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Resting-state Brain in Cognitive Decline: an Analysis of Brain Network Architecture Using Graph Theory

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Abstract— **Resting-State functional magnetic resonance imaging (rs-fMRI) provides the assessment of some brain functions without tasks. Through rs-fMRI, it is possible to discover that the brain is organized in spatially distributed and interconnected brain regions. Studies suggest that aging and certain neurological or neuropsychiatric diseases affect brain connectivity, such as Alzheimer's disease (AD) and mild cognitive impairment (MCI). The general objective of this work is to investigate the evolution of the brain connectivity of individuals with healthy aging who convert to MCI, and individuals with MCI who convert to AD, using rs-fMRI and analysis based on graph theory (GT). The processing was implemented in SPM12-MATLAB, and the analysis was performed in the CONN Toolbox. The GT metrics chosen to describe the main topological characteristics of the networks were: characteristic path length, global efficiency, local efficiency, clustering coefficient, and degree. Two main findings emerged from this study. When using GT metrics and analyzing healthy subjects converting to MCI, it was possible to observe a decrease in all GT metrics. Second, changes in GT metrics indicated a rupture in the functional connectivity when the cognitive decline occurs from healthy aging to MCI, and from MCI to AD.**

Keywords — **brain connectivity, graph theory, AD, MCI.**

I. Introduction

As in the early years of life, in aging, the brain undergoes notable changes as structure and function tend to decline. The decline is associated with cognitive skills and is common in healthy aging. However, the decline may be more pronounced due to some diseases, such as Alzheimer's disease (AD). AD is a neurodegenerative disease characterized by progressive impairment of memory and executive functions. It is the most common dementia associated with aging and affects millions of older people worldwide [1]. There is an intermediate stage between typical aging and dementia, known as mild cognitive impairment (MCI). Individuals with MCI are characterized mainly by impairments in learning and memory, although cognitive deficits are also frequent. An increasing number of studies have shown that these declines are related to changes in functional brain connectivity [2].

The diagnosis of AD is classically based on clinical and cognitive assessments and, in general, diagnosed individuals already have severe brain damage [3]. Therefore, resting-state functional magnetic resonance imaging (rs-fMRI) has been taking an important and promising role in the early detection of the disease. This imaging technique allows us to measure the brain's spontaneous activity and evaluate functional connectivity without tasks. Functional connectivity was defined initially as a temporal dependence on neural activity patterns, manifested by the BOLD signal (Blood Oxygen Level Dependent) from anatomically separated regions [4]. It allows neurons to display a wide range of physiological responses, distribute information, and coordinate activities over short and long distances [5]. Therefore, it is widely studied in the context of brain diseases and disorders that alter the individual's cognitive process, with AD being the one with the most significant changes.

From rs-fMRI, it is possible to identify that the brain is organized in resting-state networks (RSNs), consisting of brain regions spatially distributed and interconnected, linked by long-distance structural connections [6]. Six RSNs were identified: Default Mode Network (DMN), visual network, sensory-motor, executive control, salience, dorsal and auditory attention. Studies showed that DMN has a decrease in functional connectivity associated with cognitively healthy aging [7, 8], is made up of regions known to be affected in prodromal AD. Studies suggest that certain neurological and/or neuropsychiatric diseases affect brain connectivity, such as MCI [10] and AD [11], multiple sclerosis (MS) [12], schizophrenia [13], depression [14] and autism [15].

Graph Theory (GT) is widely used to analyze brain connectivity since it allows the description as a single interrelated network. GT uses a wide variety of local and global network metrics to characterize brain network architecture [9].

The analysis of functional connectivity using rs-fMRI represents a new and promising approach to understand how neurodegenerative diseases can lead to connection interruption in brain networks [16, 17]. Quantification using GT can capture and compare variations in the brain network topology

of individuals with the disease concerning healthy participants [16, 18]. According to previous studies, a decrease in degree and global efficiency, and an increase in characteristic path length and local efficiency indicate a rupture or decrease in the functional connectivity in individuals with AD compared to healthy controls [2, 3, 5, 6, 9]. These variations provide connectivity characteristics that can be investigated in the context of a comparison between groups, producing new biomarkers for brain and mental disorders. However, the vast majority of studies use cross-sectional samples when analyzing AD progression. The assessment at one time-point might not represent how functional connectivity alters the brain topology, requiring more longitudinal studies to characterize the disease progression better.

This work aims to investigate the evolution of the brain connectivity of individuals with healthy aging who convert to MCI, and individuals with MCI who convert to AD, using rs-fMRI and analysis based on GT.

II. Methodology

A. Data

Structural MRI and rs-fMRI data were collected from the public database ADNI (Alzheimer's Disease Neuroimaging Initiative). ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weriner, MD. ADNI's primary goal has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD).

The data contains longitudinal data from individuals who experienced disease progression throughout the study, who converted from one state to another. The conversions investigated in this study were from the healthy aging individuals (CN) to MCI (Group CN-MCI), and from individuals with MCI to AD (Group MCI-AD). Samples were divided into two conditions: when the acquisition was produced in the baseline, and later, the follow-up was acquired. The first condition refers to individuals before converting, that is, CN individuals from the CN-MCI group (CN_1) and MCI individuals from the MCI-AD group (MCI_1). The second condition refers to individuals who converted, that is, individuals from the MCI group of the CN-MCI (MCI_2) and individuals from the AD group of the MCI-AD (AD_2). Thus, we will have four conditions: CN_1, MCI_1, MCI_2, and AD_2. In total, five individuals were found to convert CN–MCI and five individuals to convert MCI–AD.

The data were always selected from Siemens MRI equipment, with a tridimensional T1 -weighted (T1 3D) and without significant movement during the acquisition.

B. Pre-processing

All the processing steps, construction of the connectivity matrix, and calculation of graph metrics were performed using the CONN toolbox (http://www.conn-toolbox.org) implemented in the software Statistical Parametric Mapping 12 (SPM12) in MATLAB.

The first three images of each rs-fMRI acquisition were discarded to reduce the initial fluctuation of the BOLD signal [2,]. As the functional acquisition is acquired in an interleaved way, the slice time correction was performed to correct the time differences between the slices, and afterward, they were realigned. The purpose of the realignment is to remove mainly the motion artifact in time series, redirecting all images in relation to the reference slice. Participants with head movement above 1.5 mm or above 1.5° in rotation were excluded. Next, the coregistration between functional and structural acquisitions (T1 3D) was executed. The resulting images were normalized to the MNI space (Montreal Neurological Institute) and resampled in 2 mm isotropic voxels. Segmentation divided the brain into masks of gray matter, white matter, and cerebrospinal fluid (CSF). Images were smoothed by performing a spatial convolution with a 6 mm Gaussian kernel and a bandpass filter 0.0008 - 0.09 Hz.

After this initial pre-processing step, the confounding factors were regressed to reduce noise, which may include respiratory, cardiac movements, and residual effects of head movements present in the BOLD signal. Confounding effects included: the white matter and CSF noise components [20]; movement parameters using Friston model 24 [21]; and outlier scrubbing, used to remove any influence from outliers (voxels that are outside the values of the BOLD signal and are identified as noise) in the BOLD signal [22].

C. Construction Networks

The RSNs were constructed using regions of interest (ROI) distributed throughout the brain. These regions were obtained by parceling the gray matter (excluding the cerebellum) from the rs-fMRI data pre-processed in thirty ROIs, using the cortical and subcortical areas of the Harvard-Oxford atlas. The thirty ROIs cover the following networks:

- Default Mode Network (DMN): MPFC (medial prefrontal cortex), LP (bilateral parietal) and PCC (posterior cingulate cortex).
- Sensory Motor: Bilateral and superior lateral.
- Visual: bilateral, medial and occipital lateral.

- Overhang: ACC (anterior cingulate cortex), AI (anterior insula) bilateral, RPFC (rostral prefrontal cortex) bilateral and SMG (supramarginal gyrus) bilateral.
- Dorsal attention: bilateral FEF (frontal eye fields) and bilateral IPS (intraparietal sulcus).
- Frontal Parietal: LPFC (lateral prefrontal cortex) bilateral and PPC (posterior parietal cortex) bilateral.
- Language: bilateral IFG (inferior frontal gyrus) and bilateral pSTG (superior temporal gyrus).

For each individual, the time series of the BOLD signal was extracted from each ROI, and the correlation coefficients between the time series of each pair of all ROIs were calculated using Pearson's bivariate correlation. The correlation coefficients were converted into Z-scores normally distributed using Fisher's transformation. Thus, a functional connectivity matrix 30 x 30 elements (ROIs) was built. The value of each element of the matrix was the bivariate correlation coefficient of the Z transform, representing the node between each pair of the regions that define the edges.

D. Graph Theory

All values of the functional connectivity matrix were calculated using a certain threshold (K). According to a previous study [24], using intermediate threshold level K = 0.15, GT metrics showed results with a high degree of reliability. Thus, graph metrics were calculated using K = 0.15 and a $p < 0.05$ in the connectivity matrix. The graph metrics chosen to describe the main topological characteristics of the networks were: characteristic path length, global efficiency, local efficiency, clustering coefficient, and degree [9].

E. Statistical analysis

Statistical analysis was performed in two stages. First, one-sample Student's t-tests were calculated for individuals in the baseline condition (CN_1 and MCI_1) to determine the functional connectivity between networks and the graph metrics. Then, we used the analysis of variance (ANOVA) in the four conditions to examine the main effects of time in the group. The following hypotheses were evaluated: $CN_1 < MCI_2$ and $MCI_1 < AD_2$, to determine if there is an increase in both connectivity strength and metrics throughout longitudinal cognitive decline; $CN_1 > MCI_2$ and $MCI_2 > AD_2$ to determine if there is a reduction in both connectivity strength and metrics.

III. Results

A. Demographic data

The individuals' demographic data in this study are shown in Table 1 with the minimum and maximum age in years, formal education in years, and two cognitive tests: MMSE (Mini-mental State Exam) and the CDR-SB values (Clinical Dementia Ratio - Sum of Box Scores).

Table 1 Demographic data of baseline and follow-up groups

	Baseline	*Follow-up*	*Baseline*	*Follow-up*
	CN	MCI	MCI	AD
Age (years)	65.5 – 91.5	62.2 – 88.3	66.6 – 93.5	63.2 – 89.4
Gender (M/F)	3/3	4/1	3/3	4/1
Education (years)	12 - 20	12 - 18	12 - 20	12 - 18
MMSE	22 - 30	23 - 30	24 - 30	19 - 27
CDR-SB	0 – 0.5	0.5 - 4	0 – 3.5	2.5 - 10

Abbreviations: MMSE – *Mini-mental state exam*; CDR-SB - *Clinical Dementia Ratio – Sum of Box Scores*; CN – Controle; MCI – mild cognitive impairment; AD - Alzheimer; M – Male; F – Female

B. Graph Theory

Table 2 shows the highest correlations between the graph metrics and the networks in CN_1 baseline condition. All network regions were identified in the metrics, totaling 100% connections.

Table 2 Correlation between metrics and regions in CN_1 baseline condition

Metric	Network	t value	p-FDR
Global efficiency	Salience	41.22	0.000023
Local efficiency	Visual	109.78	0.000001
Characteristic path length	Salience	25.01	0.000228
Clustering coefficient	Visual	43.85	0.000024
Degree	Dorsal Attention	19	0.000678

Table 3 indicates the highest correlations values between the graph metrics and the networks in MCI_1 baseline condition. All network regions were identified in the metrics, totaling 100% connections.

Table 3 Correlation between metrics and regions in MCI_1 baseline condition

Metric	Network	t value	p-FDR
Global efficiency	Visual	19.58	0.000212
Local efficiency	Salience	21.23	0.000536
Characteristic path length	Fronto Parietal	15.88	0.000726
Clustering coefficient	Visual	16.67	0.000587
Degree	Fronto Parietal	8.96	0.008164

Comparing baseline and follow-up condition $CN_1 > MCI_2$, correlations indicate a reduction in all graph metrics, shown in Table 4. No correlations indicated an increase in graph metrics in the networks, meaning, in the comparison of baseline and follow-up condition $CN_1 < MCI_2$ no significant values were found ($p < 0.05$).

Table 4 Comparison of graph metrics between CN_1 and MCI_2 groups. ($CN_1 > MCI_2$)

Metric	Network	t value	p
Global efficiency	Visual	-2.19	0.046905
	Sensory Motor	-2.16	0.048176
Local efficiency	Visual	-7.16	0.009467
	DMN	-3.47	0.036995
	Dorsal Attention	-3.46	0.020364
	Salience	-2.45	0.045749
Characteristic path length	Fronto Parietal	-3.39	0.038529
Clustering coefficient	DMN	-6.45	0.011603
	Visual	-5.66	0.014894
	Dorsal Attention	-4.74	0.008830
	Sensory Motor	-2.60	0.040032
	Salience	-2.60	0.010251
Degree	Salience	-3.16	0.017125
	Sensory Motor	-2.62	0.029432
	Language	-2.48	0.034032
	Visual	-2.26	0.043491

Comparing baseline and follow-up $MCI_1 > AD_2$, the correlations indicate a reduction in networks using graph metrics were shown in Table 5. Comparing baseline and follow-up $MCI_1 < AD_2$, the correlations indicate an increase in networks using graph metrics were shown in Table 6.

Table 5 Comparison of graph metrics between MCI_1 and AD_2 groups. ($MCI_1 > AD_2$

Metric	Network	t value	p
Global efficiency	Fronto Parietal	-6.18	0.001741
	Visual	-3.36	0.014162
	Salience	-2.30	0.041666
Degree	Fronto Parietal	-6.08	0.001850
	Visual	-3.51	0.012356
	Salience	-3.26	0, 016061

Table 6 Comparison of graph metrics between MCI_1 and AD_2 groups. ($MCI_1 < AD_2$)

Metric	Network	t value	p
Local efficiency	Salience	5.25	0.017189
	Visual	2.20	0.046220
Characteristic path length	Fronto Parietal	3.40	0.013690
	Visual	2.72	0.026431
Clustering coefficient	Salience	5.67	0.014847
	Visual	2.56	0.031212

A comparison of the representation of the global efficiency metric between CN1> MCI2 and MCI1 <AD2 can be seen in Fig. 1.

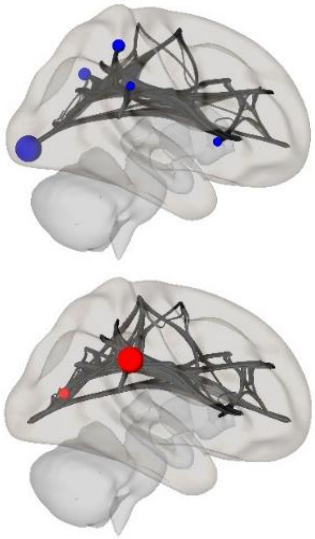

Fig. 1 Representation of the global efficiency metric in the brain sagittal plan. The circles represent the nodes, and the bars are the edges (strength of connectivity between the ROIs). Superior: Comparing $CN_1 > MCI_2$. Inferior: Comparing $MCI_1 > AD_2$

IV. Discussions and Conclusion

This study aimed to investigate the evolution of brain connectivity in individuals with healthy aging who had cognitive decline, converting to MCI, and individuals with MCI who converted to AD, using rs-fMRI and GT. The findings suggest brain topologies of different networks in individuals converting from healthy aging to MCI and from MCI to AD.

Two main findings emerge from this study. When using GT metrics, comparing only the conditions CN_1 and MCI_1 (Tables 2 and 3) was possible to observe a decrease in all metrics. Second, both groups showed changes in metrics that indicate a rupture in the functional connectivity when the cognitive decline occurs (Tables 4, 5, and 6).

The first finding refers to the baseline conditions, comparing Tables 2 and 3. A reduction was found in all graph metrics in individuals before converting to MCI_2 (Table 2) and AD_2 (Table 3), that is, the follow-up group. These findings of decreased metrics in individuals with AD agree with previous studies [25, 26]. However, no studies were found to assess longitudinal changes in individuals' functional connectivity

when the cognitive decline occurs using graph theory, as performed in this work.

The second finding refers to the changes that occurred between the groups. Only a reduction in metrics graphs was observed in healthy aging subjects that convert to MCI (Table 4). The average values of GT metrics, from the highest to the lowest reduction, are: clustering coefficient (t = -4.41), local efficiency (t = -3.79), characteristic path length (t = -3.39) degree (t = -2.57) and global efficiency (t = -2.18). In converting individuals MCI to AD; however, graph metrics showed a reduction (Table 5) in some metrics and an increase (Table 6) in others. The average values of the metrics that decreased with cognitive decline in this group were: degree (t = -4.04) and global efficiency (t = -3.8). There was an increase in the average values of the metrics: clustering coefficient (t = 3.86), local efficiency (t = 3.73) and characteristic path length (t = 2.95). Thus, one observed that the cognitive decline presents a reduction of two metrics in both groups of individuals with advancing cognitive decline: global efficiency and degree. However, when the cognitive decline of the MCI group occurs, and subjects are considered with AD in follow-up, some graph metrics increased.

Analyzing MMSE and CDR-SB results, it is noted that there was practically no difference in the MMSE average compared to the baseline and follow-up group CN-MCI. The difference in diagnosis is due to CDR-SB values. When comparing the MCI-AD group at baseline and follow-up, there is a difference in MMSE and CDR-SB.

Our results highlight a topology of the brain networks with several similarities found in other studies. However, the comparison of our results is limited to cross-sectional studies of individuals with AD and MCI. Such studies suggest that a more prominent topological alteration occurs in individuals with AD and intermediate in individuals affected with MCI [27, 28]. Tijms et al. [29] evaluated GT metrics in AD individuals compared with control individuals, showing an increase in characteristic path length and clustering coefficient and a decrease in global efficiency. These findings are consistent with the results found in our study.

Other studies evaluating the efficiencies and the characteristic path length of graph metrics and the diseases of aging, found an increase in local efficiency, a reduction in global efficiency and an increase in the characteristic path length in patients with MCI and AD [30, 31, 32, 33]. The study by Yao and collaborators [27] determined the metrics of graphs comparing individuals with MCI and control individuals, showing no significant difference in clustering coefficient and characteristic path length, but there was a decrease in degree. Other studies [34,35] have shown that the functional connectivity of DMN in MCI and AD individuals suffer a rupture in connectivity by decreasing the clustering coefficient and increasing local efficiency and the characteristic path length. Our results showed a decrease in DMN in local efficiency and clustering coefficient in the CN-MCI group. In the MCI-AD group, no significant difference was found ($p < 0.05$). Despite the consistency of our results with most studies, there are some divergences, particularly in the converter group of healthy aging who progress to MCI. However, as most studies do not carry out longitudinal monitoring of individuals, our results need to be confirmed through analysis with a larger sample.

The importance of quantifying global and local efficiency metrics is related to the exchange of brain information both at an anatomical (local) or distant (global) level. High-efficiency networks ensure that brain regions effectively process and share specific information; simultaneously, these exchanges of information must be unified to create groups of brain states (networks). GT's metrics provide a quantitative view of the relevant network parameters that affect the performance of these networks, such as the speed of information transfer and the robustness of connection changes due to disease [36]. Brain networks characterized by a high degree, clustering coefficient, and low characteristic path length are related to a model of complex brain networks, which maximizes the efficiency of information propagation [24]. Comparing this information with our results and previous studies, we identified a rupture in functional connectivity in individuals who convert from MCI to AD. This rupture was identified by the increase in the metric of characteristic path length, local efficiency, and clustering coefficient, and a decrease in global efficiency and degree. In individuals who convert from controls to MCI, we find the opposite results in some metrics. It might identify a decrease in functional connectivity, but not as marked as the other group. The group with the most significant difference in MMSE and CDR-SB averages is directly correlated with TG metrics' variations that identify rupture in connectivity.

Regarding the longitudinal assessment of healthy aging who convert to MCI, one of the hypotheses for conflicting results is the fact that MCI is an intermediate level before DA, where the networks have not been significantly changed, so that they reflect in their metrics, as discussed in other studies [27, 28, 29].

Besides, the main reason for the variations found in this study is the exclusive use of longitudinal data. Other studies have evaluated the brain's functional connectivity in the progression from MCI to AD [37, 38], but have not used graph metrics. Such studies have found disruptions in the brain networks, but it is impossible to characterize the brain topology of the functional networks completely without the information from the graph metrics data.

The main limitation of this study is that it was carried out with a small sample size, which can mitigate the statistical power in detecting the differences between the groups in some of our measurements, mainly in the metrics of graphs. Thus,

further studies have to increase the number of subjects to validate our findings.

Conflict of interest

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