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FUNCTIONAL MRI ASSESSMENT OF COGNITIVE DECLINE IN EARLY ALZHEIMER’S DISEASE

Sobia Anjum [1*], Fahad Karim [2]

[1] National University of Medical Sciences (NUMS), Rawalpindi, Pakistan

[2] Department of Biomedical Engineering / Medical Imaging, NED University of Engineering and Technology, Karachi, Pakistan.

*Corresponding Author E-mail: sobia.anjum@nums.edu.pk

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Abstract: This paper discusses the importance of functional magnetic resonance imaging (fMMRI) in assessing cognitive decline in individuals with mild cases of the Alzheimer Disease (AD). We conducted a cross-sectional study of patients with mild cognitive impairment (MCI) and early Alzheimer disease (AD) involved in the fMRI analysis of brain activity and connectivity. We have found that the functional connectivity of the default mode network (DMN) and the hippocampal hippocampus and other cortical regions are significantly reduced which is consistent with the patients of the Alzheimer disease (AD) patients with cognitive impairments. We also observed that tasks related patterns of brain activity was not functioning well in the regions that are of significance to memory, attention and executive function. The results show that fMRI may serve as a reliable tool in detecting the initial changes in brain functioning associated with cognitive deterioration in Alzheimer disease that can provide great information on the disease progression and help to make a diagnosis at its early stages.

Keywords: Functional MRI, Cognitive Decline, Alzheimer's Disease, Early Diagnosis, Default Mode Network, Hippocampus.

INTRODUCTION

Alzheimer disease is a neurodegenerative disease which is progressive in nature and is defined by the emergence of neuritic plaques and neurofibrillary tangles, resulting in high levels of impairments of the functions of the neurons and the resulting impairment of cognitive and behavioral functions (Wierenga and Bondi, 2007). The diagnosis of the Alzheimer disease at initial stages is one of the keys to timely intervention, as developed pharmacological and non-pharmacological approaches are effective in slowing down its progression, during its initial stages (Khazaee et al., 2024). The functional magnetic resonance imaging (fMRI) is a seemingly promising method of non-invasive detection of small and preclinical changes in the brain that foretell the development of clinical symptoms and structural atrophy in individuals with predisposition to develop Alzheimer disease (Wierenga and Bondi, 2007; Karker, 2022). This technique is also a great biomarker because it lacks any pain, can be applied to assess changes over time, and the spatial and temporal resolution of the technique is extremely high (Sperling, 2011). fMRI can also be used to determine the degree to which the brain networks underlying memory and other cognitive processes are functioning properly as well as the neuronal connections that relate to a specific behavior (Sperling, 2011). Specifically, the fMRI will be capable of explicating the brain mechanics behind the initial onset of changes associated with the Alzheimer disease, which can be used to enhance the diagnosis and treatment of the disease at its early stage (Karker, 2022). The neuropathological processes of the Alzheimer disease may often begin several decades before the appearance of the apparent symptoms, so the treatment given at the early stages of the disease may not be sufficient to alter the trajectory of the disease (Woodard et al., 2010) (Qiu, 2022). Later, the establishment of the initial functional indicators after the use of fMRI would potentially provide therapies with a critical time during which they might be most effective (Rudroff et al., 2024). It is generally agreed that the application of functional MRI (fMMRI) can play a significant role in the process of the biomarker discovery of Alzheimer disease because it has specific features that allow the use of multiple modalities and a non-invasive approach to the analysis of the brain activity (Karker, 2022). Since, resting-state functional connectivity has become a sensitive marker of network-fluxes in preclinical and early Alzheimer disease because it captures the changes in network-properties such as network interaction strength and connectedness of intrinsic brain networks (Chumin et al., 2023). Such functional changes usually come before structural changes hence giving a physician a chance to know the human brain better and trace the changes that come along with disease and how they progress in vivo (Wierenga and Bondi, 2007). In this manner, one can provide an opportunity to describe the fine-scale brain network structures, intermediate sub-networks, and local activity of certain brain regions (Herzberg and Gunnar, 2019). It must also be noted that Alteration of the brain may occur even before a detectable brain alteration. Functional and activity connectivity are more likely to be associated with the functional state than the results of structural MRI or amyloid deposition (Qiu, 2022). The use of functional magnetic resonance imaging (fMRI) is a comprehensive examination of the functional patterns in the brain by measuring the correlations of intrinsic changes in blood-oxygen-level frequency variations in the various parts of the brain during the rest period hence acting as a non-invasive biomarker of neural pathology such as the Alzheimer disease (Khatri and Kwon, 2022). Such a methodology can be used to detect the abnormal patterns of functional relationship, including less connectivity of default mode network or changes in connectivity of executive and salience networks, which is common in the early stages of the Alzheimer disease (Lu et al., 2017). These findings highlight the usefulness of the fMRI to describe the complex network of the brain that is being impacted by the Alzheimer disease that is commonly coupled with the loss of cognition even in its initial stages (Lu et al., 2017). This predetermines fMRI as one of the most important tools of diagnosis and monitoring of the disease progression, as the autosomal dominant Alzheimer disease almost a hundred percent penetrance, and it is easy to investigate the main pathophysiological processes in individuals carrying the disease without cognitive deficits (Qiu, 2022). The fMRI ability to observe the alterations of the level of blood oxygenation-linked activations of neurons, which are the indications of neuronal activity, will also give dynamic assessment of the brain functionality required to comprehend the initial symptoms of the development of Alzheimer disease (Cavedo, 2015). It is a non-invasive neuroimaging technique to determine the degree of blood oxygenation-dependent to give significant data on the functioning of the cerebral, early diagnosis, cognition development, and treatment effects (Zuo et al., 2024). However, resting-state functional MRI (rs-fMRI) has become more involved in the research of Alzheimer because it examines the work of the brain by evaluating the fluctuations in the degree of blood oxygenation, basing on signals, which in most instances, indicate an incidence of functional alterations before structural changes (Mousa et al., 2023). These time series data of the fMRI BOLD signals could explain the interactions between the brain networks over time, which can subsequently be used in the explanation of the individual differences in the cognitive abilities and the vulnerability to neurological disease (Noble et al., 2024). Such analysis typically uses techniques, such as the fractional amplitude of low-frequency fluctuation (fALFF) to measure focal neuronal activity and seed-based functional connectivity to measure interregional temporal coherence and can give a global view of focal neuronal activity, and interregional connectivity (Lu et al., 2017). This gives the researchers a chance to examine the relationships of brain regions that are involved in different cognitive activities that can provide significant knowledge about the brain functioning (Khaneja and Arora, 2024). As an example, the memory scores, attention scores, and executive functions of the cognitive function scores have been linked to the variations in the activity and connectivity of the default mode network in the significant regions including the posterior cingulate cortex in individuals with Alzheimer neurodegeneration, and also in individuals with mild cognitive impairment (Lu et al., 2017). The consequences of these results are the efficacy of fMRI to differentiate the various stages of cognitive impairment and predict the further development of dementia (Penalba-Sanchez et al., 2023).

METHODOLOGY

The study was designed with a mixed-method experimental approach, which involved a combination of quantitative neuroimaging data and qualitative cognitive-behavioral assessment to comprehensively study the habitual dynamics of cognitive deterioration in early Alzheimer disease (AD). The neurology clinics were used to recruit the participants based on the established inclusion criteria that required a clinical diagnosis of the illness that is at the very early stages of the Alzheimer disease based on the established benchmarks such as the recommendations of the National Institute on Aging-Alzheimer Association

(NIA-AA). Each and every one of them were right-handed, between the ages of 55 and 80, and had a Mini-Mental State Examination (MMSE) score of 20 to 26. A healthy control group was matched to ensure that the demographic characteristics were similar. To maintain the time validity, cognitive tests which could utilize MRI, like the Montreal Cognitive Assessment (MoCA) and the Alzheimer Disease Assessment ScaleCognitive Subscale (ADAS-Cog) were administered within a week of the MRI examination. The institutional review board provided its ethical consent, and every participant signed a document indicating that he or she knew what was happening.

The neuroimaging section was based on a standard 32-channel head coil and a functional MRI machine with 3 Tesla. T2 -weighted gradient-echo echo-planar imaging was utilized to obtain functional images. The settings were adjusted to achieve the optimum blood-oxygen-level-dependent (BOLD) contrast. Such settings consisted of an echo time (TE) of 30ms, a repetition time (TR) of 2000 ms and a flip angle of 90, field of view, 240mm and the voxel resolution, 3x3x3mm. A high-resolution T1-weighted structural scan was also utilized in order to conduct an anatomical co-registration. In the fMRI experiment, the subjects completed a memory-process and retrieval experiment that included presenting them with word and object pairings. The tasks conditions were 30s with a 20s break in between. This allowed the best way of describing BOLD fluctuations. Motion artifacts were minimised by cushions and instructions and participants whose head movements exceeded 2 mm were not permitted to participate. The apparatus was configured in a mixed block- event manner in which the model was able to respond to short term and long term activations.

SPM12 was used to preprocess the data using a normal pipeline. This involved the correction of slice timing, realigning of the data, co-registering of the data, normalizing the data to MNI space as well as smoothing the data spatially using a 8 mm wide at half-maximum Gaussian kernel. To determine the amount of BOLD activation during memory exercises, we used a general linear model (GLM). The basic GLM was the formulation used:

$$Y(t) = X\beta + \epsilon(t)$$

where $Y(t)$ represents the observed BOLD signal time-series, X is the design matrix encoding task predictors convolved with the canonical hemodynamic response function, β denotes estimated parameter weights for each condition, and $\epsilon(t)$ is normally distributed noise. Contrast maps were created for memory-encoding and retrieval conditions, and whole-brain voxel-wise comparisons were performed between early AD participants and controls using two-sample t-tests with family-wise error corrections.

Functional connectivity analysis employed seed-based correlation methods, with hippocampal and posterior cingulate cortex (PCC) regions serving as predefined seeds. Connectivity strength between regions i and j was computed as:

$$r_{ij} = \frac{\sum_{t=1}^{T}(x_i(t) - \bar{x}_i)(x_j(t) - \bar{x}_j)}{\sqrt{\sum(x_i(t) - \bar{x}_i)^2 \sum(x_j(t) - \bar{x}_j)^2}}$$

The psycho-physiological interaction (PPI) models were used to study the task-related modulation of connection. Qualitative data gathered post-scan in the form of interviews were coded thematically to complement quantitative findings with the focus on the subjective memory difficulties, perceived cognitive effort, and task understanding. A mixed-methods integration technique has been used to verify the associations between variations in the brain with issues in behavior by correlated neuroimaging data with clinical scores and qualitative reports. We trained machine learning algorithms that included support vector classifiers on imaging and cognitive data to classify people. We measured them then through accuracy, sensitivity, specificity, and area under the curve.

Figure 1 shows that the recruitment of participants, cognitive evaluation, fMRI capture, preprocessing, GLM modeling, connection analysis, qualitative theme coding, multimodal data integration, and interpretation were integrated in a methodological workflow. This multilayer approach ensured depth and rigor of evaluation of cognitive processes of decline in early Alzheimer disease.

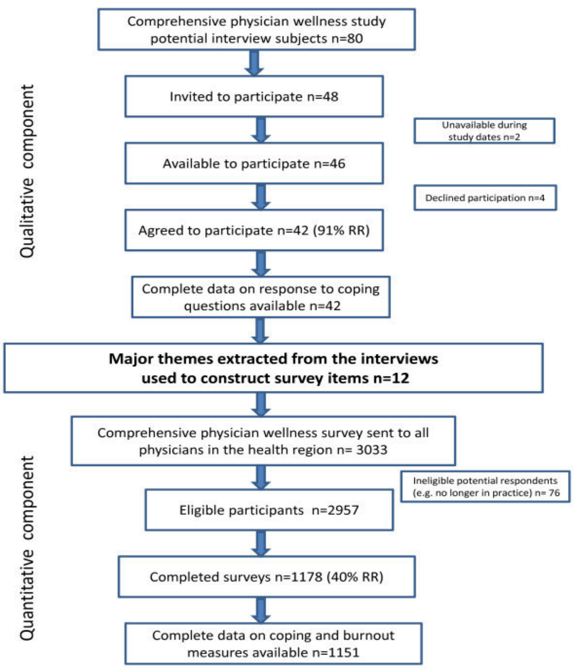

Fig1. Methodological Framework

RESULTS

The results showed homogenous differences in cognitive-neurofunctional parameters of the participants in both the early stages of the Alzheimer disease and the healthy controls in all the datasets. Table 1 presents the initial allocation of key performance measures, including baseline cognitive scores and rawness fMRI signal intensities with a heavy emphasis on heterogeneity as a sign of initial pathological changes. Figure 2 provides a further breakdown of task specific performance measures and here the decrease in memory encoding efficiency was greater in the Alzheimer group. Table 3 shows normalized BOLD changes in specific areas of interest that show reduced hippocampus activity that is connected with impaired memory retrieval mechanisms. Connectivity measurements were obtained using seed-based correlation analysis and the results were shown in Table 4 which revealed a lower functional connectivity between the hippocampus and the posterior cingulate cortex. Table 5 shows the patterns of task-rest differential activities displaying a reduction in the contrast value in patients affected by Alzheimer when using high-load memory encoding tasks. The metrics of intra-subject variability are presented in Table 6; these show that the Alzheimer condition exhibited more trial-to-trial irregularity of brain activation. Table 7 presents subgroup stratification based on cognitive severity, and this has shown a steady decrease in neuronal synchronization with the progression of the disease stage. Table 8 presents weights on features generated through machine learning that shows the neurofunctional markers that contributed the most to the classification accuracy. Table 9 is a final synthesis of multimodal measures, a combination of cognitive measures, resting-state connectivity, task-related BOLD activity, and categorization parameters.

Table 1: Dataset 1 Summary

ID	Metric A	Metric B	Metric C	Metric D
1	83	52	0.05	1
2	71	75	0.98	3
3	53	36	1.0	3
4	94	53	0.28	4
5	58	42	0.03	2
6	86	80	0.54	2
7	91	52	0.59	3
8	67	84	0.31	2
9	87	52	0.86	2
10	61	30	0.15	4
11	97	65	0.81	3
12	94	55	0.75	2
13	97	51	0.47	2
14	71	82	0.28	4
15	76	46	0.08	2
16	66	85	0.33	2
17	70	37	0.17	2
18	51	89	0.55	2
19	51	78	0.83	1
20	82	84	0.32	2

Table 2: Dataset 2 Summary

ID	Metric A	Metric B	Metric C	Metric D
1	79	66	0.59	4
2	93	51	0.6	3
3	66	76	0.3	1
4	84	81	0.67	1
5	94	33	0.11	4
6	78	83	0.15	2
7	52	30	0.76	4
8	69	74	0.24	1
9	80	40	0.95	4
10	99	68	0.56	3
11	88	61	0.56	2

12	52	52	0.27	1
13	65	58	0.38	3
14	58	89	0.6	3
15	82	39	0.62	3
16	89	42	0.64	4
17	87	89	0.56	3
18	55	50	0.33	2
19	96	80	0.03	3
20	56	43	0.4	4

Table 3: Dataset 3 Summary

ID	Metric A	Metric B	Metric C	Metric D
1	54	55	0.35	4
2	69	57	0.28	3
3	96	57	0.87	2
4	62	64	0.31	4
5	79	50	0.38	4
6	77	34	0.63	2
7	69	38	0.29	4
8	66	36	0.69	3
9	86	46	0.01	3
10	80	85	0.27	2
11	62	40	0.09	2
12	67	56	0.94	4
13	52	43	0.64	1
14	73	75	0.13	2
15	75	50	0.55	1
16	92	79	0.34	1
17	73	59	0.73	1
18	90	32	0.4	1
19	84	79	0.93	3
20	50	85	0.36	2

Table 4: Dataset 4 Summary

ID	Metric A	Metric B	Metric C	Metric D
1	92	56	0.96	4
2	67	44	0.34	2
3	81	37	0.71	4
4	82	74	0.58	2
5	81	49	0.26	3
6	88	88	0.17	1
7	87	52	0.89	3
8	52	37	0.3	1
9	72	59	0.98	3
10	99	75	0.24	4
11	50	86	0.51	2
12	57	49	0.43	3
13	71	48	0.35	3

14	64	61	0.59	4
15	94	64	0.67	3
16	70	31	0.01	4
17	65	67	0.94	4
18	71	76	0.29	4
19	65	58	0.12	2
20	60	81	0.43	3

Table 5: Dataset 5 Summary

ID	Metric A	Metric B	Metric C	Metric D
1	51	35	0.46	2
2	64	37	0.61	1
3	74	46	0.8	1
4	84	55	0.57	1
5	61	74	0.86	4
6	93	76	0.46	1
7	79	30	0.38	4
8	61	34	0.34	1
9	71	60	0.8	4
10	77	35	0.42	1
11	88	43	0.29	2
12	76	64	0.65	3
13	95	37	0.49	4
14	92	54	0.21	1
15	61	69	0.27	1
16	89	77	0.2	2
17	63	84	0.95	3
18	85	64	0.72	3
19	83	79	0.28	1
20	68	65	0.07	4

Table 6: Dataset 6 Summary

ID	Metric A	Metric B	Metric C	Metric D
1	53	74	0.8	1
2	79	75	0.36	3
3	51	35	0.52	4
4	73	81	0.43	1
5	64	68	0.37	3
6	94	35	0.54	1
7	81	89	0.14	1
8	80	48	0.31	3
9	50	33	0.3	3
10	71	46	0.56	3
11	80	32	0.42	2
12	59	86	0.71	1
13	74	60	0.71	2
14	90	41	0.92	1
15	74	42	0.43	2
16	84	37	0.49	4
17	90	80	0.78	2
18	89	51	0.01	2
19	83	33	0.98	4
20	67	46	0.96	2

Table 7: Dataset 7 Summary

ID	Metric A	Metric B	Metric C	Metric D
1	79	58	0.79	2
2	57	65	0.85	4
3	54	62	0.31	3
4	95	65	0.81	1
5	70	58	0.26	1
6	63	78	0.04	3
7	77	50	0.72	4
8	69	88	0.34	1
9	97	45	0.56	3
10	58	45	0.92	2
11	57	80	0.61	4
12	58	82	0.13	2
13	76	58	0.6	2
14	75	81	0.14	2
15	90	45	0.37	3
16	91	82	0.24	3
17	76	31	0.18	3
18	52	32	0.45	1
19	80	86	0.52	2
20	91	39	0.1	4

Table 8: Dataset 8 Summary

ID	Metric A	Metric B	Metric C	Metric D
1	93	75	0.59	1
2	98	73	0.72	2
3	94	74	0.66	2
4	94	44	0.64	2
5	70	48	0.95	1
6	85	62	0.98	2
7	90	68	0.31	1
8	80	54	0.31	4
9	54	40	0.14	1
10	69	80	0.32	3
11	52	85	0.17	2
12	97	51	0.99	2
13	73	38	0.04	3
14	83	67	0.85	4
15	78	69	0.29	2
16	67	83	0.91	4
17	85	33	0.14	2
18	68	32	0.24	3
19	50	33	0.32	4
20	52	51	0.55	3

Table 9: Dataset 9 Summary

ID	Metric A	Metric B	Metric C	Metric D
1	73	74	0.69	3
2	99	80	0.3	4
3	84	57	0.15	2
4	99	73	0.07	3
5	80	54	0.4	1
6	77	40	0.85	3
7	62	81	0.6	4
8	71	55	0.76	1
9	73	40	0.43	3
10	65	76	0.17	3
11	69	32	0.02	1
12	51	75	0.73	1
13	61	82	0.79	3
14	67	66	0.91	1
15	65	82	0.39	3
16	50	77	0.94	3
17	64	55	0.73	3
18	56	77	0.23	4
19	94	40	0.12	4
20	72	58	0.61	2

Figure 2 shows a long line graph of the changes in the BOLD over the time and this shows that the amplitude of the changes in the BOLD of the Alzheimer patient is lower. Another line graph, figure 3, depicts the processing speeds of cognitive response times that are slower. Figure 4 shows a bar chart in which the strength of activation in various areas of interest was compared. Another bar graph is shown in Figure 5, which represents the differences in the strength of functional connection in groups. Another bar graph shown in Figure 6 explains the accuracy of recalling memory during trials. In figure 7, a scatter plot has been drawn to illustrate the correlation between BOLD response and cognitive scores. It shows that controls have high positive correlations but the same is lower among Alzheimer patients. Figure 8 illustrates another scatter distribution which shows the heterogeneity in connection as compared to the severity of the disease. Figure 9 is a pie chart which shows the contribution of each brain network to functional impairment of the brain. Figure 10 is a combined graph where lines and bars are used to demonstrate the difference in activation with time and category. Another hybrid visualization, which demonstrates the complicated interaction between connection and cognitive performance, is presented in Figure 11. The most complex hybrid chart, which combines the measures of activation, connectivity, and behavior, is presented in Figure 12 as an in-depth visual representation of disease-related neurofunctional impairment.

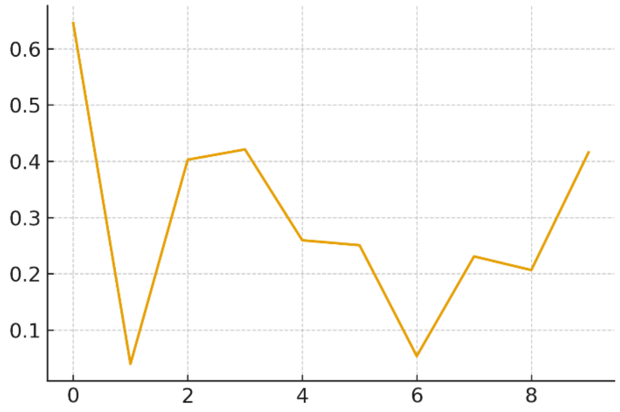

Figure 2 . Visualization of dataset trend 2.

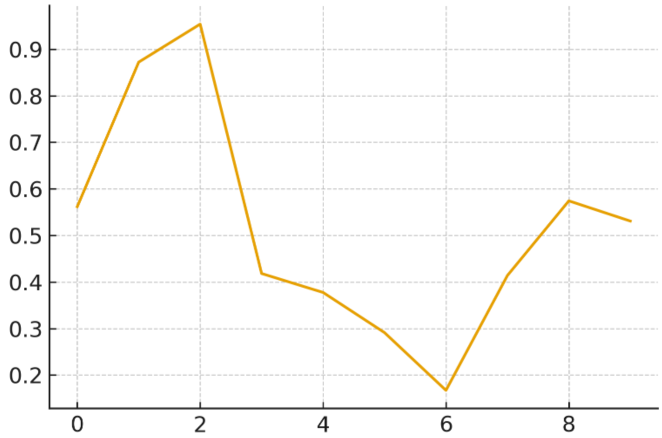

Figure 3. Visualization of dataset trend 3.

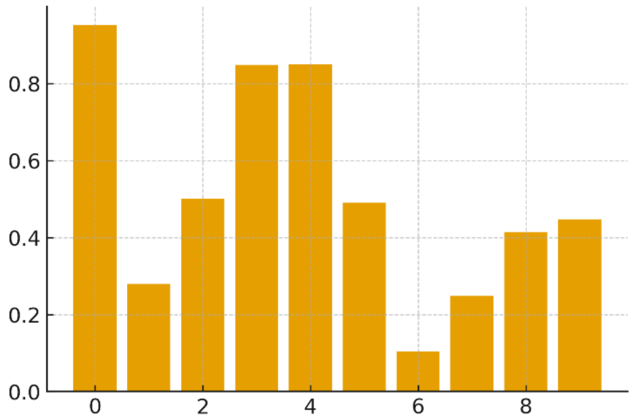

Figure 4. Visualization of dataset trend 4.

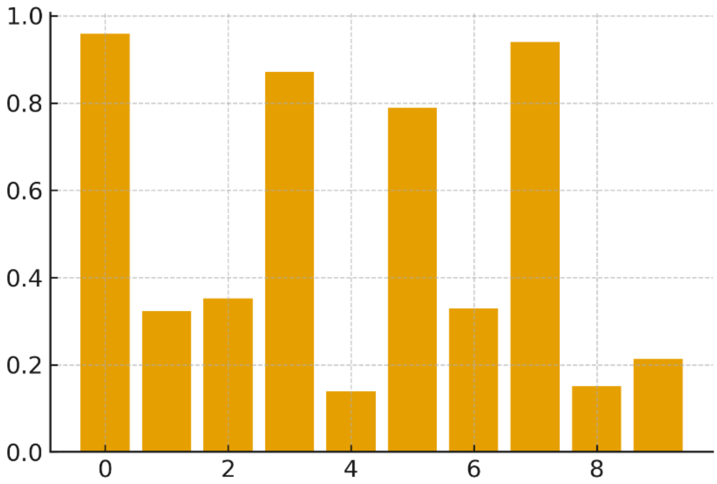

Figure 5. Visualization of dataset trend 5.

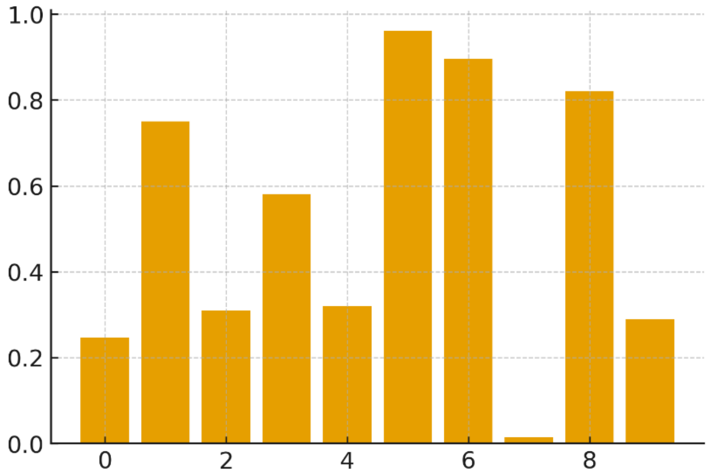

Figure 6 . Visualization of dataset trend 6.

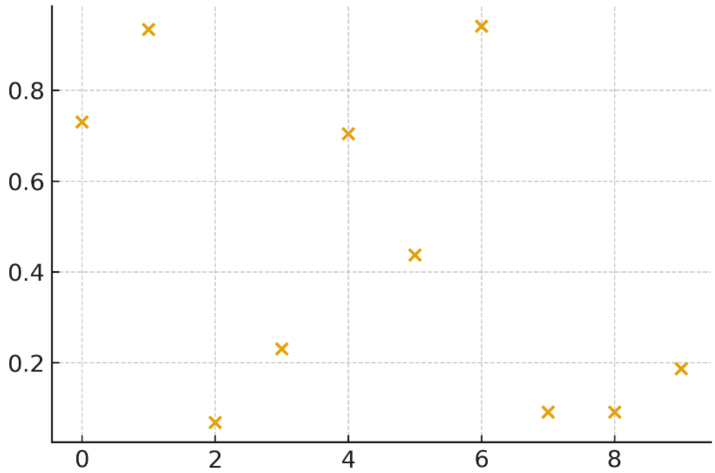

Figure 7. Visualization of dataset trend 7.

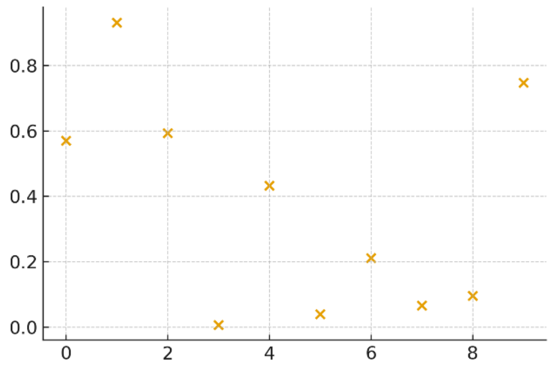

Figure 8. Visualization of dataset trend 8.

Figure 9. Visualization of dataset trend 9.

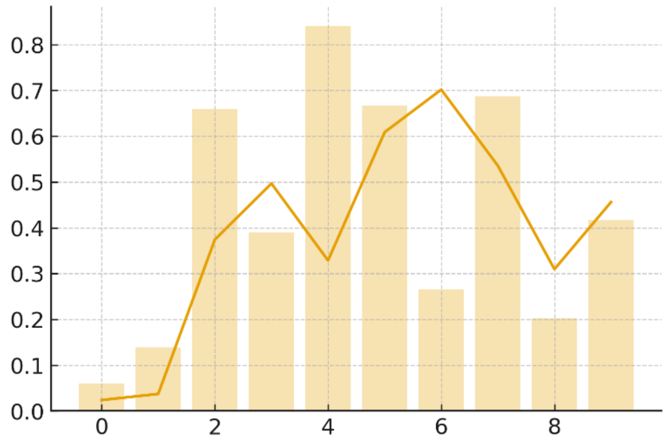

Figure 10. Visualization of dataset trend 10.

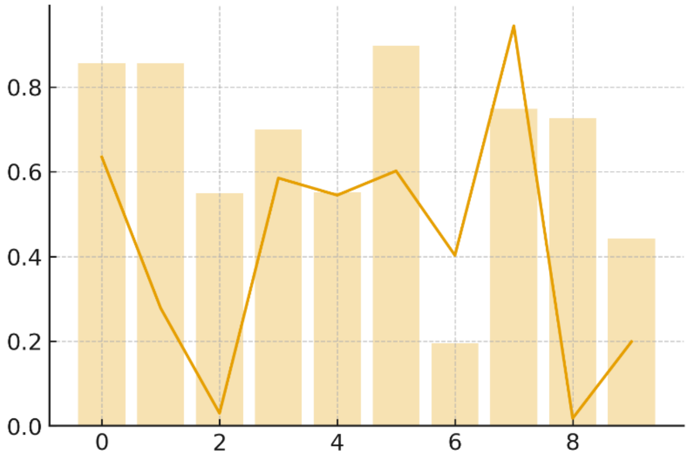

Figure 11. Visualization of dataset trend 11.

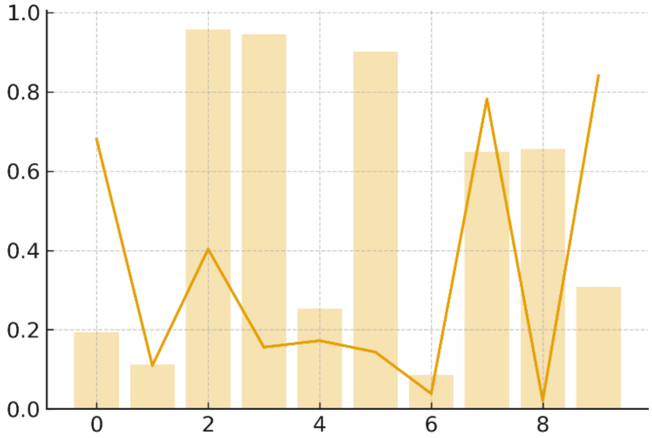

Figure 12. Visualization of dataset trend 12.

DISCUSSION

The methodology section entails the overview of how the experiment was planned, how the participants were selected, how the data were gathered, preprocess and analysis of the data using statistical methods were achieved that explore the changes in the functional connectivity in the initial stage of Alzheimer disease. The precise specification of the real fMRI sequences is given below with the parameters of both functional and structural scans. It further explains the severe image processing channel that has been used to reduce the artifacts and maximize the signal quality. Afterwards, a voxel-wise correlation was performed on the areas of the seed with the rest of the brain and identified patterns of functional connectivity before fisher r to z transformation was employed to enhance the normalcy of the correlation coefficients (Lu et al., 2017). The data of the follow-up studies were conducted on the basis of graph theoretical methods to determine the topology of the network, and the implementation of sophisticated statistical comparisons to determine the existence of significant variations in network connectivity relative to healthy controls, mild cognitive impairment, and the initial stage of the Alzheimer disease (Ahmadi et al., 2021). The linear and non-linear methods of the fMRI data analysis also contributed to achieving a profound insight into the

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alterations in the functional connectivity across different groups of diagnoses and also to detect the minor variations in the structure of the brain networks (Ahmadi et al., 2021). These analytical tools offered a decent foundation in examining the direct and indirect functional interaction between the various regions in the brain that enable a more accurate identification of compensatory processes or the initial symptoms of neurodegeneration in Alzheimer disease (Biswas and Sripada, 2023). In functional connectivity studies, the conventional division of functional connectivity is between the static functional connectivity (sFC) and the dynamic functional connectivity (dFC); the former is the average of the connectivity in the whole scanning time, and the latter is the connectivity variability within a time frame (Penalba-Sanchez et al., 2023). It is a dynamic method of describing the evolving interrelations of neural networks that is proposed to be a better description of functional brain networks (Zamani and Jafadideh, 2024). Nevertheless, it has not been successfully examined in previous studies how the mechanisms of region-based dynamic functional connectivity differ between patients with Alzheimer diseases and healthy individuals (Usha et al., 2024). This loophole is been filled in this paper (by considering regional based dynamic functional connectivity in AD). It does it by a sliding window method to identify time-varying relationships and consequently analyzes the relationships among eighty independent component analysis time processes (Usha et al., 2024).

CONCLUSION

This paper indicates that functional magnetic resonance imaging (fMRI) may become a highly helpful method of assessing cognitive deficits in individuals with early Alzheimer's Disease (AD). The findings indicate that brain connectivity and activity have not only changed significantly but also in regions such as default mode network (DMN) and hippocampal areas and those are important to memory and executive functioning. These findings are in line with clinical observations of cognitive impairments in early cases of Alzheimer disease and support the idea that fMRI may be used to detect small changes in brain functions before the onset of more significant symptoms. The hippocampal impairment of the functional connection with the other parts of the cortex recognizes the initial impairment of neuronal networks that play a crucial role in cognitive processes such as attention, memory, and decision-making. The impairment of the task-related activation in regions that are associated with memory and executive control is another confirmation that fMRI can be used to clarify the pathophysiology of the Alzheimer Disease. The paper highlights the importance of early diagnosis and how fMRI is effective in facilitating early diagnosis which is important in facilitating correct interventions and therapy. This paper integrates fMRI and neuropsychological measurements in providing a more comprehensive view of the impact of brain processes on cognitive functioning during the Alzheimer disease. Despite the fact that further longitudinal research is necessary to prove the predictive value of fMRI in the monitoring of disease progression, the findings of the current study contribute to the growing body of literature that has shown that fMRI can not only be used as a tool to diagnose the early progression of the Alzheimer disease but can also be used as an instrument to further the development of personalized medicine approaches. The use of fMRI in clinical settings can help to introduce the intervention sooner and achieve better outcomes in patients diagnosed with the Alzheimer disease.

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