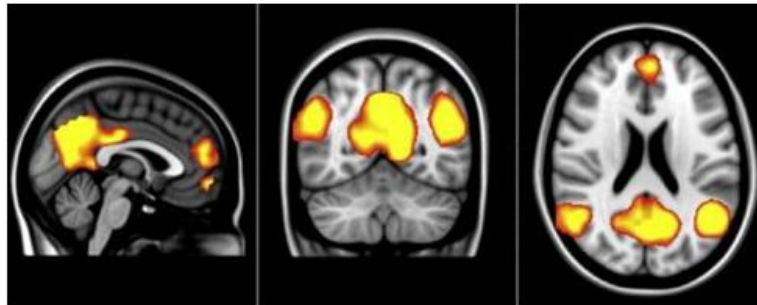
Where X is the observed data vector, A is the mixing matrix and S is the source matrix.



**FIGURE 1:** The methodological framework for analysis of structural MRI data. The rows of the data matrix X and sources matrix S. The corresponding columns of the mixing matrix A are the time-courses.

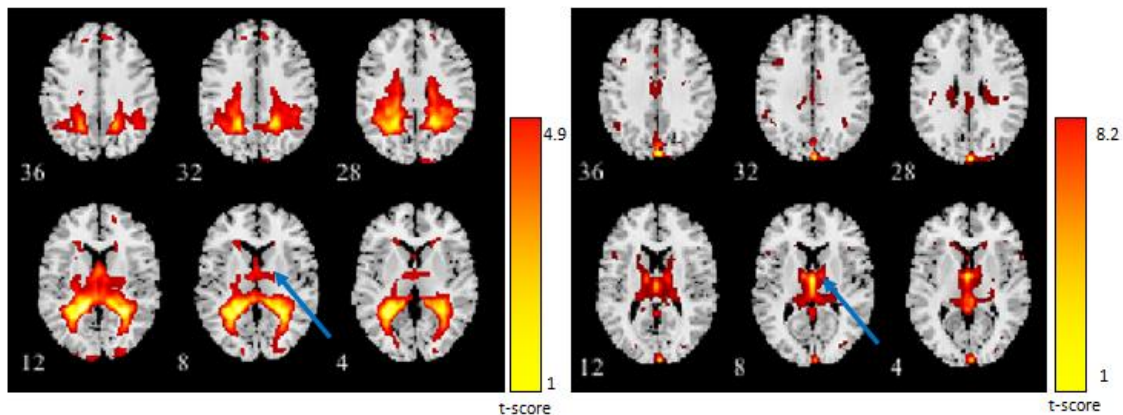
In this study, we applied Independent component analysis (ICA) investigating resting-state data, The data were analyzed with Group ICA of Functional magnetic resonance imaging toolbox (GIFT) supported by the Medical Image Analysis Laboratory (<http://mialab.mrn.org>) Implemented in MATLAB R2014b (Math works). ICA in principle related to principal component analysis and factor analysis. ICA is a much more powerful and useful technique, however, capable of finding the underlying factors or sources when these classic methods fail completely. Most recently, ICA has been used to identify low-frequency neural networks that are active during resting-state (visual fixation) fMRI data.

We analyzed output of 50 components data, separately, 10 components from Healthy control (HC) 15 components from (MCI) and 25 components from (AD). Mild cognitive impairment (MCI) is a syndrome with cognitive decline greater than expected for an individual's age and educational level but not interfering notably with activities of daily living; prevalence of MCI is 15% in adults older than 65 years; more than half of patients with MCI progress to dementia within 5 years; the amnesic subtype of MCI has a high risk of progression to AD. More specifically, these Regions including the posterior cingulate, inferior parietal, and medial prefrontal cortex, constitute a RSN called default mode network (DMN). The areas of the DMN show consistently greater BOLD activity during rest than during any attention-demanding task, a phenomenon called deactivation.



**FIGURE 2:** Default mode network. The DMN includes the medial Prefrontal Cortex (mPFC), Posterior cingulate cortex (PCC) and anterior cingulate cortex ACC, and the parietal cortex.

In AD subjects, the regions of the DMN altered functional connectivity (FC) at the rest time within DMN activation. According to these findings, FC at rest-time in individuals at high risk for AD progression, most previous studies investigating RSNs have used region of-interest (ROI)-based correlation analyses. The signal time course of a selected ROI is correlated with remaining brain areas, resulting in a ROI specific correlation map. More recently, the number of studies used approaches involving independent component analysis (ICA) to describe RSNs in rest-fMRI data.



**FIGURE 3:** The Default-mode network in healthy elderly and MCI subjects, axial images showing the default-mode network for the healthy elderly (A) and MCI (B) groups. More specifically, images showing the default-mode network as detected with regions of interest (ROI) in a group of healthy control (HC). The blue arrows indicate the posterior parietal cortex (PCC). T score bars are shown at right [1-8.2/1-4.9].

Regions of interest (ROIs) were obtained from these RSN prototypes to compute between-group differences (HC, MCI, AD). For each, RSN, between-group differences were assessed by means of Z values obtained from individual ICA group maps.

Means	Table2: <i>Default-mode network in healthy elderly and AD subjects (HC, MCI, AD)</i>			
	Sub.	Dynamic range	Power (LF/HF)	Peak Coordinate (mm)
Group 1	001	0.108	0.074	(28.5, -49.5, 17.5)
	002	0.067	0.016	( 30.5, 42.5, -19.5)
	003	0.064	0.142	(7.5, -84.5, -19.5)
	004	0.000	0.049	(3.5, -36.5, -5.5)
	005	0.000	0.040	(42.5, -35.5, 57.5)
Group 2	006	0.040	0.002	(23.5, 50.5, 25.5)
	007	0.015	0.044	(11.5, -34.5, -21.5)
	008	0.079	0.087	(42.5, -56.5, 50.5)
	009	0.041	0.075	(-5.5, -45.5, -34.5)
	010	0.002	0.061	(1.5, -61.5, 28.5)
Group 3	011	0.040	0.002	(23.5, 50.5, 25.5)
	012	0.015	0.044	(11.5, -34.5, -21.5)
	013	0.079	0.087	(42.5, -56.5, 50.5)
	014	0.041	0.075	(-5.5, -45.5, -34.5)
	015	0.002	0.061	(1.5, -61.5, 28.5)

**TABLE 2:** Default-mode network in healthy elderly and AD subjects (HC, MCI, and AD): HC (Healthy control), Group2: MCI (Mild Cognitive Impairment), Group3: AD (Alzheimer’s disease). Each group has five components [1-5], Dynamic Rang (Power/Frequency), Peak Coordinate (mm).

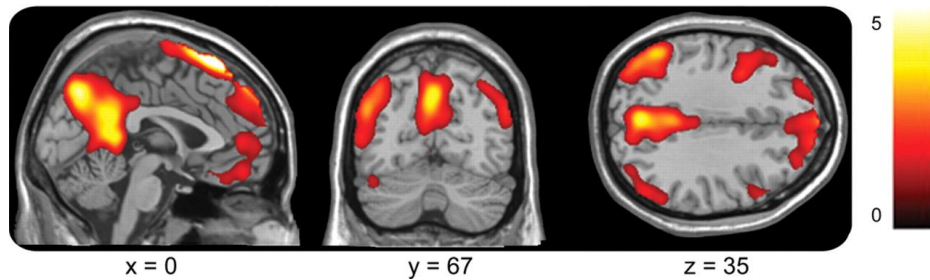
### 2.3 fMRI in MCI and AD

Functional Magnetic Resonance Imaging (fMRI) is a useful tool to investigate the modifications in functional connectivity, also allow the evaluation of brain changes and the progression from healthy aging to MCI and AD. Many studies have extensively investigated functioning and anatomical correlates of the Default mode network (DMN). More importantly, with functional Magnetic Resonance Imaging (fMRI), we investigated resting state network (RSN) activities, resting state (Rs) fMRI data were analyzed by using Independent Component Analysis (ICA).

Functional MRI has been used to investigate abnormalities in patterns of regional brain activation during a variety of cognitive tasks in patients diagnosed with AD compared to control subjects. It is important to keep in mind that the abnormalities found in an fMRI study of an AD or other patient group are dependent on the type of behavioral task used in the study if the task does not engage a given brain circuit, functional abnormalities will not likely be observed in that circuit even if it is affected by the disease. Also, the nature of functional abnormalities may depend on whether the activated brain regions are directly affected by the disease, are indirectly affected via connectivity, or are not pathologically affected. Analytic and visualization software tools are now available to directly investigate the overlap of disease-related alterations in brain structure and task-related functional activity, but further efforts in computational and visualization software development are essential. It should also be kept in mind that even brain regions usually not thought to be affected by AD have been shown to exhibit abnormal function in AD patients.

### 2.4 Large-scale Brain Networks Supporting Normal Memory Function

Functional neuroimaging has made valuable contributions to the cognitive neuro scientific investigation of brain networks, overall, multiple fMRI studies using a “subsequent memory” paradigm have demonstrated that greater fMRI activity during encoding in specific brain regions is associated with the likelihood of subsequent successful retrieval of the information. Regions within the prefrontal cortex particularly the left inferior prefrontal cortex and ventral temporal cortex have consistently demonstrated this subsequent memory effect.



**FIGURE 4:** Cortical regions in which activity is increased during successful encoding of new items (yellow/red) and in which activity is decreased during successful encoding of new items.

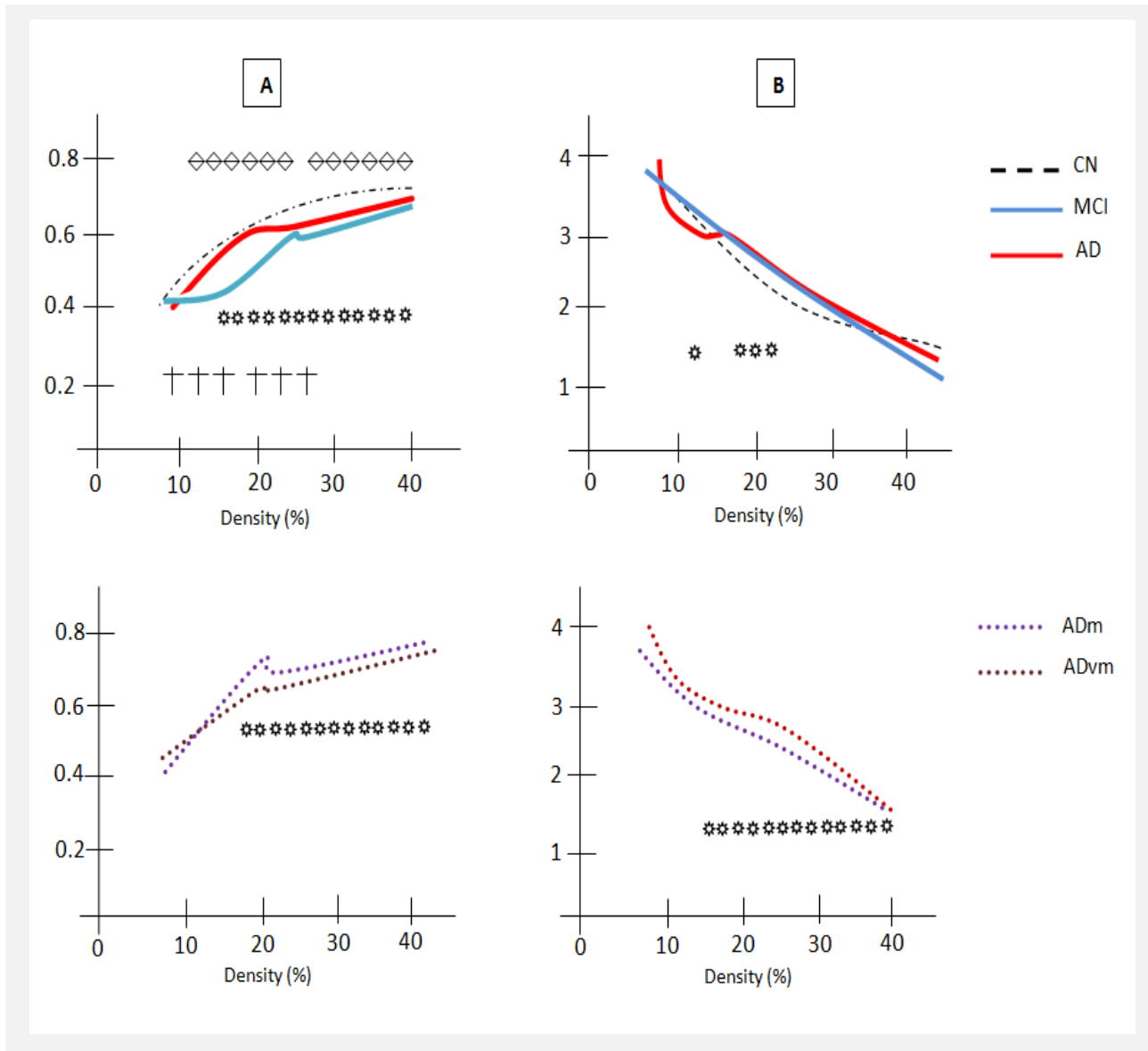
## 2.5 Statistical Analysis

In this study, all the image processing was carried out using SPM8 implemented in MATLAB. (Version8, Statistical Parametric Mapping, Well-coming Trust Centre for Neuroimaging, Institute of Neurology, UCL, London, UK, <http://www.fil.ion.ucl.ac.uk/spm/>). Statistical Parametric Mapping, is a popular neuroimaging analysis software that implements a VBM pipeline thoroughly described at the theoretical level in Ashburner and Friston (2000, Ashburner and Friston, 2005 and Ashburner, 2007, and Ashburner and Friston (2009) and at the practical level in Ashburner (2010). In this work, we compared the characteristics of DMN among these three groups (Healthy control, Mild Cognitive Impairment and Alzheimer's disease). More important, we investigated the characteristics of groups in age, gender and educational background. As we mentioned earlier, for the subgroups of very mild AD (CDR=0.5) and Mild AD (CDR=1).

For group comparisons, the HC and aMCI group, the HC and AD group, as well as the aMCI and AD group were compared by the variables of age, gender, and education background. All three groups (HC, MCI, and AD) improved the population over the density. The comparisons showed a difference among groups over the range of density except 12%–15% (CN compared to MCI) or 14% and 17% (AD compared to MCI).

More specifically, the individual parameters, both AD and MCI group had lower coefficients than CN over the density. MCI showed significantly lower coefficients than AD at certain densities (10%, 13%, 17%, and 20%). AD had significantly longer coefficients than MCI at certain densities (13%, 20%, 25%, and 26%). In subgroup analysis, mild AD subgroup had increased coefficients and longer coefficients than very mild AD subgroup.





**FIGURE 5:** The statistical approach, Diagram (A) from Healthy control, Diagram (B) Cognitively normal (CN, Black dotted line), Mild Cognitive Impairment (MCI, Blue line) and Alzheimer's disease (AD, Red line). Moreover, (A diagram) \*p, 0.04 from CN, MCI with density of 19%, 40% and \*p, 0.04 from CN, AD with density of 18%, 30%, \*p0.05 from MCI and AD with density of 15%, 20%. (B diagram): \*\*p0.05 CN, MCI with density of 14%, 22%. AD with clinical dementia rating (CDR=0.5, AD very mild, Red dotted. And AD with CDR 1 (AD Mild, purple dotted).

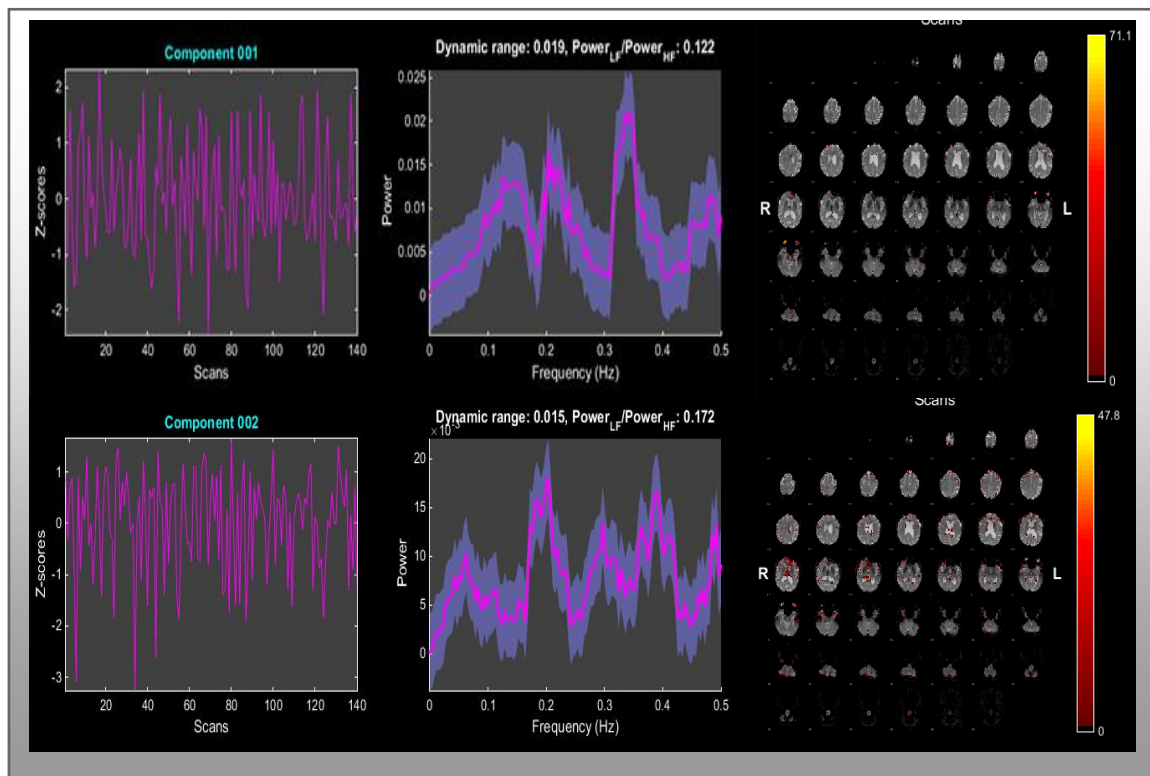
### 3. RESULTS AND DISCUSSION

#### 3.1 Rs-fMRI Evaluation

Resting-state functional magnetic resonance imaging (fMRI) is emerging as an interesting biomarker for measuring connectivity of the brain in patients with Alzheimer's disease (AD). In this work, we discuss the origins of resting-state fMRI, common methodologies used to extract information from these fMRI scans, and important considerations for the analysis of these scans. Then we present the current state of knowledge in this area by summarizing various AD resting-state fMRI studies presented in the first section and end with a discussion of future developments and open questions in the field. The previous studies of Resting State networks (RSN) included

the Default Mode Network (DMN), the Fronto Parietal Control (FPC) network, Sensory Motor Network (SMN) and Dorsal Attention Network (DAN), in this study, we analyzed the DMN showed significant differences between subject groups as well in the classification of DMN in MCI and HC subjects.

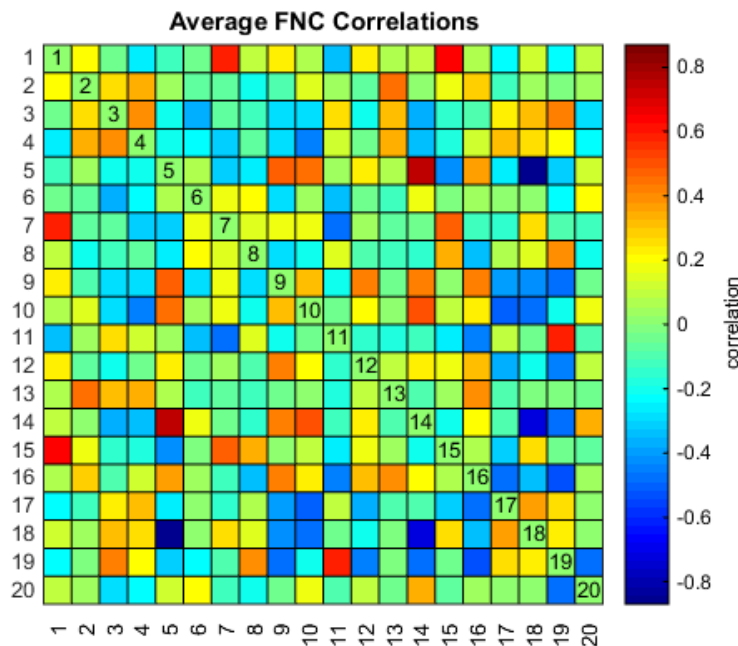
In order to improve the Independent Component Analysis (ICA), we compare the default-mode network as detected in our previous publication by the ROI approach and as detected here by the ICA approach. Significant between all the networks including the PCC, bilateral inferior parietal cortex (IPF), left infer lateral temporal cortex (IFC), medial prefrontal cortex (MPC) and ventral anterior cingulated cortex (ACC). For each RSN between-group differences were assessed by means of Z group differences were assessed by means of Z values obtained from individual ICA group maps Regions of interest (ROIs) were obtained from these RSN prototypes to compute between-group differences (HC, MCI, AD).



**FIGURE 6:** Using FastICA, Default-mode network in healthy elderly and AD subjects (HC, MCI, and AD): HC (Healthy control), Group2: MCI (Mild Cognitive Impairment), Group3: AD (Alzheimer's disease). Each group has five components [1-5], Dynamic Rang (Power/Frequency), Peak Coordinate, these data investigated by using GIFT MATLAB toolbox.

The MCI group showed significant increased Z values for the DMN. Moreover, the MCI-AD converted group showed significant increased Z values for the DMN with  $p < 0.05$  corrected for multiple comparisons. In the case of the DMN, significant increased values of connectivity were observed in the PCC for the MCI group when compared to the HC group. In the MCI-AD converted group comparison to HC by showed increased connectivity values in the right, the MCI group, when compared to HC, showed significant increased connectivity in the right. The MCI-AD converted group showed increased levels of connectivity compared to other groups of MCI or HC.



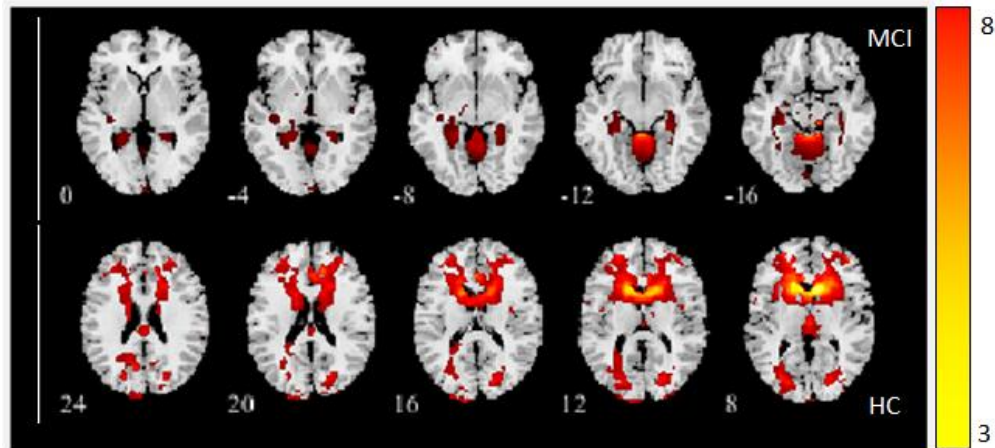


**FIGURE 7:** Functional network connectivity correlations are computed for each data-set and averaged across sessions.

### 3.2 Default Mode Network In MCI and AD

In this paper, our findings could indicate the low connectivity in MCI patients relative to HC and AD groups in the DMN regions, Including PCC, These findings are generally already fine with previous DMN studies in MCI and AD. Moreover, we notify the possibility of decrease in functional connectivity within the DMN in the early stages of AD, specifically, our findings indicate functional changes in the Default mode network which may precede large brain disorders in participants likely to progress to AD, and more important, specific regions of the DMN, particularly the PCC, are selectively vulnerable to early AD. The patients presented increased DMN connectivity between the medial prefrontal regions and the posterior cingulated. Our findings suggest that increasing DMN connectivity may contribute to semantic memory deficits in MCI, Increased DMN connectivity with posterior cingulated.

Task-induced deactivation of the DMN is generally studied with standardized analysis methods, focusing on decreases in the BOLD signal during experimental conditions compared to control conditions. In contrast, resting state functional connectivity studies utilize a variety of post-processing methods. The majority of approaches are model-driven, with strong a priori hypotheses regarding the functional connectivity between a small brain region (seed) and the rest of the brain (seed-based analysis). Another often applied technique is independent component analysis (ICA). With this data-driven technique, the functional connectivity within large-scale networks can be analyzed.



**FIGURE 8:** Cortical representation of Default Mode Network (DMN) in MCI patients and HC.

The MCI group showed significant increased Z values for the DMN. Moreover, the MCI-AD converted group showed significant increased Z values for the DMN with  $p < 0.05$  corrected for multiple comparisons. In the case of the DMN, significant increased values of connectivity were observed in the PCC for the MCI group when compared to the HC group. In the MCI-AD converted group comparison to HC by showed increased connectivity values in the right, the MCI group, when compared to HC, showed significant increased connectivity in the right. The MCI-AD converted group showed increased levels of connectivity compared to other groups of MCI or HC.

### 3.3 Validation of ICA Approach

In order to improve the Independent Component Analysis (ICA), we compare the default-mode network as detected in our previous publication by the ROI approach and as detected here by the ICA approach. Significant between all the networks including the PCC, bilateral inferior parietal cortex (IPF), left infer lateral temporal cortex (IFC), medial prefrontal cortex (MPC) and ventral anterior cingulated cortex (ACC). For each RSN between-group differences were assessed by means of Z group differences were assessed by means of Z values obtained from individual ICA group maps Regions of interest (ROIs) were obtained from these RSN prototypes to compute between-group differences (HC, MCI, AD).

## 4. CONCLUSION

In this study we investigated the evaluation of Default mode network in Mild Cognitive Impairment and Alzheimer's disease individual's healthy elderly and patients with amnesic MCI and AD. By applying ICA method, and ROI-based correlation analyses, we characterized the RSNs in all subjects. More important, the study based on the DMN and the executive attention network showed diminished functional connectivity in patients (HC, MCI, and AD). Functional connectivity between both HCs and left PCC of the DMN was absent in patients. These results suggest that in aMCI a selected subset of RSNs is affected by altered functional connectivity.

Mild cognitive impairment has been defined by biological variables with its core characteristics drawn from concepts of dementia. Other terms describe related clinical and pathological states, but amnesic mild cognitive impairment relates to a pathological state which differs from normal ageing, there is objective evidence of memory impairment, and patients are more likely to develop into Alzheimer's disease than the normal population. Mild Cognitive Impairment is becoming a very important subject for researchers and deserves more recognition and further study in order to increase the ability to recognize earlier symptoms of Alzheimer's disease. More research is needed on the biological changes associated with normal aging, MCI, and Alzheimer's disease and other dementias to better understand the causes of and risk factors for MCI, as well as the prognosis for those with MCI.

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