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Default mode network perturbations in Alzheimer's disease: an fMRI study in Klang Valley, Malaysia

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Abstract: The default mode network (DMN) is a large neural network that has a significant correlation with Alzheimer's disease (AD). Grey matter volume (GMV) and functional connectivity (FC) involving the regions of the DMN have been noted to differ significantly between AD and healthy older adults. Nevertheless, there is a paucity of data on the structural and functional changes in the DMN of AD patients in Malaysia. We conducted a cross-sectional study in Klang Valley, Malaysia, to evaluate AD subjects compared to healthy controls (HC) using a resting-state functional MRI (rs-fMRI) experiment. We recruited 22 subjects (AD=11, HC=11) and conducted neuropsychological tests such as the Montreal Cognitive Assessment (MoCA), Mini Mental State Examination (MMSE), and Clinical Dementia Rating (CDR). The subjects then underwent rs-fMRI scans, and subsequently, we quantitatively analysed the GMV by Voxel based Morphometry (VBM) using the structural data. We also utilised the CONN toolbox on Statistical Parametric Mapping

(SPM) software to evaluate the FC and activation of the nodes of the DMN. In comparison with the HC group, the AD group demonstrated a reduction in GMV in the right and left inferior temporal gyrus, left superior frontal gyrus, right superior frontal gyrus medial segment, right gyrus rectus, right temporal lobe, left putamen, and right precuneus. Moreover, there was a significant decrease in the FC of the nodes of the DMN noted on rs-fMRI (cluster-size corrected $p<0.05$). In particular, the precuneus and anterior cingulate cortex had decreased FC in AD compared to HC. Hence, structural and resting-state fMRI can detect distinct imaging biomarkers of AD based on GMV and DMN functional connectivity profiles. This tool can be used as a non-invasive tool for improving the feature detection and diagnosis of AD in the Malaysian population.

Keywords: Alzheimer's disease; Voxel-based morphometry; Seed-based analysis; Grey matter volume; Fault mode network

1.0 INTRODUCTION

Alzheimer's disease (AD) is the most prevalent form of dementia and is a progressive neurodegenerative disorder associated with memory loss. Historically, AD begins with atrophy in the hippocampus and spreads to other brain regions due to accelerated neuronal inflammation and death (Piersson et al., 2021; Ribeiro & Busatto Filho, 2016). AD is one of the important illnesses of the elderly, in which the incidence has increased significantly in the recent years (Azmi et al., 2017). An earlier study among senior Malaysian citizens revealed that older age, no formal education, female gender, low self-rated health quality, and Malay or Bumiputera ethnicity were significant risk factors for dementia (Ibrahim et al., 2021; Szabo-Reed et al., 2019). Moreover, the estimated number of people extrapolated to have dementia in the year 2030 in Malaysia is reported to be 261,000, which comprises 0.72% of the estimated population of 36.09 million, based on the United Nations World Population Prospects 2019 (Harding et al., 2017).

Currently, neurophysiological tests such as the Montreal Cognitive Assessment (MoCA), Mini-Mental State Examination (MMSE), and Clinical Dementia Rating (CDR) Scores, are routinely used to diagnose AD (Rankin et al., 2021; Su et al., 2019; Zheng et al., 2018). However, the MoCA test should not be used as a substitute for a more in-depth neuropsychological assessment (Rubinov & Sporns, 2010; Tang et al., 2019; Verfaillie et al., 2016). Meanwhile, the MMSE is an effective instrument for screening dementia in older individuals with basic literacy abilities. Nonetheless, it has a high risk of misclassification in illiterate elderlies, which has significant implications for detecting AD in developing nations with low literacy rates among older adults (Wind et al., 1997). Meanwhile, the CDR is a global dementia rating scale that determines the presence of dementia and evaluates cognitive change (Ersche et al., 2013). Therefore, there is a need for more objective tests to determine the features that can help to classify AD.

Consequently, neuroimaging research has been utilised to support the diagnosis of AD (Suckling & Nestor, 2017; Takamiya et al., 2021). Neuroimaging studies using T1-weighted MRI images are used to evaluate abnormalities in the brain structure (Ferreira et al., 2011; Kiesow et al., 2021; Wu et al., 2020). Structural MRI images can be processed using voxel-based morphometry (VBM), a quantitative brain volume assessment performed using statistical parametric mapping. Subsequently, the grey matter volume (GMV) loss in the brain structures can be identified in AD patients. In AD, GMV atrophy initially occurs in the temporo-parietal lobes (Shiino et al., 2006; Wang et al., 2015a; Woodworth et al., 2022; Zang et al., 2021). VBM, an MRI analytic technique, can be used to investigate the morphological abnormalities of the brain (Ferreira et al., 2011; He et al., 2017). It is a computational tool for examining anatomical sections of the neuronal cortices and quantifying differences in local brain tissue concentrations, mainly involving GMV (Connolly et al., 2013; Ko et al., 2015).

Grey matter atrophy has been identified to carry an increased risk for developing AD (Younan et al., 2020). Grey matter density (GMD) at each voxel can be compared across the brain between AD patients

(Alexander-Bloch et al., 2013; Cui et al., 2022). An increase in GMD is inversely correlated with decreased GMV, which has been found to involve the medial temporal lobe extending to areas in the temporal gyri, precuneus, insular and cingulate cortex, and caudate nucleus in AD patients (Cui et al., 2022; Frisoni et al., 2002).

Meanwhile, resting-state functional MRI (rs-fMRI) neuroimaging can evaluate the function of brain networks at rest by determining the change in gradient on the scans based on the blood flow to activated brain regions. Using independent component analysis (ICA), the functional connectivity (FC) between various nodes in the brain can be evaluated. The seed-based analysis (SBA) method can be utilised to evaluate a single connectivity metric for each pair of nodes in a region based on a priori knowledge (Xia et al., 2018; Zhou et al., 2017). SBA is useful for the detailed analysis of a particular Region of Interest (ROI), to measure functional changes between subjects and to reveal the FC among the nodes of the default mode network (DMN) (Lv et al., 2018; Wu et al., 2020). The DMN is a constellation of nodes in the brain that are functionally connected to the posterior cingulate cortex node in the brain and appear to be activated when a person is at rest and not performing any tasks. Historically, the FC of the nodes of the DMN have been implicated with altered brain morphometry in various neurological and psychological disorders (Rashid et al., 2021). A previous study has revealed that decreased FC is widespread in the brain of AD subjects compared to HC subjects, particularly involving the nodes of the DMN (Soman et al., 2020). In AD subjects, the FC of the DMN was noted to be decreased in certain brain areas that were significantly correlated with reduced cortical thickness, namely in the superior temporal, supramarginal gyrus of the left cerebral hemisphere (Park et al., 2017; Wang et al., 2015b).

The DMN has been implicated in numerous neuroimaging studies involving AD patients, particularly there is a priori knowledge regarding the affected nodes of the DMN, which include the precuneus (Prec), posterior cingulate cortex (PCC), retro-splenial cortex, medial parietal cortex (MPC), lateral parietal cortex (LPC), and inferior parietal cortex (IPC), medial prefrontal cortex (mPFC), and medial temporal gyrus (MTG) (Ibrahim et al., 2021; Park et al., 2017; Wang et al., 2020). The gap in the literature is that despite many studies conducted among Caucasian and North Asian populations, there is a lack of data regarding rs-fMRI imaging biomarkers in the Malaysian population. Therefore, there is a need to elucidate the changes that occur in AD and identify imaging biomarkers in our population. Moreover, there are genetic and structural variations in the models proposed by data from the Western developed countries, which can be interesting to compare with data from an Asian population.

We hypothesise that there will be a significant difference in the neuropsychological profile of AD compared with healthy controls (HC). We also hypothesise there will be altered GMV in a priori areas of the brain of AD subjects compared to HC. Additionally, we hypothesised that the decreased activations in the nodes of the DMN would be observed in AD subjects and correlated with regions of GMV atrophy in AD subjects in our population.

We aimed to describe the processing of structural MRI data using VBM that can help to detect the differences in regional GMV in AD patients compared to HC. The other objective of this study is to identify the differences in rs-fMRI FC in AD compared to HC using ICA method.

2.0 MATERIALS AND METHODS

2.1 Study design and subject recruitment

This prospective cross-sectional study received ethical clearance from Universiti Putra Malaysia ethical committee with ethical clearance number JKEUPM-2019-328 and Malaysian national ethical clearance, MREC (NMRR-19-2719-49105). The data for the study was collected from March 2021 to June 2022. The database of AD patients attending Hospital Kuala Lumpur (HKL) memory clinic, Klinik Kesihatan Pandamaran Klang, and Hospital Sultan Abdul Aziz Shah Universiti Putra Malaysia (HSAAS UPM) were surveyed to recruit suitable AD subjects. We recruited age-matched cognitively healthy controls (HC) by sending out flyers to the community and posting them on community bulletin boards. The subjects who met the inclusion criteria were selected for this study. In accordance with the principles outlined in the Declaration of Helsinki 1964, participation in the study was voluntary, and informed consent was acquired from potential participants before recruitment. The participants were compensated, and all data were anonymised.

2.2 Inclusion and exclusion criteria

The inclusion criteria are subjects with a clinically verified diagnosis of AD as well as being Malaysian citizens aged between 55 and 90 years old. The physicians classified the participants into AD and HC groups using DSM-5, MoCA, MMSE, and CDR scores based on their clinical assessment. Participants in the HC group were required to have a good memory and no brain diseases, including cancer and stroke. The subjects did not suffer from claustrophobia, had no metal implant, and cooperated for the rs-fMRI scan. Exclusion criteria are non-citizens of Malaysia and those with neurological diseases other than AD. Relative and absolute contraindications for MRI examination include claustrophobia, irremovable metallic implants that are not MRI compatible, and electronic implants such as pacemakers, cochlear or ear implants, and metallic tattoos.

2.3 Montreal Cognitive Assessment (MoCA)

An 8-item self-reported MoCA questionnaire was used to evaluate short-term memory, executive functions, visuospatial abilities, attention, and concentration, including working memory, language, and orientation to time and place). The scores are 5 points for a short-term memory recall task involving two learning trials of five nouns and delayed recall after approximately five minutes, for visuospatial abilities using 3 points for clock-drawing and 1 point for a three-dimensional cube copy. A verbal language task was also administered. One point was given for attention, concentration, and working memory, which were assessed using a sustained attention task; then 3 points for a serial numbers' subtraction task, and 1-point digits span forward and digit span backwards task. Three points for language are assessed using a three-item confrontation naming task with low-familiarity animals (lion, camel, rhinoceros), 2 points for repetition of two syntactically complex sentences, and the fluency above task. Finally, 6 points for orientation to time and place are evaluated by asking the subject for the date and the city where the test occurred. The MoCA score ranges from 0 to 30. After evaluating the MoCA questionnaire, a normal score is regarded as 26 or higher. People without cognitive impairment scored an average of 27.4 in research, while those with mild cognitive impairment (MCI) scored 22.1, and those with Alzheimer's disease scored 16.2 (Chan et al., 2017; Razali et al., 2014; Smith et al., 2007).

2.4 Screening tool: The Mini-Mental State Examination (MMSE)

A 5-item self-reported MMSE or Folstein test is a 30-point questionnaire. The questionnaire was used to screen for dementia. The scores range from 10 points for orientation (time and place), 3 points for registration, 5 points for attention and calculation, 3 points for recall and 9 points for language (language, repetition, and complex commands). After evaluating the MMSE questionnaire, subjects who scored <26 for Alzheimer's disease and those who scored ⩾26 were normal (Folstein et al., 1975; Ibrahim et al., 2009). Furthermore, a study conducted in Malaysia by Cheah et al. (2014), detected that MoCA had a sensitivity of 82.4% and specificity of 81.8% to detect cognitive impairment, compared to the Malay version of the MMSE, which had a lower sensitivity of 76.5% and specificity of 63.6% with the cut-off point of less than 27. They concluded that the Malay MoCA is a validated and useful cognitive screening instrument that can be administered in patients with cognitive impairment (Cheah et al., 2014).

2.5 Clinical Dementia Rating (CDR)

The CDR tool is a numerical scale that is used worldwide to identify the dementia severity stages by assessing dementia symptoms (Morris et al., 1993). A qualified medical or psychological personnel will determine a patient's cognitive and functional performance in 6 cognitive areas: orientation, memory, judgement & solving problems, home & hobbies, community affairs, and personal care, by administering a structured interview-based protocol developed in 1982 by Charles Hughes (Stenger et al., 2001; Teh et al., 2021). The results of each of these are added together to get a composite score that ranges from 0 to 3. This score is useful for characterising and tracking a patient's level of cognitive impairment/dementia: 0 = Normal, 0.5 = Questionable Dementia, 1 = Mild Dementia, 2 = Moderate Dementia, and 3 = Severe Dementia.

2.6 MRI data Acquisition

The MRI was performed on a Siemens 3.0T scanner (PRISMA, Siemens, Erlangen, Germany). A 12-channel head coil was used for structural MRI. T1 MPRAGE MRI data with high resolution was acquired. The sequence's parameters were as follows: TR = 2300ms, TE = 2.27ms, TI=1100ms, number of slices =160, ascending sagittal oriented, FOV =256 x 256 mm2, matrix size =256 x 256, and slice thickness=1mm.

Blood-oxygen-level-dependent (BOLD) imaging was performed using an echo-planar imaging (EPI) sequence. The rs-fMRI images were obtained with a field of strength of 3.0 Tesla, a repetition time of 2500 msec, an echo time of 30ms, a flip angle of 90°, matrix 64 x 64, 250 volumes, 38 slices per volume, and a slice thickness of 3.5mm—the voxel size: 2.5 x 2.5 x 3 mm^3. The phase encoding direction was from anterior to posterior, with the subjects being asked to lie down with closed eyes but not fall asleep.

2.7 Pre-processing Voxel-Based Morphometry (VBM) Analysis

The VBM toolbox in the Statistical Parametric Mapping software (SPM 12, http://www.fil.ion.ucl.ac.uk/spm/software/spm12) implemented in MATLAB was used to pre-process structural images (Ribeiro & Busatto Filho, 2016; Rolls et al., 2020; Wang et al., 2021).

First, all images were checked for artefacts and structural abnormalities. Secondly, temporal processing involved slice timing, and thirdly, spatial processing involved realignment and estimate, set origin, co-registration, normalisation, and smoothing were performed. The group-specific AD and HC templates were utilised to reduce variability among subjects. The Asian brain map template was then used to normalise the images using the "DARTEL Normalise to Montreal Neurological Institute (MNI) Space" program. The volume for a specific ROI based on a priori knowledge was generated using T1-weighted images that were spatially registered to the MNI template. Based on spatial registration and modulated images of the grey matter that mirrored the tissue volumes, segmented images of the GMD and GMV were retained to measure the amount of volume changes. After that, a Gaussian filter was used to smooth the normalised brain pictures (8mm FWHM). The family-wise error (FWE) was used for multiple comparisons, using a $p<0.05$ threshold. The threshold in the SPM analysis, which was deemed uncorrected for FWE, was decreased to $p<0.001$ to find regions with low signals.

The GMV differences between the AD and HC groups were evaluated using 2-sample t-test in SPM12. A voxel-wise uncorrected $p < 0.001$ threshold and cluster-level $p < 0.05$ FWE correction were applied to the rs-fMRI data. Uncorrected $p<0.001$ was used due to the small sample size.

2.8 Resting-state functional connectivity (Rs-FC) analysis using seed-based analysis

The resting-state functional connectivity (Rs-FC) analysis was performed using a seed-based approach using the CONN toolbox v20.b (http://www.nitrc.org/projects/conn). We conducted whole-brain research and seed-based analysis (SBA) using ROIs based on a priori knowledge. The functional images were pre-processed with SPM12 software by applying the following steps: slice-timing correction; spatial realignment; co-registration to the T1-weighted anatomical image; spatial normalisation to the MNI space, and smoothing (Wang et al., 2021). The significance level was set at $p<0.001$, FWE uncorrected.

2.9 Statistical analysis

The SPM12 and Statistical Package for the Social Sciences (SPSS software Version 25.0, SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The descriptive statistic was performed to analyse subjects' sociodemographic data, and the chi-square test was used to analyse the association between two groups with neuropsychological tests. Two-sample t-test were used to compare the differences in brain GMV in AD versus HC subjects using VBM. The significance level was set FWE uncorrected at a voxel threshold $p<0.001$. Regression analysis was performed in ROI-based DMN data analysis to identify brain activation regions in AD subjects using SBA of rs-fMRI data. The significance level was set FDR uncorrected at a voxel threshold $p<0.05$.

3.0 RESULTS

3.1 Demographic characteristics

Twenty-two subjects were recruited for this study (AD=11, HC=11). The subjects were divided into AD and HC groups based on the clinician's evaluation using DMN-5 and their MoCA and MMSE scores. Both groups were compared by age distribution, gender, education level, marital status, and neuropsychological tests, i.e., MoCA, MMSE, and CDR (**Table 1**). The range of age of the AD and HC groups is 64–84 and 60–79 years old, respectively. An independent sample t-test indicated that age significantly differed between AD and HC, $t(20) = -2.66$, $p=0.015$.

An independent sample t-test also indicated that MoCA, MMSE, and CDR were significantly different between AD and HC, $t(20)=8.03$, $P=0.001$, $t(20)=5.50$, $p=0.001$ and $t(10)=-6.90$, $P=0.001$.

A Chi-square test for independence indicated that the gender (male vs. female), duration of formal education (less than or equals 6 years vs. more than 6 years), and marital status (single vs. married) were not statistically significant between AD and HC subjects (gender, $p=0.38$; education level, $p=0.27$; and marital status; $p=0.53$ respectively). Therefore, there was no significant association between gender, education level, and marital status with AD and HC in our population (refer to **Table 1**).

3.2 Neuropsychological assessment test

The descriptive statistics of neuropsychological test scores for the AD and HC groups with neurophysiological assessment parameters are tabulated (**Table 1**). Using MoCA, we detected HC group scores ranging from 26–30, which indicates normal cognitive function, and the AD group scores ranging from 6–21, which showed reduced cognitive function in the dementia range. Using MMSE, we detected that the HC group had scores ranging from 24 to 30 in keeping with no cognitive impairment, and the AD group had scores ranging from 22 to 30, ranging from mild to severe cognitive impairment, respectively. While using CDR, subjects in the HC group were detected to have normal daily functioning, and subjects in the AD group were detected to have mild dementia and impairment of daily living activities.

Table 1: Comparison of sociodemographic and neuropsychological profile of AD with HC

Variable n=22		AD, n=11 Freq. (%)	HC, n=11 Freq. (%)	X^2 statistic[a] (df) P-value[a]
Demographic data	**Gender**			
	Male	5 (45.5%)	3 (27.3%)	0.79 (1) 0.38
	Female	6 (54.5%)	8 (72.7%)	
	Education Level			
	>6 years	8 (72.7%)	10 (90.9%)	1.22 (1) 0.27
	<6 years	3 (27.3%)	1 (9.1%)	
	Marital Status			
	Single	2 (18.2%)	1 (9.1%)	0.39 (1) 0.53
	Married	9 (81.8%)	10 (90.9%)	
		Min-max (mean ± SD)	**Min-max (mean ± SD)**	**t statistic[a] (df) P-value[b]**
	Age	64 – 84 (76.36 ± 0.52)	64 – 79 (69.91 ±5.34)	-2.66 (20) 0.015
Neuropsychological test scores	**MoCA**	6 – 21 (16.00 ± 4.88)	26 – 30 (28.45 ± 1.64)	8.03 (20) 0.001
	MMSE	22 – 30 (20.4 ± 11.85)	24 – 30 (28.3 ± 2.00)	5.50 (20) 0.001
	CDR	1 – 3 (4.0 ± 0.91)	0 (1.08 ± 1.21)	-6.90 (10) 0.001

Note: AD: Alzheimer's disease group; HC: healthy control group; MoCA: Montreal Cognitive Assessment; MMSE: Mini-Mental State Examination; CDR: Clinical Dementia Rating Score; n: frequency; df: degree of freedom.
[a] Chi-square test for independence
[b] t-test for independence

3.3 Voxel-based morphometry analysis

Right inferior temporal gyrus (ITG r), left inferior temporal gyrus (ITG l), left superior frontal gyrus (SFG l), right superior frontal gyrus medial segment (MSFG r), right gyrus rectus or straight gyrus, right temporal lobe, left putamen, and right precuneus were found to have high grey matter density or voxel density for AD compared to the HC group (p<0.001, FWE corrected), as shown in **Table 2** and **Figure 1**.

3.4 Independent component analysis functional connectivity analysis

Table 3 and **Figure 2** show the brain regions with significant FC differences between the nodes of AD and HC subjects. The warm colours represent high values, and the cool colours represent the low values or deactivations. High values were found in the precuneus and anterior cingulate gyrus (ACG) for both groups. In HC subjects, the high values were found in the right and left lateral occipital, as well as the right and left frontal lobes. For AD subjects, the high values were found in the superior left occipital cortex and superior lateral occipital cortex.

Table 2: Tabulated values of regional difference in voxel density for AD > HC group and HC > AD (FWE uncorrected, p<0.001)

AD>HC	Side	Cluster Peak (mm)			Voxel	Peak T	P-value (FWE)
Inferior temporal gyrus (ITG r)	Right	40	-9	-38	849	5.57	<0.001
Inferior temporal gyrus (ITG l)	Left	-45	-32	-27	17	3.73	<0.001
Superior frontal gyrus (SFG l)	Left	-21	-8	56	55	4.91	<0.001
Superior frontal gyrus medial segment (MSFG r)	Right	8	58	-4	57	4.25	<0.001
Gyrus rectus	Right	6	52	18	7	3.67	<0.001
Temporal lobe	Right	30	6	-40	11	3.66	<0.001
Putamen	Left	-24	9	-2	5	3.15	<0.001
Precuneus	Right	8	-52	39	2	3.57	<0.001
AD<HC	**Side**	**Cluster Peak (mm)**			**Voxel**	**Peak T**	**P-value (FWE)**
-	-	-			-	-	-

Note: AD: Alzheimer's disease group; HC: healthy control group; AD>HC group: used in the analysis of fMRI data to indicate brain regions or networks where there is greater activity in individuals with AD compared to HC; HC>AD group: used in the analysis of fMRI data to indicate brain regions or networks where there is greater activity in individuals with HC compared to AD; FEW: family-wise error.

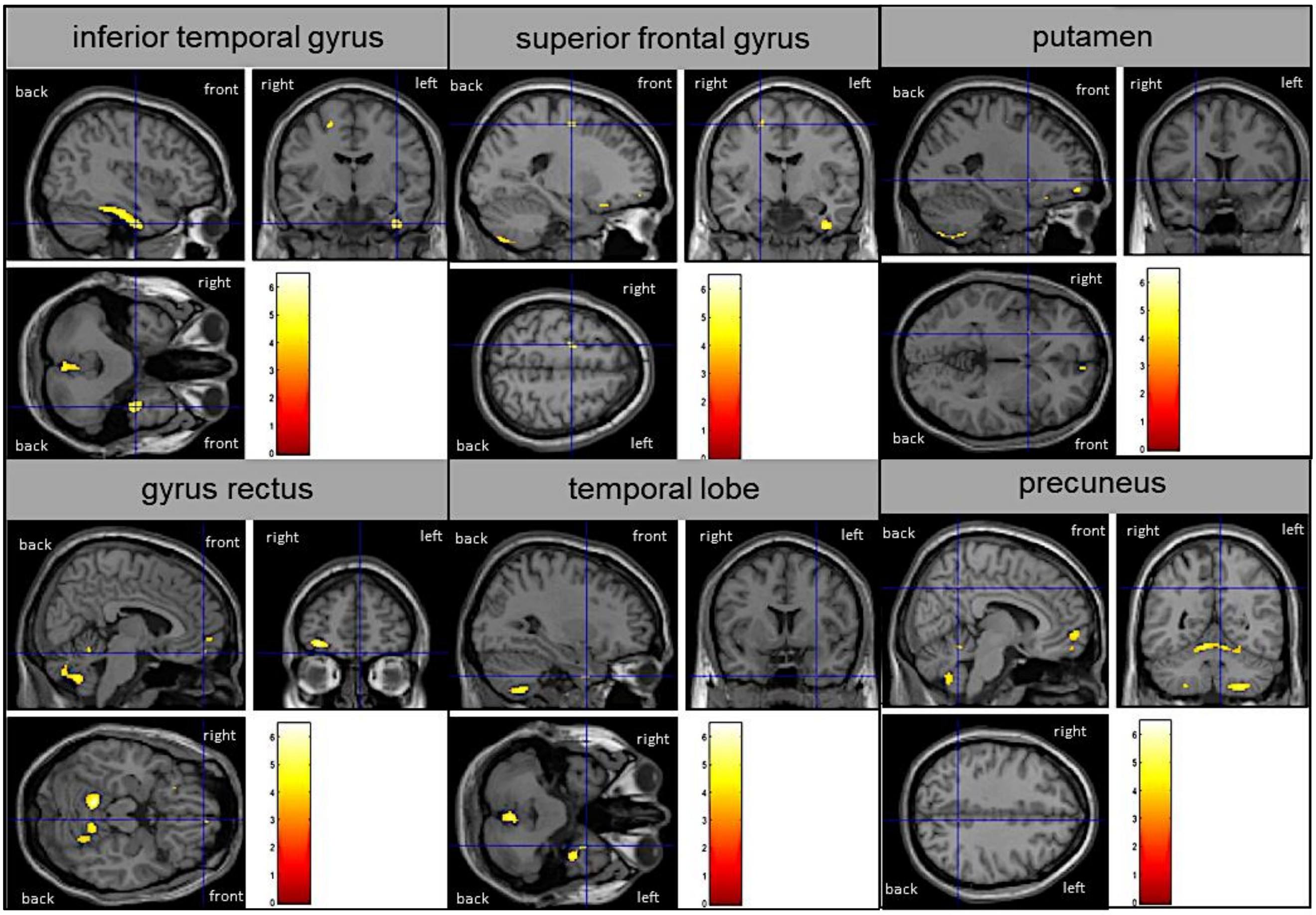
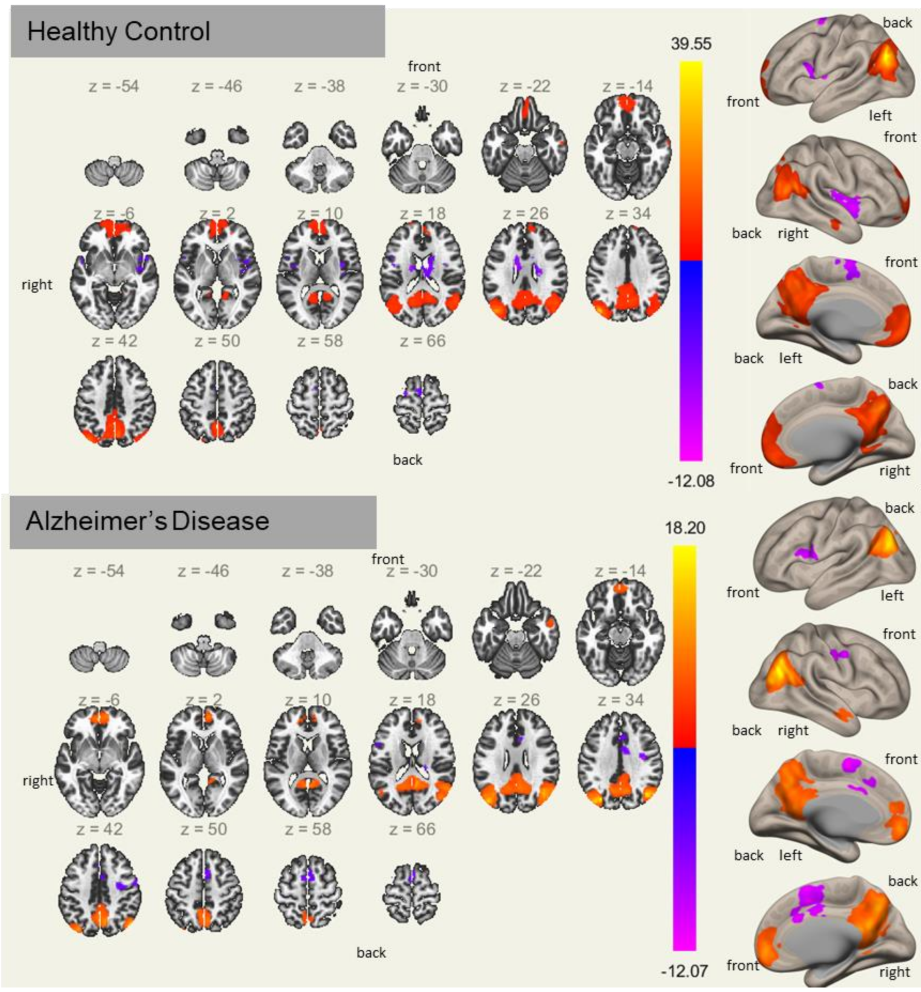


Figure 1: VBM results had different density and reduced grey matter volume in AD more than HC subjects using T1 MRI structural data (FWE uncorrected, p<0.001)

Table 3: Tabulated values of regional difference in seed-based Rs-fMRI functional connectivity in AD, HC, and AD>HC (FDR uncorrected; voxel threshold: p<0.05)

Brain regions	Side	Cluster Size (voxels)	MNI coordinates x	y	z	P -value
HC						
Precuneous		4138				
Lateral Occipital Cortex	Left	2957	-40	-78	+32	
Lateral Occipital Cortex	Right	2745				0.452
Frontal Lobe	Right	1238				
Frontal Lobe	Left	1082	+00	+58	-02	
Cingulate Gyrus	Anterior	934				
AD						
Precuneous		3755	+02	-68	+50	
Lateral occipital cortex	Superior, Left	2301				0.246
Cingulate gyrus	Anterior	1014	+02	+52	-04	
Lateral occipital cortex	Superior	1599	+46	-70	+34	
AD>HC						
-	-	-	-	-	-	-

Note: AD: Alzheimer's disease group; HC: healthy control group; AD>HC group: used in the analysis of fMRI data to indicate brain regions or networks where there is greater activity in individuals with AD compared to HC; HC>AD: used in the analysis of fMRI data to indicate brain regions or networks where there is greater activity in individuals with HC compared to AD.



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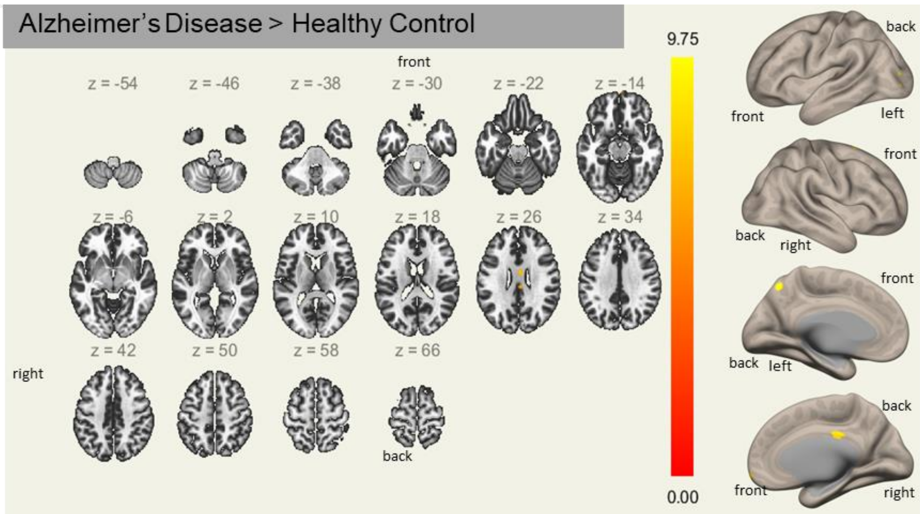

Figure 2: FC Analysis differences between AD and HC. Activation maps are graphical representations of activation regions in the brain. Hot colours represent greater mean regional activation between specific regions, and cold colours represent lower activation group differences. Activation values are based on T values (i.e., activation colorbar range from -12.08 to 39.55 for HC, -12.07 to 18.20 for AD, and 0 to 9.75 for differences between AD and HC). Rs-FC analysis found the significance level was set at FDR uncorrected, voxel threshold $p<0.05$. FC: Functional connectivity.

4.0 DISCUSSION

This study prospectively recruited AD subjects in Klang Valley, Malaysia and conducted neuropsychological tests and fMRI examinations for the subjects and age-matched healthy controls. There were significantly reduced MMSE, MoCA and CDR values among the AD subjects compared to the controls, which indicates the tools are good screening tests to identify neurocognitive deficits in the subjects. The MoCA neuropsychological exam correlated with the MMSE similar to other studies (Zheng et al., 2018). To specify the outcome, we examined the CDR scores and found that the AD participants had performance levels in the mild to severe categories (Liu et al., 2014). The CDR score also made it easier to identify the subjects with AD compared to HC, as well as identify the severity of the neurocognitive deficit based on mild, moderate, and severe stages of the disease. Nevertheless, these tests are semi-objective and have a variable level of specificity. Neuropsychological tests and fMRI serve different but complementary roles in studying the brain, and each has its strengths and limitations. While neuropsychological tests are valuable for assessing cognitive functions and behaviour (Zucchella et al., 2018), fMRI provides a more direct measure of brain activity and connectivity (Agosta et al., 2012). The fMRI generates quantitative data that can be analysed statistically, providing more precise measurements of brain activity (Chen et al., 2022). Neuropsychological tests often rely on qualitative observations, and the interpretation of results may be subject to greater variability. Neuropsychological tests of cognitive impairments show less specificity and new relationships between tests, with AD patients showing worse performance but also a reorganisation of the cognitive system (Tosi et al., 2020).

Given the limitations of neuropsychological tests, such as the challenges in administration in illiterate or non-cooperative subjects, neuroimaging tools such as MRI can help in diagnosing AD. Structural MRI can detect small changes in the GMV, and rs-fMRI detects FC of neuronal networks that help differentiate AD features from HC. Based on our study, we evaluated the intrinsic pathophysiological changes that occurred in subjects with AD using morphological data from the structural MRI images and functional data from rs-fMRI examination.

Our first aim was to describe the processing of structural MRI data using VBM that can help to detect the differences in regional GMV in AD patients compared to HC. We identified some similarities with other studies from the Western population, such as atrophy of the precuneus (Hoflich et al., 2017). We detected that AD had reduced GMV at the ITG r and ITG l (Ikeda et al., 2019), SFG l, MSFG r, right gyrus rectus or straight gyrus (Li et al., 2019), right temporal lobe (Zhao et al., 2021), left putamen (Lukito et al., 2020) and right precuneus. Furthermore, Guo et al. (2017) found decreased GMV in the ventral precuneus and postulated that this region helps to boost the efficiency of conscious processes, allowing individuals to transition between different temporal frames depending on the situation and lead to more balanced time perspectives, which then becomes impaired in AD patients. Interestingly, as we have hypothesised, no brain region had significantly atrophied GMV at any specific node in the age-matched HC compared to the AD subjects because of accelerated degeneration that occurs in AD compared to normal ageing (Shen et al., 2017).

Although the atrophy of the hippocampus has been implicated in many other studies (Lukito et al., 2020; Shen et al., 2017), our study did not demonstrate a significant difference in GMV between the AD and HC groups. This may be due to the ICA method that detected larger regions of GMV atrophy in other salient regions involved in the AD continuum, particularly in the temporal lobes and precuneus. Our AD subjects also demonstrated a marked loss of attention during the performance of their neuropsychological tests, which reflects the atrophy in the precuneus, a brain region involved in the integration of recollection and memory, as well as the integration of information. Furthermore, considering the HC subjects were also in their 60s and 70s, hippocampal atrophy due to age-related involutional changes may have already occurred in these cognitively normal subjects.

Moreover, rs-MRI detected reduced FC in regions of the DMN, similar to previous findings by Park et al. (2017). Our second objective of this study was to identify the differences in rs-fMRI FC in AD compared to HC. Thus, in our study, we were able to detect reduced FC in AD among our Malaysian population. Specifically, we detected deactivation in the Prec and the anterior cingulate gyrus. It is hypothesised that reduced activations in the regions of the DMN are caused by accelerated neurodegeneration that occurs in the related nodes, which can be detected at an early stage using fMRI with improved diagnostic accuracy of approximately 82.6% sensitivity and 79.1% specificity, respectively in discriminating AD from healthy controls (Yokoi et al., 2018).

The limitations of our study include a small sample size, which was due to our recruitment period occurring during the COVID-19 pandemic and restricted by the movement control orders, causing the subjects to have difficulty accessing the imaging centre. Furthermore, some AD subjects were not cooperative during the scan, and the data had to be removed from the final analysis due to artefacts.

Our future recommendation is to incorporate a multicentre study protocol to improve the sample size and to utilise artificial intelligence algorithms that can extract imaging features in an automated pipeline for improved diagnostic accuracy. In addition, with a better sample size and adequate representation of all the stages of AD, future studies can extract specific imaging features that can be utilised as early markers of the disease in the Alzheimer's continuum.

5.0 CONCLUSION

Voxel-based morphometry identifying reduced GMV of the precuneus and temporal lobes and independent component analysis of the DMN network can help classify patients with Alzheimer's disease compared to healthy controls in the Klang Valley, Malaysian population.

Ethical clearance:

This study was approved by the Ethics Committee of Research Involving Human Subjects of Universiti Putra Malaysia (JKEUPM-2019-328) and MREC (NMRR-19-2719-49105).

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Author contributions:

NHMA, SS, NSNI, VPS, were involved in data collection and analysis. AAR also performed data interpretation and prepared the first draft of the manuscript. NHMA and SS were responsible for the conceptual framework and study design, secured financial support, conducted data interpretation and supervised the project. MM also helped formulate the conceptual framework, study design, and data analysis and interpretation. NHMA and SS, conducted the literature search, data analysis, and data interpretation. NHMA, SS, TK, FO, and BI were involved in the study design, project supervision, and verification of the analytical methods. YNT was involved in securing part of the financial support for this study and data collection. NHMA, SS, RMR, HNH, HS, NS, and UA were involved in the conceptual framework, verification of analytical methods, and data interpretation. All the authors were involved in editing and verifying the final completed manuscript.

Conflict of interest:

The authors declare no conflict of interest regarding the publication of this work.

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