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Reduced Default Mode Network Functional Connectivity Correlates with Stroke and Uncontrolled Hypertension among Patients with Alzheimer's Disease: An fMRI Study in Klang Valley Malaysia.

Buhari Ibrahim[1,2†], Vengkatha Priya Seriramulu[1†#], Subapriya Suppiah[1,3,4*], Mazlyfarina Mohamad[5], Albert Dayon Piersson[5,6], Rizah Mazzuin Razali[7], Hasyma Abu Hassan[1,2], Normala Ibrahim[3,8], Syahril Abdullah[9], Nur Shahidatul Nabila Ibrahim[1], Nur Hafizah Mohad Azmi[1]

[1]Department of Radiology, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Malaysia.
[2]Department of Physiology, Faculty of Basic Medical Sciences, Bauchi State University,Gadau, Nigeria
[3]Unit Pengimejan Nuklear, Hospital Sultan Abdul Aziz Shah, Universiti Putra Malaysia, Malaysia
[4]Pusat Pengimejan Diagnostik Nuklear, Universiti Putra Malaysia, Malaysia.
[5]Center for Diagnostics, Therapeutic and Investigative, Faculty of Health Sciences, Universiti Kebangsaan Malaysia, Malaysia.
[6]University of Cape Coast, School of Allied Health Sciences, Department of Imaging Technology & Sonography, Cape Coast, Ghana
[7] Geriatric Unit, Department of Medicine, Hospital Kuala Lumpur, Kementerian Kesihatan Malaysia, Malaysia.
[8]Department of Psychiatry, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Malaysia.
[9]Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Malaysia.

†Equal contribution as first authors
#Presenter
*Corresponding author: subapriya@upm.edu.my

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Introduction

Risk factors for cardiovascular disease (CVD) have been increasingly implicated in the development of dementia, especially Alzheimer's disease (AD), which has been tagged as Type III diabetes [1]. These lifestyle-associated risk factors or CVD risk factors have been linked to the development and the acceleration of cognitive deterioration by means of causing sluggish brain perfusion, and impairment of the process of amyloid clearance from being excessively deposited in the brain cortices [2]. Although dementia due to CVD risk factors is historically closely linked to the development of vascular dementias (VaD), recent research findings have discovered its harmful influence on the development of AD. However, there is limited data on these metabolic effects on the brain morphological changes and neuronal functional connectivity (FC).

Our study was undertaken to predict the neuroimaging biomarkers of brain structural and functional abnormality with regards to CVD risk factors in AD patients compared to age-matched cognitively healthy controls (HC) in central Malaysia. Both structural and functional connections between brain regions can be studied using different sequences on MRI machines to help rule out AD. Structural MRI (sMRI) test is traditionally used as part of the standard clinical investigation of AD to diagnose brain atrophy and rule out other secondary causes of dementia [3]. Whereas resting-state functional MRI (rs-fMRI) networks have been shown to be highly sensitive to AD [4].

Methodology

A phase I cross-sectional study of patients presenting with memory impairment and cognitive decline was conducted in the memory clinic at Hospital Kuala Lumpur (HKL). Sociodemographic data, and CVD risk factors were reviewed from medical records data from 2014 to 2019 and analysed based on patients diagnosed with various neurocognitive disorders. The second phase of the study involved recruiting AD subjects from HKL, Hospital Sultan Abdul Aziz Shah and Klinik Kesihatan Pandamaran, Selangor as well as HC subjects from Klang Valley for an fMRI study. Differences in CVD risk factors, grey matter volume (GMV) deficit, and neuronal FC were compared between AD and HC.

Results and Discussion

In phase I study, a total of 298 patients (30 mild cognitive impairment (MCI), and 268 dementia) were evaluated, with dementia patients consisting of 78 AD, 93VaD, 94 mixed dementia, 2 early-onset Alzheimer's disease (EOAD) and 1 Logopenic Progressive Aphasia type of AD (LPA). History of stroke was strongly associated with MCI and dementia ($p=0.023$). Hypertension was associated with diagnosis of AD but did not achieve statistical significance ($p = 0.168$).

Hypertension was associated with the diagnosis of AD, with both systolic blood pressure (SBP) and diastolic blood pressure (DBP) being significant in Phase 2 study ($p \leq 0.001$). AD patients had reduced GMV compared to HC in the left posterior cingulate cortex, bilateral precuneus, bilateral middle temporal gyrus, and medial prefrontal cortex (p-value<0.05). There was also significantly reduced FC in the default mode network (DMN) of AD compared to HC.

Conclusion & Future Work

CVD and imaging biomarkers of reduced GMV at precuneus, middle temporal lobes, medial prefrontal cortex, and left posterior cingulate cortex and decreased FC of DMN and other resting-state networks are predictors of AD among the patients in central Malaysia. Special focus needs to be given when identifying these biomarkers as they can help identify individuals at higher risk for developing accelerated cognitive decline.

Keywords
cardiovascular risk factors, DMN, functional MRI, metabolic disorder, neurodegenerative disorders.

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Table 1: Association between socio-demographic & cardiovascular risk factors and neurocognitive disorders among the memory clinic patients in HKL, Malaysia.

	MCI (n=30) (10.24%)	AD (n=78) (26.62%)	VaD (n=93) (31.1%)	Mixed dementia (n=94) (32.1%)	Total (n=293) (100%)	F/X2	p value
Age (years)	74 (7.22)	75.47(8.90)	75.48 (7.77)	77.35 (7.49)	75.93 (7.98)	1.77	0.153
Gender							
Male	17 (56.7)	35 (44.9)	44 (47.3)	36 (40.4)	133 (46)	2.24	0.524
Female	13 (43.3)	43 (55.1)	49 (52.7)	53 (59.6)	156 (54)		
Years of education:							
≤ 6 years	9 (34.6)	39 (54.9)	45 (57)	55 (62.5)	148 (56.1)	6.39	0.094
≥ 6 years	17 (65.4)	32 (45.1)	34 (43)	33 (37.5)	116 (43.9)		
Marital status:							
Unmarried	7 (29.2)	13 (22)	18 (25.4)	28 (35)	66 (28.2)	3.23	0.358
Married	17 (7.3)	46 (78)	53 (74.6)	52 (65)	168 (71.8)		
Employment							
Yes	18 (78.3)	40 (80.0)	47 (77.0)	52 (75.4)	157 (77.3)	0.369	0.946
No	5 (21.7)	10 (20.0)	14 (23.0)	17 (24.6)	46 (22.7)		
T2DM							
Yes	10 (33.3)	29 (37.2)	46 (50)	41 (43.6)	126 (42.9)	4.077	0.253
No	20 (66.7)	49 (62.8)	46 (50)	53 (56.4)	168 (57.1)		
Hypertension							
Yes	17 (56.7)	47 (60.3)	68 (73.9)	64 (68.1)	196 (66.7)	5.051	0.168
No	13 (43.3)	31(39.7)	24 (26.1)	30 (31.9)	98 (33.3)		
Hypercholesterolemia							
Yes	1 (3.3)	3 (2.8)	1 (1.1)	2 (2.1)	7 (2.4)	1.53	0.676
No	29 (96.7)	75 (96.2)	91 (98.9)	92 (97.9)	287 (97.6)		
Stroke							
Yes	1 (3.3)	3 (3.8)	15 (16.3)	13 (13.8)	32 (10.9)	9.374	0.023*
No	29 (96.7)	75 (96.2)	77 (83.7)	81 (86.2)	262 (89.1)		
Heart disease							
Yes	0 (0.0)	1 (1.3)	1 (1.1)	4 (4.3)	6 (2)	3.574	0.311
No	30 (100)	77 (98.7)	91 (98.9)	90 (95.7)	288 (98)		

Note: Data were expressed as n (%) or mean ± SD; Significant difference between risk of MCI and dementia was determined by One-way ANOVA test or Chi-square test ($\chi 2$) at 0.05 level of significance; *$p<0.05$.

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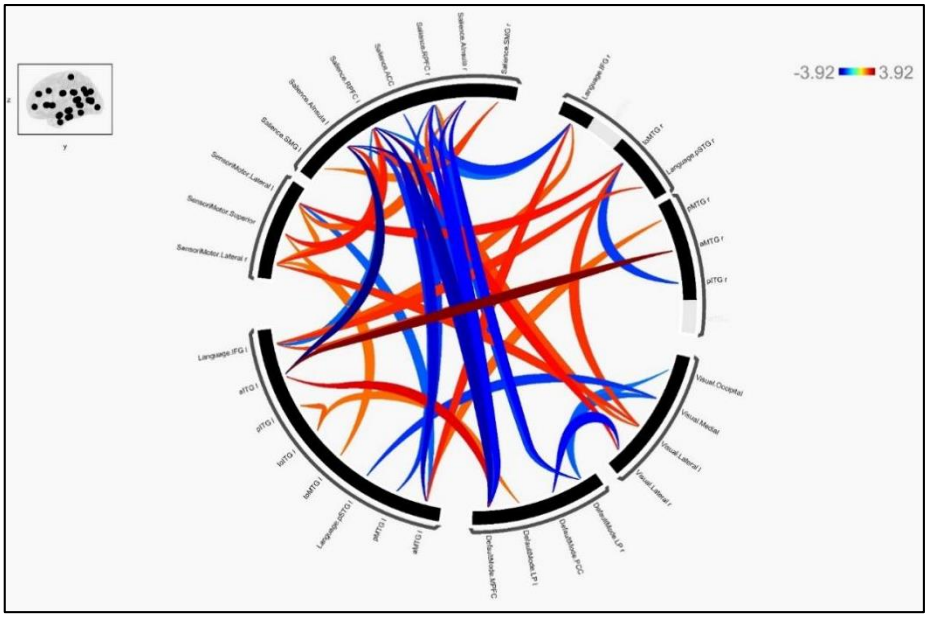

Figure 1: Brain connectogram of FC for HC > AD showing the strength of connectivity among the nodes of various resting state networks. The red lines and dark blue lines indicate a strong neuronal connectivity between the nodes of the DMN, Language, Salience and central executive networks.

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References

1. Tini G, Scagliola R, Monacelli F, La Malfa G, Porto I, Brunelli C, Rosa GM. Alzheimer's Disease and Cardiovascular Disease: A Particular Association. Cardiol Res Pract. 2020 May 5;2020:2617970
2. Wanleenuwat, P., Iwanowski, P., & Kozubski, W. (2019). Alzheimer's dementia: pathogenesis and impact of cardiovascular risk factors on cognitive decline. Postgraduate medicine, 131(7), 415-422.
3. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7(3):280-292.
4. Sheline YI, Morris JC, Snyder AZ, Price JL, Yan Z, D'Angelo G, et al. APOE4 allele disrupts resting state fMRI connectivity in the absence of amyloid plaques or decreased CSF Aβ42. J Neurosci. (2010) 30:17035–40.