PREVENTION OF ALZHEIMER'S DISEASE: FROM COGNITIVE RESERVE TO PRECISION MEDICINE

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PREVENTION OF ALZHEIMER'S DISEASE: FROM COGNITIVE RESERVE TO PRECISION MEDICINE

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Variability in Total Cholesterol Concentration Is Associated With the Risk of Dementia: A Nationwide Population-Based Cohort Study

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Introduction: Although total cholesterol (TC) variability is suggested as a risk factor for cardiovascular and cerebrovascular disease, there is no previous study to evaluate the association between TC variability and the development of dementia.

Methods: Using the Korean National Health Insurance Service–Health Screening Cohort (NHIS-HEALS), the main outcomes were newly diagnosed all-cause dementia, Alzheimer's disease (AD), or vascular dementia (VaD) between January 1, 2008, and December 31, 2015. Visit-to-visit TC variability was measured as variability independent of the mean (TC-VIM), coefficient variance (TC-CV), and standard deviation (TC-SD).

Results: In a total of 131,965 Koreans, there were 3,722 all-cause dementia (2.82%), 2,776 AD (2.10%), and 488 VaD (0.37%) during the median follow-up of 8.4 years. Kaplan–Meier curves showed increased cumulative incidences for all in the group of the highest quartiles of TC variability compared to the others. Regression using the Fine and Gray hazards model showed a steadily increasing risk of all-cause dementia with higher quartiles of TC variability. After adjusting for confounders including mean TC level and comparing the highest and lowest TC-VIM quartiles, the hazard ratios (HRs) for all-cause dementia and AD were 1.15 [95% confidence interval (CI) = 1.05–1.27; $P = 0.003$] and 1.12 (95% CI = 1.00–1.25; $P = 0.040$), respectively. The incidence of VaD was not significantly higher in the higher-quartile groups compared to that in the lowest-quartile group in TC-VIM variability (HR 1.22; 95% CI = 0.95–1.59; $P = 0.122$). These associations were consistent with TC variability defined by TC-CV or TC-SD.

Conclusions: For the first time, we have demonstrated that a higher visit-to-visit variability in TC independent of mean TC is associated with an increased risk of all-cause dementia and AD in the general population.

Keywords: variability, total cholesterol, dementia, Alzheimer's disease, vascular dementia

INTRODUCTION

With increasing numbers of elderly individuals in the population, the prevalence of dementia is also gradually increasing. The worldwide burden of dementia is presumed to be 5–7% among those over 60 years of and 80% among those over 90 years (1). In Korea, the disability-adjusted life years of dementia per 100,000 people in 2008 was 528 person-years overall and 5,117 person-years among those 65 years and older, and the burden of dementia is expected to increase steeply (2). Therefore, communities are encountering this growing burden, and caregivers must provide long-term care for patients with dementia (3).

Numerous studies have reported that visit-to-visit variability in cardiovascular risk factors is independently associated with the development of cognitive dysfunction or dementia. In a prospective study including 5,461 participants over 70 years of age, a higher visit-to-visit variability of blood pressure was associated with cortical infarcts, lower hippocampal volume, and impaired cognitive function even after adjusting for mean blood pressure (4). In a three-city study, higher visit-to-visit variability in systolic blood pressure was significantly related to an increased risk of Alzheimer's disease (AD) (5). Additionally, Lattanzi et al. showed that AD patients had an increased coefficient of variation (CV) and standard deviation (SD) in both systolic and diastolic blood pressure compared to those of healthy controls (6). Moreover, Nagai and Kario suggested that higher visit-to-visit variability in blood pressure was significantly associated with cognitive impairment, vascular dementia (VaD), and AD through the pathophysiology of arterial remodeling, amyloid β-peptide deposition, silent cerebral injury, and dysregulated cerebral circulation (7). Another study of 311 community-dwelling women older than 65 years of age reported that reduced heart rate variability reflecting cardiac autonomic dysfunction was correlated with impaired cognitive function (8). In a Taiwan diabetes study cohort including 16,706 patients with type 2 diabetes, increased glycemic variability measured as fasting plasma glucose (FPG)-CV and glycated hemoglobin-CV was related to high risks of AD (9). Finally, a cross-sectional study reported that higher low-density lipoprotein cholesterol (LDL-C) variability was related to lower cognitive function in older participants with a high risk of vascular disease (10).

Nevertheless, to the best of our knowledge, no study has assessed the association between long-term total cholesterol (TC) variability and dementia. Therefore, the present study examined the relationships between visit-to-visit TC variability and the incidence of dementia, including AD and VaD, using the longitudinal National Health Insurance Service–National Health Screening Cohort (NHIS-HEALS) database.

MATERIALS AND METHODS

Data Sources

The NHIS in the Republic of Korea is a government-operated compulsory social health insurance program that includes nearly all citizens (about 98%), who are recommended to receive standardized national health examination programs biannually (annually for manual workers) (11, 12). All health examinations such as anthropometric measurement and laboratory tests are conducted after an overnight fast, and the Korean Association of Laboratory Quality Control superintends the quality control procedures. The NHIS-HEALS comprises a randomly sampled database of ∼10% of all participants, aged between 40 and 79 years, within the NHIS data. This study consisted of individuals who underwent the national health examinations in 2007 (the index year) and three or more health examinations between January 1, 2002, and December 31, 2007. After excluding individuals with missing data in at least one variable and who had a previous diagnosis of dementia, stroke, or diabetes mellitus before 2007, a total of 131,965 individuals were finally included in the analysis (**Figure 1**). Informed consent was waived because anonymous and de-identified information was used for analysis. These protocols were approved by both the NHIS review committee and the institutional review board (IRB). The Korea University IRB approved the study protocol in accordance with the Declaration of Helsinki of the World Medical Association.

Measurements and Definitions

Body mass index (BMI) was computed as weight (kilograms)/height squared (meters^2). The smoking and alcohol drinking statuses were obtained from responses to the health examination questionnaire. Regular exercise was defined as strenuous physical activity for at least 20 min and ≥n times/week. Income level was dichotomized at the lower 10%. The presence of diabetes was defined based on the criterion of FPG level ≥7 mmol/L or the presence of at least one claim per year for the prescription of antidiabetic medication under the International Classification of Diseases, Tenth Revision (ICD-10), codes (E10–E14). The presence of hypertension was defined based on the criterion of systolic/diastolic blood pressure ≥140/90 mmHg or the presence of at least one claim

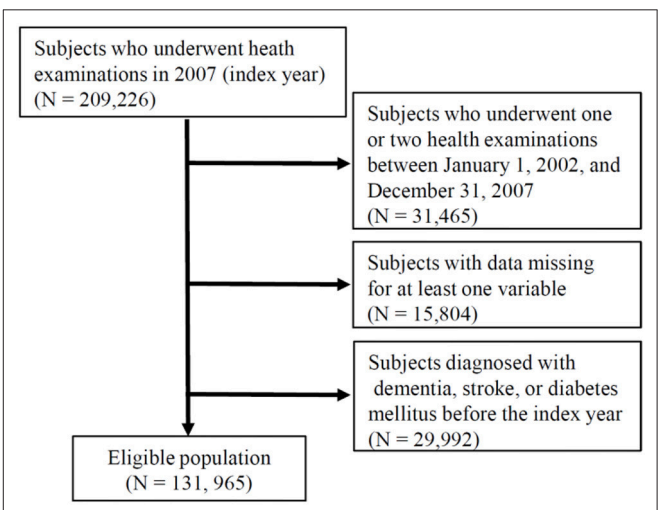

FIGURE 1 | Flowchart of the study population. NHIS-HEALS, National Health Insurance Service–National Health Screening Cohort.

per year for the prescription of an antihypertensive agent under ICD-10 codes (I10–I15). The presence of dyslipidemia was defined based on the criterion of TC level ≥6.2 mmol/L or the presence of at least one claim per year for the prescription of a lipid-lowering agent under ICD-10 code (E78). Diagnosis of stroke was defined as ICD-10 codes (I60–I64) on the admission record with computerized tomography or magnetic resonance imaging claim data. Diagnosis of myocardial infarction (MI) was defined as ICD-10 codes (I21–I22) during hospitalization or these codes having been recorded at least two times.

Definition of Total Cholesterol Variability

The TC variability was determined from at least three measurements of TC values during health examinations: three measurements (n = 67,609, 51%), four measurements (n = 14,069, 11%), five measurements (n = 18,840, 14%), and six measurements (n = 31,447, 24%). For descriptive TC variability, we used three indices of variability: TC—variability independent of the mean (VIM), TC—CV, and TC—SD. VIM was defined as $100 \times SD/Mean^{\beta}$, where β is the regression coefficient, based on the natural logarithm of the SD over the natural logarithm of the mean. CV was defined as SD/mean × 100 (%).

Study Outcomes

We examined newly diagnosed all-cause dementia, AD, and VaD as primary outcomes between January 1, 2008, and December 31, 2015. Diagnosis of all-cause dementia was defined based on the first prescription of an anti-dementia drug [acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine) or N-methyl-D-aspartate (NMDA) receptor antagonist (memantine)] under ICD-10 codes (F00–F03, G30) among outpatients or hospitalized patients. Diagnosis of AD, the most common subtype of dementia, was defined based on the first prescription of an anti-dementia drug with an ICD-10 code for AD (F00, G30), and the diagnosis of VaD was defined based on the first prescription of an anti-dementia drug with an ICD-10 code for VaD (F01). In Korea, in order to prescribe anti-dementia drugs, the Korea National Health Insurance Reimbursement Criteria require that physicians record evidence of cognitive dysfunction: (a) Mini-Mental State Examination (MMSE) ≤26 and either (b) Global Deterioration Scale (GDS) ≥3, or (c) Clinical Dementia Rating (CDR) ≥1.

Statistical Analysis

Baseline characteristics are presented as means ± SDs for continuous variables and as percentages for categorical variables. Participants were classified into quartiles according to the

TABLE 1 | Baseline characteristics of the subjects according to the total cholesterol (TC) variability measured as variability independent of the mean (VIM).

	Q1	Q2	Q3	Q4	*P*-value
N	32,991	32,991	32,992	32,991	
Age (years)	55.5 ± 8.7	54.5 ± 8.2	54.9 ± 8.4	56.9 ± 8.9	<0.001
Sex (male) (*n*, %)	18,724 (56.8)	20,140 (61.0)	19,063 (57.8)	16,900 (51.2)	<0.001
Body mass index (kg/m^2)	23.8 ± 2.8	23.8 ± 2.8	23.8 ± 2.8	24.0 ± 2.9	<0.001
Systolic BP (mmHg)	124.3 ± 15.4	124.5 ± 15.3	124.9 ± 15.4	125.8 ± 15.9	<0.001
Diastolic BP (mmHg)	77.6 ± 10.1	77.9 ± 10.1	78.1 ± 10.2	78.2 ± 10.2	<0.001
AST (IU/L)	25.1 ± 11.6	25.4 ± 13.0	25.8 ± 15.3	27.1 ± 18.8	<0.001
ALT (IU/L)	23.5 ± 15.5	24.2 ± 18.9	24.5 ± 17.9	25.7 ± 21.6	<0.001
GGT (IU/L)	32.7 ± 36.6	35.1 ± 40.3	36.1 ± 42.9	39.2 ± 54.8	<0.001
Fasting plasma glucose (mmol/L)	5.10 ± 0.63	5.10 ± 0.64	5.10 ± 0.65	5.13 ± 0.66	<0.001
Mean TC (mg/dl)	194.9 ± 29.4	196.1 ± 29.2	198.2 ± 29.6	203.8 ± 31.4	<0.001
TC variability					
VIM (%)	8.40 ± 2.77	15.00 ± 1.59	21.05 ± 2.06	34.82 ± 10.51	<0.001
CV (%)	4.30 ± 1.45	7.65 ± 0.95	10.69 ± 1.24	17.44 ± 5.13	<0.001
SD (IU/L)	8.29 ± 2.83	14.87 ± 2.03	20.99 ± 2.75	35.39 ± 12.07	<0.001
Current smoker (*n*, %)	6,059 (18.4)	6,894 (20.9)	6,544 (19.8)	5,829 (17.7)	<0.001
Alcohol consumption (*n*, %)	14,024 (42.5)	14,950 (45.3)	14,291 (43.3)	12,640 (38.3)	<0.001
Regular exercise (*n*, %)	3,446 (10.4)	3,077 (9.3)	3,088 (9.4)	3,420 (10.4)	<0.001
Income (lower 10%) (*n*, %)	2,299 (7.0)	2,309 (7.0)	2,555 (7.7)	2,871 (8.7)	<0.001
Hypertension (*n*, %)	17,457 (52.9)	18,077 (54.8)	18,726 (56.8)	20,336 (61.6)	<0.001
Dyslipidemia (*n*, %)	5,528 (16.8)	7,696 (23.3)	10,644 (32.3)	18,531 (56.2)	<0.001
History of myocardial infarction (*n*, %)	182 (0.6)	154 (0.5)	202 (0.6)	430 (1.3)	<0.001
Use of antihypertensive agent (*n*, %)	10,170 (30.8)	9,776 (29.6)	10,536 (31.9)	13,596 (41.2)	<0.001
Use of lipid-lowering agent (*n*, %)	2,487 (7.5)	2,677 (8.1)	3,530 (10.7)	8,054 (24.4)	<0.001

AST, aspartate transaminase; ALT, alanine transaminase; BP, blood pressure; GGT, γ-glutamyl transferase; VIM, variability independent of the mean; CV, coefficient of variation; SD, standard deviation.

P-value by ANOVA and chi-square test. Data are expressed as mean ± SD, or n (%).

TC variability. Differences between groups were identified by analysis of variance (ANOVA) for continuous variables and χ^2-tests for categorical variables. Kaplan–Meier curves of cumulative incidence for all-cause dementia were produced for the four quartile groups of TC variability. The hazard ratios (HRs) and 95% confidence interval (CI) values for all-cause dementia, AD, and VaD were analyzed using the method of Fine and Gray, in order to take into account the competing risk of mortality (13), for the quartile groups of TC variability, adjusted for age, sex, BMI, alcohol consumption, smoking, regular exercise, income, hypertension, dyslipidemia, history of MI, and mean TC. Cumulative incidence functions (CIFs) were used to estimate the probability of the occurrence of all-cause dementia, AD, and VaD. We applied the proportional hazards model for the subdistribution of a competing risk to estimate the subdistribution HR and 95% CI.

We also performed subgroup analyses of the association between TC-VIM variability and incidence of all-cause dementia, AD, or VaD by age, sex, BMI, hypertension, use of an antihypertension medication, dyslipidemia, use of a lipid-lowering agent, history of MI, current smoking, and income. In subgroup analyses, the HR and 95% CI of the group of the upper three quartiles (Q2–Q4) were compared with those of the lowest quartile (Q1) as the reference group using cox proportional hazards regression analyses with interaction effect. Because of *post hoc* subgroup analyses, we did not adjust for multiple testing.

All statistical results were analyzed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA), and *P*-values <0.05 were assumed to indicate statistical significance.

RESULTS

Baseline Characteristics of the Study Population

Table 1 describes the characteristics of the study participants according to the VIM quartiles for TC variability. The ranges of the VIM quartiles with TC variability were 8.40 ± 2.77%, 15.00 ± 1.59%, 21.05 ± 2.06%, and 34.82 ± 10.51%, respectively (*P*-value <0.001). The higher-quartile groups of TC variability were older and had higher proportions of women and lower income compared to the lower-quartile group. The prevalence of comorbid conditions such as hypertension, dyslipidemia, and MI also increased incrementally according to quartiles of TC variability. Expectably, BMI, systolic blood pressure, diastolic blood pressure, FPG level, TC level, and proportion of antihypertensive or lipid-lowering agent use were higher in the higher-quartile groups of TC variability. Similar relationships in the baseline characteristics were observed in the quartiles of TC-CV (**Supplementary Table 1**) and TC-SD (**Supplementary Table 2**).

Implication of Total Cholesterol Variability With All-Cause Dementia, Alzheimer's Disease, and Vascular Dementia

There were 3,722 all-cause dementia (2.82%), 2,776 AD (2.10%), and 488 VaD (0.37%) during the median follow-up of 8.4 years in the entire cohort. The unadjusted cumulative incidences for all-cause dementia, AD, and VaD showed significantly higher incidences among the subjects in the fourth quartile of TC variability compared with those in the first quartile, measured as VIM (**Figure 2**), CV (all-cause dementia: *P* for Gray test <0.001, AD: *P* for Gray test <0.001, VaD: *P* for Gray test <0.001), and SD (all-cause dementia: *P* for Gray test <0.001, AD: *P* for Gray test <0.001, VaD: *P* for Gray test = 0.005). The Fine and Gray hazards regression models revealed a steadily higher risk of all-cause dementia in the higher quartiles compared with

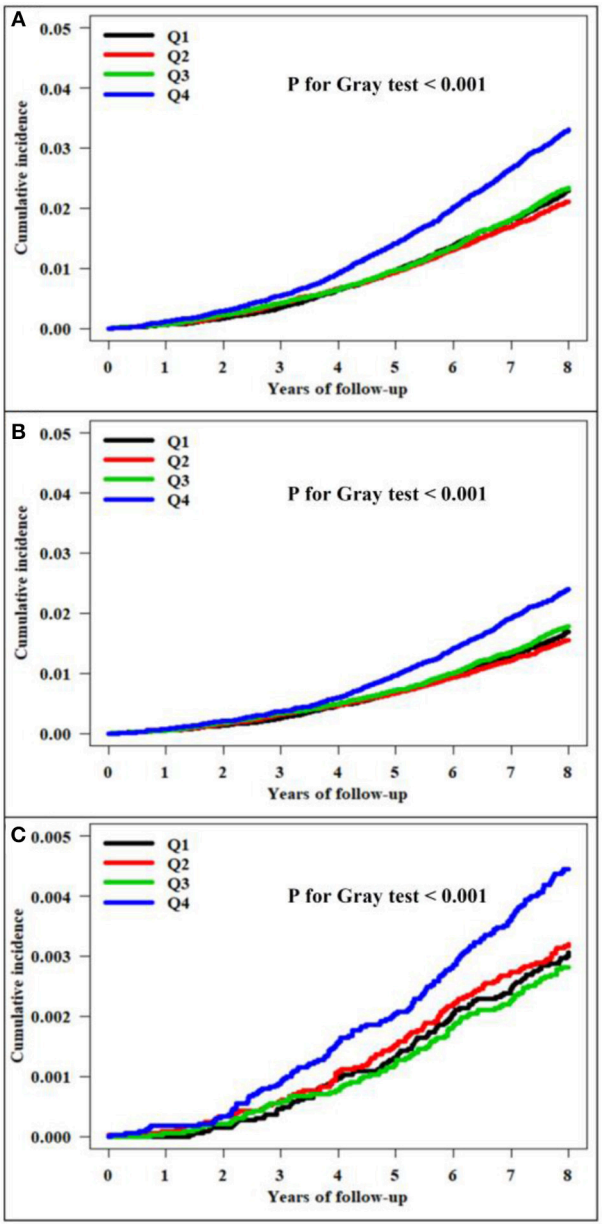

FIGURE 2 | Kaplan–Meier estimates of the cumulative incidence by quartile of total cholesterol variability measured as the variability independent of the mean (VIM). **(A)** All-cause dementia. **(B)** Alzheimer's disease. **(C)** Vascular dementia.

that of the lowest-quartile group in TC variability (**Table 2**). In TC variability as measured by VIM, CV, and SD, the HRs for incident all-cause dementia were 1.15 (95% CI = 1.05–1.27; $P = 0.003$), 1.20 (95% CI = 1.09–1.32; $P < 0.001$), and 1.12 (95% CI = 1.02–1.23; $P = 0.023$) in the group of the highest quartile of TC variability compared to those of the lowest-quartile group after adjusting for multiple variables and the mean TC. Furthermore, TC variability was also identified as a meaningful predictor of AD, even after adjusting for confounding factors (**Table 3**). In TC variability as measured by VIM, CV, and SD, the adjusted HRs for incident AD were 1.12 (95% CI = 1.00–1.25; $P = 0.040$), 1.16 (95% CI = 1.04–1.29; $P = 0.009$), and 1.10 (95% CI = 0.98–1.23; $P = 0.094$) in group of the highest quartiles of TC variability compared to that of the lowest-quartile group. However, the risk of VaD was not significantly increased in the higher-quartile groups compared to that of the lowest-quartile group in TC variability as measured by VIM, CV, and SD [1.22 (95% CI = 0.95–1.57; $P = 0.122$), 1.34 (95% CI = 1.04–1.73; $P = 0.023$), and 1.12 (95% CI = 0.87–1.45; $P = 0.374$)] (**Table 3**).

Subgroup analyses stratified by age, sex, BMI, hypertension, use of antihypertensive agents, dyslipidemia, use of lipid-lowering agents, history of MI, current smoking, and level of income were performed (**Figure 3**). The Q2–Q4 group of TC-VIM variability remained predictive of all-cause dementia in the subgroups of older (≥70 years) individuals, those without obesity, those not taking lipid-lowering agents, those without history of MI, non-smokers, and those with high income, irrespective of gender, history of hypertension and antihypertensive agents, and history of dyslipidemia, compared with the Q1 groups (**Figure 3A**). Additionally, the associations between TC-WIM variability and AD were consistent in subjects who were older (≥70 years), female, with or without obesity, without hypertension, using antihypertensive agents, with a history of dyslipidemia, not taking lipid-lowering agents, with no history of MI, and non-smokers, irrespective of income (**Figure 3B**). There was no statistically different incidence of all-cause dementia and AD within categories of several risk factors. A substantially higher risk of VaD was observed in the high-income subgroup compared to that of the low-income group (*P*-value for interaction = 0.004; **Figure 3C**).

DISCUSSION

Using a large-scale cohort data set with long follow-up duration, we demonstrated that high visit-to-visit TC variability was associated with the occurrence of all-cause dementia and AD independently of mean TC levels in the Korean population. However, there was no association between visit-to-visit TC variability and VaD. These results infer that variability in cholesterol level may be a novel predictor of upcoming dementia, including AD.

Variability in anthropometric or laboratory parameters may be surrogate markers for diverse diseases rather than measurement error. High intraindividual variability in cholesterol levels is linked to adverse outcomes. In the long-term

TABLE 2 | Hazard ratios (HRs) and 95% confidence intervals (CIs) of all-cause dementia by quartiles of total cholesterol (TC) variability.

	Events (*n*)	Follow-up duration (person-years)	Incidence rate (per 1,000 person-years)	Adjusted HR (95% CI)	*P*-value
TC Variability (VIM)					
Q1	853	271,508	3.14	1 (ref)	
Q2	787	271,396	2.90	1.12 (1.02–1.24)	0.020
Q3	865	271,030	3.19	1.13 (1.03–1.25)	0.012
Q4	1,217	268,717	4.53	1.15 (1.05–1.27)	0.003
P for trend			0.004		
TC variability (CV)					
Q1	848	271,568	3.12	1 (ref)	
Q2	822	271,365	3.03	1.20 (1.09–1.32)	<0.001
Q3	819	271,217	3.02	1.09 (0.99–1.20)	0.091
Q4	1,233	268,503	4.59	1.20 (1.09–1.32)	<0.001
P for trend			0.002		
TC variability (SD)					
Q1	861	271,356	3.17	1 (ref)	
Q2	772	271,475	2.84	1.07 (0.97–1.18)	0.167
Q3	886	270,821	3.27	1.11 (1.01–1.22)	0.032
Q4	1,203	269,001	4.47	1.12 (1.02–1.23)	0.023
P for trend			0.018		

VIM, variability independent of the mean; CV, coefficient of variation; SD, standard deviation.
Adjusted for age, sex, income, body mass index, hypertension, dyslipidemia, history of myocardial infarction, smoking, alcohol intake, exercise, and mean TC level.
Using regression methods of Fine and Gray for competing risk data (death is a competing event for dementia).

TABLE 3 | Hazard ratios (HRs) and 95% confidence intervals (CIs) of Alzheimer's dementia and vascular dementia by quartiles of total cholesterol (TC) variability.

	Events (n)	Follow-up duration (person-years)	Incidence rate (per 1,000 person-years)	Adjusted HR (95% CI)	*P*-value
ALZHEIMER'S DISEASE					
TC variability (VIM)					
Q1	632	271,508	2.33	1 (ref)	
Q2	591	271,396	2.18	1.14 (1.02–1.28)	0.020
Q3	664	271,030	2.45	1.17 (1.05–1.31)	0.005
Q4	889	268,717	3.31	1.12 (1.00–1.25)	0.040
P for trend			0.046		
TC variability (CV)					
Q1	633	271,568	2.33	1 (ref)	
Q2	617	271,365	2.27	1.21 (1.08–1.35)	0.001
Q3	630	271,217	2.32	1.12 (1.01–1.26)	0.040
Q4	896	268,503	3.34	1.16 (1.04–1.29)	0.009
P for trend			0.035		
TC variability (SD)					
Q1	633	271,356	2.33	1 (ref)	
Q2	585	271,475	2.15	1.11 (0.99–1.24)	0.084
Q3	664	270,821	2.45	1.12 (1.00–1.25)	0.041
Q4	894	269,001	3.32	1.10 (0.98–1.23)	0.094
P for trend			0.101		
VASCULAR DEMENTIA					
TC variability (VIM)					
Q1	109	271,508	0.40	1 (ref)	
Q2	114	271,396	0.42	1.21 (0.93–1.58)	0.147
Q3	101	271,030	0.37	1.00 (0.76–1.31)	0.988
Q4	164	268,717	0.61	1.22 (0.95–1.57)	0.122
P for trend			0.235		
TC variability (CV)					
Q1	104	271,568	0.38	1 (ref)	
Q2	119	271,365	0.44	1.33 (1.02–1.73)	0.034
Q3	91	271,217	0.34	0.94 (0.70–1.24)	0.645
Q4	174	268,503	0.65	1.34 (1.04–1.73)	0.023
P for trend			0.136		
TC variability (SD)					
Q1	116	271,356	0.43	1 (ref)	
Q2	102	271,475	0.38	1.02 (0.78–1.33)	0.884
Q3	115	270,821	0.42	1.06 (0.82–1.38)	0.658
Q4	155	269,001	0.58	1.12 (0.87–1.45)	0.374
P for trend			0.360		

VIM, variability independent of the mean; CV, coefficient of variation; SD, standard deviation.
Adjusted for age, sex, income, body mass index, hypertension, dyslipidemia, history of myocardial infarction, smoking, alcohol intake, exercise, and mean total cholesterol level.
Using regression methods of Fine and Gray for competing risk data (death is a competing event for dementia).

Framingham Study including 2,912 men and women, high intraindividual variability in TC was related to increased risks of CVD and mortality (14). In addition, Kim et al. showed that high visit-to-visit variability in TC level is associated with the risk of stroke, MI, and mortality in Koreans (15). In the Treating-to-New-Targets (TNT) trial, Bangalore et al. reported that high LDL-C variability was also associated with stroke, MI, any coronary event, any cardiovascular event, and mortality after adjusting for mean LDL-C levels and statin treatment (16). In subjects with previous ST-segment elevation MI events, visit-to-visit LDL-C and high-density lipoprotein cholesterol (HDL-C) variability is an independent predictor of major adverse cardiovascular events including stroke and MI (17). Moreover, recent studies demonstrated that visit-to-visit variability in lipids is related to other chronic inflammatory outcomes such as the incidence of diabetes (18), diabetic nephropathy progression

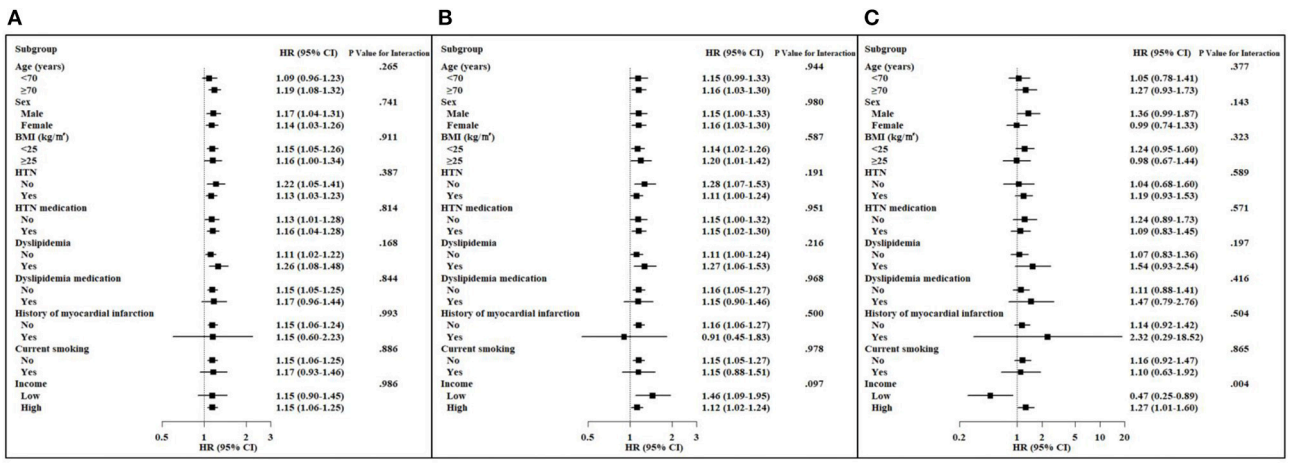

FIGURE 3 | Hazard ratios (HRs) and 95% confidence intervals (CIs) of dementia in the highest three quartiles vs. the lowest quartile of total cholesterol variability (VIM) in subgroups. Adjusted for age, sex, body mass index (BMI), hypertension (HTN), use of antihypertension medication, dyslipidemia, use of a lipid-lowering agent, history of myocardial infarction, current smoking, and income. **(A)** All-cause dementia. **(B)** Alzheimer's disease. **(C)** Vascular dementia.

(19), and end-stage renal disease progression (20). Notably, Smit et al. reported that higher LDL-C variability, independent of statin use and mean LDL-C levels, is related to lower function in four cognitive domains, greater white matter hyperintensity volume, and lower cerebral blood flow (10). Similarly, positive correlations between LDL-C variability and dementia risk factors such as maximum carotid intima media thickness (21) or severity of obstructive sleep apnea (22) have been reported. Recently, using the data of NHIS, Lee et al. showed an association between increased variabilities in metabolic parameters, including blood pressure, glucose, cholesterol, and BMI, and risk of dementia during a median follow-up of 5.5 years (23). They concluded that there was a linear relationship between the number of increased variability parameters and risk of dementia. On the other hand, our study focused on the impact of higher visit-to-visit TC variability on long-term risk of dementia using the NHIS-HEALS database for a longer follow-up period (8.4 years). Therefore, we presented detailed results regarding the relationship between visit-to-visit TC variability and dementia, such as Kaplan–Meier curves by quartiles of TC variability (**Figure 2**) and HRs (95% CIs) in various subgroups of risk factors (**Figure 3**).

Several epidemiologic studies have revealed the relationship between TC level and the risk of cognitive outcomes. Although the relationship between hypercholesterolemia and impaired cognitive function was shown in animal studies (24–26), the findings were controversial and varied according to the study design in human studies. In a longitudinal population-based study, high TC level (≥6.5 mmol/L) or systolic blood pressure (≥160 mmHg) in midlife was predictive of an elevated the risk of AD during a mean 21 years of follow-up (27). However, another longitudinal study conducted over 32 years revealed that TC level in midlife was not significantly related to the risk of dementia (28). Additionally, Beydoun et al. used Cox proportional hazard models to show that increased first-visit TC level is associated with a decreased risk of mild cognitive impairment but not with dementia (29). A meta-analysis including these previous studies reported that high TC measured in midlife ($40 < \text{age} \leq 60$ years) was significantly associated with an increased risk of late-life all-cause dementia (relative risk: 1.82; 95% CI: 1.27–2.60; $P < 0.01$) and AD (relative risk: 2.14; 95% CI: 1.33–3.44; $P < 0.01$) compared to individuals without high TC levels (30). Meanwhile, most studies that measured TC in late life have reported that high TC level is not associated with all-cause dementia (30–32) or AD (30–33). However, there is insufficient epidemiologic evidence to determine if high TC level is a predictable risk factor for dementia, including AD.

Although epidemiologic studies have assessed whether average TC level is a risk factor for cognitive outcomes, few have reported on serial changes in TC level. In a prospective study of 1,462 Swedish women, declining TC levels from midlife to late life were potentially related to an increased risk of AD (28). Beydoun et al. showed that a decline in TC level compared to baseline level was associated with an elevated risk of dementia among men but not women in subgroup analysis (29). Another study with 1,027 Japanese-American men reported that participants with dementia had sharply decreased serum TC levels in the early stages of dementia compared to those without dementia (34). Similarly, in Finnish men, the serial mean TC level in those with AD declined more drastically than that in the group without dementia (35). However, most previous studies on changes in TC focused on the decreasing trend of mean TC levels and dementia. To the best of our knowledge, the association between visit-to-visit variability in TC level and incident dementia or its subtypes has not been evaluated. The present study used nationwide population to confirm that visit-to-visit variability in TC level was independently associated with the risk of all-cause dementia and AD after adjusting for confounding factors.

The results of the present study showed that increased TC variability was not significantly associated with the risk of VaD. A possible reason for no association was the relatively younger

age of the study population. Previous studies reported that the incidence of VaD increases exponentially as age increases after the age of 65 years (36, 37). Additionally, several previous studies demonstrated no meaningful associations between TC and VaD, concordant with our study findings. In a study of 1,027 Japanese-American men, Stewart et al. showed that a 26-year change in TC in midlife was not related to incident VaD (34). Another study in the general Japanese population older than 65 years of age reported that the risk factors for incident VaD included age, being an alcohol consumer, diabetes mellitus, stroke, blood pressure, and hematocrit, but not TC (38). In American community-based cohort studies of older age (>65 years), Reitz et al. reported that the risk of VaD was not related to TC, even though a weak relationship between VaD and subtypes of cholesterol including LDL cholesterol and HDL cholesterol was observed (33). Further investigation is necessary to confirm the association between TC variability and VaD, considering the relatively low incidence of VaD, as well as to understand the mechanisms.

Although the pathophysiological mechanisms of TC variability in dementia are not fully known, several pathways have been suggested. The predicted pathogenic role of variability in cholesterol levels is connected to inflammation and endothelial dysfunction, which results in the development of atherosclerosis (39). A previous study showed that increased levels of serum markers of endothelial dysfunction were associated with an increased risk of developing cognitive impairment (40). Another pathway contributing to dementia or cerebrovascular damage is plaque instability (41, 42), use of lipid-lowering medication, and non-adherence to the use of lipid-lowering medication (43). Animal studies have demonstrated that intermittent high-fat diets lead to atherosclerosis (44). Furthermore, in animal and human studies, lipid-lowering agents caused changes in the composition of atherosclerotic plaques and plaque rupture (45, 46). However, our study reported a consistent association between TC variability and all-cause dementia or AD in the subgroup without lipid-lowering medication. Additionally, there is a need to evaluate the cholesterol metabolism and metabolic products in the brain affected by TC level variability in the blood.

This study has several limitations. First, due to inherent limitations of the observational study design, we could not infer a causal relationship between visit-to-visit TC variability and dementia. Second, although we tried to eliminate the covariates known to affect the risk of dementia in our multivariate analyses, unmeasured confounding factors such as depression, cognition level, and education are possible. Third, the NHIS health examinations did not assess other lipid profile data including LDL-C, HDL-C, and triglyceride levels. Nevertheless, the present study has notable strengths, including the validation of a standardized database from the Korean government with detailed and credible information regarding medication usage and medical diagnosis. Moreover, this study had a sufficiently long median follow-up period of 8.4 years to evaluate the risk of dementia in the general population. Additionally, the variability in cholesterol levels was calculated using diverse indicators such as TC-VIM, TC-CV, and TC-SD, and their associations with dementia and its subtypes were similar and consistent.

In conclusion, we report for the first time that higher visit-to-visit TC variability is independently associated with an increased long-term risk of dementia and AD after adjusting for potential risk factors including mean TC. The present study using a nationwide population provides new insight into the relevance of the serial measurement of cholesterol levels in populations at high risk of dementia. Further replication studies in other age or ethnic groups are necessary to validate these findings.

CONTRIBUTION TO THE FIELD STATEMENT

Previous studies have reported the relationship between TC level and the development of dementia. Nevertheless, no study has assessed the association between visit-to-visit variability in TC and dementia. In a longitudinal nationwide population-based cohort, we evaluated the relationships between visit-to-visit TC variability and the incidence of dementia, including AD and VaD. This study suggested that visit-to-visit TC variability, using three different indicators, is a risk factor for the development of all-cause dementia, and AD independently of other risk variables, including mean cholesterol. However, we showed that increased TC variability was not significantly associated with the risk of vascular disease. Further study is needed to replicate these findings in other age or ethnic groups and to elucidate the mechanism of TC variability in the pathogenesis of dementia or AD.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request and approval of the institutional review board.

ETHICS STATEMENT

The Korea University IRB approved the study protocol in accordance with the Declaration of Helsinki of the World Medical Association.

AUTHOR CONTRIBUTIONS

HC, JL, and KC contributed to the study concept and design, contributed to the data acquisition, and conducted the manuscript drafting. HC, JL, JK, ER, YL, SH, HY, and KC contributed to the data analysis and interpretation. NHoK, JS, SK, NHeK, and SB performed critical manuscript revision.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.00441/full#supplementary-material

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MINI REVIEW
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A Literature Overview of Virtual Reality (VR) in Treatment of Psychiatric Disorders: Recent Advances and Limitations

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In this paper, we conduct a literature survey on various virtual reality (VR) treatments in psychiatry. We collected 36 studies that used VR to provide clinical trials or therapies for patients with psychiatric disorders. In order to gain a better understanding of the management of pain and stress, we first investigate VR applications for patients to alleviate pain and stress during immersive activities in a virtual environment. VR exposure therapies are particularly effective for anxiety, provoking realistic reactions to feared stimuli. On top of that, exposure therapies with simulated images are beneficial for patients with psychiatric disorders such as phobia and posttraumatic stress disorder (PTSD). Moreover, VR environments have shown the possibility of changing depression, cognition, even social functions. We review empirical evidence from VR-based treatments on psychiatric illnesses such as dementia, mild cognitive impairment (MCI), schizophrenia and autism. Through cognitive training and social skill training, rehabilitation through VR therapies helps patients to improve their quality of life. Recent advances in VR technology also demonstrate potential abilities to address cognitive and functional impairments in dementia. In terms of the different types of VR systems, we discuss the feasibility of the technology within different stages of dementia as well as the methodological limitations. Although there is room for improvement, its widespread adoption in psychiatry is yet to occur due to technical drawbacks such as motion sickness and dry eyes, as well as user issues such as preoccupation and addiction. However, it is worth mentioning that VR systems relatively easily deliver virtual environments with well-controlled sensory stimuli. In the future, VR systems may become an innovative clinical tool for patients with specific psychiatric symptoms.

Keywords: virtual reality, psychiatric treatment, psychiatric disorders, dementia, motion sickness

INTRODUCTION

Virtual reality (VR) is defined as a computer-generated simulation, such as a set of images and sounds that represents a real place or situation, that can be interacted with, in a seemingly real or physical way by a person using special electronic equipment. It can transmit visual, auditory, and various sensations to users through a headset to make them feel as if they are in a virtual or imagined environment (1).

The concept of VR was introduced in the 1950s, and the maturity of VR for entertainment is now evident. Currently, more than 230 companies are producing various products related to VR and performing research and development, including global companies such as Samsung Electronics, Apple, Facebook, Amazon, and Microsoft. VR systems consist of VR headsets, a computer, and video. Recently, chairs, gloves, and sensors have been added. VR headsets refer to head-mounted goggles. They are equipped with a speaker or headphones. VR systems that include the transmission of vibrations and other sensations to the user through a game controller, gloves or chairs are known as haptic feedback systems (2). This tactility is advantageous as the sense of presence can be improved by actually sensing the shock or vibration to the user in the medical field, video games, and military training. A 4D (four-dimensional) system of VR refers to a VR system with a motion chair that enhances reality for users with integrated movement according to the content of the VR video. Depending on the type of system and programing, the user may interact with the environment from a first- or third-person's point of view. In the case of the latter, the user can move around a virtual representation of themselves, called an 'avatar' (3).

In medical fields, multidisciplinary research has tried to apply VR systems to domains of diagnosis, treatment, and so on. Especially, in psychiatry, traditional tools of treatment have mainly been limited to interpersonal psychotherapy and medication. However, VR can provide various types of stimulation (4). Intuitively, it helps in relieving pain, stress, and anxiety in an imagined space, and VR makes it possible to provide efficient educational and psychological training without causing harm to patients (5). It therefore has the possibility of changing PTSD, phobia, anxiety, depression, cognition, and social functions in patients with psychiatric illnesses.

Indeed, over the past few decades, therapeutic virtual reality (VR) has emerged as a successful solution for a wide range of psychiatric disorders. In the 1990s, Rothbaum et al. conducted the first study in the field of psychiatry to investigate the efficacy of VR focusing one treating acrophobia in college students and found that VR is successful in reducing their fear of heights (6). The early studies established the efficacy of VR exposure therapy for a number of anxiety and related disorders. For example, VR exposure therapies have shown benefits for patients with a specific phobia or posttraumatic stress disorder (PTSD) by the extinction of traumatic experiences through their repetitive exposures, and the extinction of pain by pulling the patients focus away from painful conditions. The broad reach of VR has enabled its use in the evaluation and rehabilitation of patients with schizophrenia and autism through improvements of their social activities. The reports included in this review, show that VR is also an efficacious way for Amnestic MCI (mild cognitive impairment) and early to moderate Alzheimer's disease through cognitive reserve and training.

VR-based treatment currently faces hurdles preventing its wide use as a real tool in psychiatry practice, such as motion sickness and dry eyes as well as user issues such as preoccupation and addiction. However, VR systems can deliver and confront virtual environments with well-controlled sensory stimuli. With a review of the current utilization of VR in the field of psychiatry, we highlight both the benefits and limitations of VR use, as it is just beginning to be applied as a new modality in psychiatry. We have tried to describe the evidence of the utility of VR in psychiatric conditions and the types of procedures followed in those studies

METHODS AND RESULTS

To identify 'virtual reality' in the field of psychiatry, a PubMed literature search was performed which included articles published prior to 31 December 2018, and which included the terms "virtual reality" and "psychiatry" and "treatment" or "therapy." We then categorized them as articles related to "posttraumatic Stress Disorders (PTSD)," "phobia," "anxiety disorders," "schizophrenia," "autism," "dementia and mild cognitive impairment (MCI)," and "pain and stress." Additional relevant articles were found through a manual bibliographic search. Eligibility criteria were: 1) articles in English; 2) human studies; and 3) articles focused on virtual reality and psychiatric disorders. We collect 36 studies that made use of VR to provide various types of stimulations for patients with psychiatric problems (**Table 1**).

DISCUSSION

Treatment of Posttraumatic Stress Disorders (PTSD)

Posttraumatic Stress Disorder (PTSD) is a psychological reaction that occurs after experiencing stress that has caused life-threatening extreme mental trauma (42). An individual's quality of life is greatly reduced by re-experiencing the situation with awakening, anxiety, agitation, and insomnia symptoms. Among PTSD, many VR studies have been focused on veterans who have been exposed to battles in Iraq and Afghanistan, to alleviate their trauma (43), reduce suicidal ideation (44), decrease depression and anger (16), and to improve their PTSD (30). Discharged soldiers can have destructive behaviors to both themselves and others as a result of rage and depression caused by PTSD. However, they can learn to solve these situations in a safe and well-controlled environment called VR. Since the key in the emotion-processing theory (EPT) is to expose and modify their unique fear structure, the virtual environment is ideal in the sense of its flexibility and customization (45). As they are exposed to sources of their disorder, they decrease the feelings of fear and anxiety in the form of VR-based habituation therapy. Dr. Rothbaum at the Emory University Hospital provided a randomized, double-blind,

TABLE 1 | Clinical trials or therapies with virtual reality (VR) in psychiatry.

Author and date of publication	Subjects	Design	Method	Conclusions
Doniger et al., 2018 (7)	Middle-aged adults with Alzheimer's disease family history (*n* = 125)	RCT	VR cognitive-motor training, 45 min, twice/week for 12 weeks	Increased cognitive function
Reger et al., 2019 (8)	Active duty soldiers with PTSD (*n* = 108)	Observational	Randomization to exposure *via* 10 sessions of prolonged exposure or VRE or 5-week minimal attention waitlist	No group differences in average or peak subjective distress during exposure therapy
Flores et al., 2018 (9)	Two patients with spinal cord injury with psychiatric symptoms	Case report	4 VR DBT sessions for Patient 1, 2 VR DBT sessions for Patient 2	Reductions in negative emotions for Patient 1, mixed results for Patient 2
Peskin et al., 2018 (10)	Men and women with World trade center-related PTSD (*n* = 25)	RCT	100 mg D-cycloserine versus placebo augmented VRE sessions for 12 weeks	Temporal relationship between posttraumatic and depressive symptoms. during VRE
Du Sert et al., 2018 (11)	Schizophrenia patients with refractory AVH (*n* = 19)	RCT	A 7-week phase-II, randomized, partial cross-over trial	Significant improvements in severity of auditory visual hallucination, depressive symptoms and quality of life
Pot-Kolder et.al., 2018 (12)	Patients with a psychotic disorder and paranoid ideation (*n* = 116)	RCT	VR-CBT with treatment as usual, 1 h long, 16 individual session versus treatment as usual	Significant reduction in momentary paranoid ideation and anxiety
Gold et al., 2018 (13)	Child and adolescent patients (*n* = 143)	RCT	Totally 5 min long VR game with standard of care versus standard of care only	Significant reduction in acute procedural pain and anxiety
Gomez et al., 2017(14)	21-year-old Latino male patient with burn injury	Observational	Immersive VR enhanced DBT mindfulness skills training, 4 sessions for 1 month	Increased positive emotions and decreased negative emotions
Ryu et al., 2017 (15)	Children scheduled for elective surgery (*n* = 69)	RCT	Preoperative VR tour of the operating theatre, 4 min video	Lower scores of the Yale Preoperative Anxiety Scale, Induction Compliance Checklist, and Procedural Behavior Rating Scale
Eijlers et al. 2017 (16)	Children undergoing elective day care surgery (*n* = 200)	RCT	Preoperative VRE intervention, 15 min	Diminished preoperative anxiety, postoperative pain, and the use of postoperative analgesics
Beidel et al., 2017 (17)	Veterans and active duty soldiers with combat-related PTSD (*n* = 92)	RCT	VRET plus group treatment versus VRET with psychoeducation control	Decrease on PTSD scale for both group and decrease in social isolation for VRET plus group treatment
Ferrer-Garcia et al., 2017 (18)	Patients with bulimia nervosa and binge eating disorder (*n* = 64)	Case control	Two second-level treatment condition: VR- Cue Exposure Therapy or additional CBT	More proportion of achievement abstinence from binge eating or purging episodes
Blume et al., 2017 (19)	Children with ADHD (*n* = 90)	RCT	15 training sessions of either NIRS based NFT in VR, NIRS based NFT in 2D or biofeedback training in VR, 60–70 min for each session	NFT in VR is expected to yield greater effects than training in 2D
Shiban et al., 2017 (20)	29 patients with aviophobia	RCT	VRE treatment either with or without diaphragmatic breathing	Higher tendency to effectively overcome the fear of flying in VR with diaphragmatic breathing
Bouchard et al., 2017 (21)	Patients with social anxiety disorder (*N* = 59)	RCT	14 weekly sessions for VR exposure or *in vivo* exposure or waiting list	Improvement in both CBT groups, more effective in VRE
Reger et al., 2016 (22)	Active-duty soldiers (*n* = 162)	RCT	Randomization to 10 sessions of Prolonged exposure, VRE, or a minimal attention waitlist	Significant reductions in PTSD symptoms in Prolonged exposure and VRE groups
Norrholm et al., 2016 (23)	Participants met criteria for PTSD (*n* = 50)	RCT	6 weeks of VRE therapy combined with d-cycloserine, alprazolam, or placebo	In the d-cycloserine group, elevated startle before VR therapy predicted better outcome
Son et al., 2015 (24)	Alcohol dependent subjects (*n* = 12)	Case control study	10 sessions of VRET, consisted of 3 steps: relaxation, presentation of a high risk situation, and aversive situation	Decreased metabolism in the basal ganglia after VRET (PET shows)
Jahani Shoorab et.al., 2015 (25)	Primiparous parturient women having labor (*n* = 30)	RCT	Randomization to VR with standard care group and only standard care group	Decreased pain during the episiotomy repair When use of VR with local anesthesia

(Continued)

TABLE 1 | Continued

Author and date of publication	Subjects	Design	Method	Conclusions
Rothbaum et al., 2014 (26)	Iraq and Afghanistan war veterans with PTSD (*n* = 156)	RCT	An introductory session and five sessions of VRE augmented with d-cycloserine or alprazolam or placebo	Significantly improved PTSD symptoms from pre- to posttreatment across all conditions
Marco et al., 2013 (27)	Participants diagnosed with eating disorders (*n* = 34)	Case control study	15 CBT group sessions and 8 individual psychotherapy sessions with VR	Improved body image and this improvement was maintained at the one-year follow-up
Pallavicini et al., 2013 (28)	Undergraduate students (*n* = 39)	Case control study	Same experience was offered using test, audio, video, and VR	VR was less effective than other procedures in eliciting stressor responses
Diemer et al., 2013 (29)	Patients with arachnophobia (*n* = 58)	RCT	A single dose of quetiapine XR or placebo prior to a VR	Effect of VR challenge on behavioral avoidance, psychophysiological reaction
Malbos et al., 2013 (30)	Agoraphobic participants (*n* = 18)	Case control study	VRET only and VRET with cognitive therapy	The isolated effects of VRET did not seem to be less than the effects of VRET with cognitive therapy
McLay et al. 2012 (31)	Active duty service members with PTSD (*n* = 20)	Observational	Open-label, single-group VRET	Reduction in PTSD symptoms, improvement in PTSD, depression and anxiety
Culbertson et al., 2012 (32)	Healthy treatment-seeking cigarette smokers (*n* = 11)	RCT	Randomization to CBT plus either smoking-VR Cue Exposure Therapy or placebo-VR Cue Exposure Therapy	Higher quit rate, smoking fewer cigarettes per day
Park et al., 2011 (33)	Inpatients with schizophrenia (*n* = 91)	RCT	Comparison social skills training using VR role playing to social skills training using traditional role playing, over 10 semiweekly sessions for 5 weeks	Improved more in conversational skills and assertiveness
McLay et al., 2011 (34)	Active duty military personnel with combat-related PTSD (*n* = 10)	RCT	Randomization to VR-graded exposure therapy or treatment as usual	Higher number of improvements reported, more improvement on the CAPS score
St-Jacques et al., 2010 (35)	Agoraphobic participants (*n* = 31)	RCT	Randomization to *in vivo* exposure alone or in virtual reality-based exposure	VR did not increase motivation toward psychotherapy
Gerardi et al., 2008 (36)	A 29-year-old veteran	Case report	90-min individual session, once weekly over 4 weeks	Decreased rating scale scores (CAPS, PTSD Symptom Scale Self-Report)
Difede et al., 2007 (37)	Male disaster workers with PTSD (*n* = 21)	Case control study	Assignment to a VR treatment or a waitlist control	Significant decline in CAPS scores
Walshe et al., 2003 (38)	Subjects with simple phobia/ accident phobia (*n* = 14)	Observational	An open study, computer games and virtual reality therapy, 12 1-h sessions	Significant post treatment reductions on all measures
Rothbaum et al., 2001 (39)	Male Vietnam combat veterans with PTSD (*n* = 10)	Observational	Open clinical trial, 8 to 16 sessions, 2 virtual environments	Significant reduction from baseline in symptoms
Rothbaum et al., 2000 (40)	Patients with fear of flying (*n* = 49)	Case control study	Randomization to VRE therapy, standard exposure therapy, or a wait-list control, 4 sessions of exposure out of 8 sessions	VRE and standard exposure both superior to wait-list
Rothbaum et al., 1999 (41)	A Vietnam combat veteran with PTSD	Observational	VRE, 2 virtual environments	Decrease on CAPS and self-rated PTSD
Rothbaum et al., 1996 (42)	A 42-year-old female with a debilitating fear and avoidance of flying	Case report	Anxiety management techniques and the VRE	All self-report measures of fear and avoidance of flying decreased

RCT, randomized controlled trial; VR, virtual reality; VRE, virtual reality exposure; VRET, virtual reality exposure therapy; DBT, dialectical behavior therapy; PTSD, posttraumatic stress disorder; CBT, cognitive-behavioural therapy; NIRS, near-infrared spectroscopy; CAPS, clinician administered PTSD scale; NFT, neurofeedback training.

six-session VR exposure treatment in 156 patients diagnosed with PTSD among discharged soldiers returning from the Iraq and Afghan wars (26). The study concluded that VR treatment was associated with the reduction in PTSD diagnoses and symptoms in Iraq and Afghanistan veterans. Another study suggested that VR with skin conductance reactivity is a diagnostic tool for PTSD as well as a treatment (47). Veterans with PTSD displayed larger skin conductance reactivity across VR combat events, but not for non-combat VR events. The VR exposure therapy system, "Bravemind," is currently distributed to over 50 sites, including VA hospitals, military bases, and university centers to provide relief from PTSD for soldiers (48).

Anxiety Disorders and Specific Phobia

These days, some VR systems create highly immersive experiences using more invasive devices such as Head mounted Display (HMDs). A new generation of realistic simulation can therefore

serve as a promising assessment and therapy for erroneous anxiety-provoking thinking. In general, these symptoms are viewed as serious conditions where patients worry about something fearful excessively and persistently. Reproducing the traditional exposure interventions in VR, Maples-Keller et al. reviewed several case studies of social anxiety disorders and generalized anxiety disorders (49). This is merely the beginning of an explosion in potential provided by ever increasing sophisticated technology. It worth noting that the effectiveness of applying VR in this domain is also quantitatively being analyzed (50).

More specifically, phobia is a type of anxiety disorder characterized by marked and persistent fears that are cued by the presence or anticipation of specific objects or situations with a desire to avoid that condition due to high levels of fear and discomfort (43). Phobia includes acrophobia, flight phobia, phobias for insects or animals, and so on. Exposure therapy in VR is helpful because we can deal with such specific phobias in a virtual world, and it can be cost-effectively performed (29). In VR, patients with phobia can reproduce the situation they actually feel fearful of and face it themselves. Repeated use of VR increases the threshold of anxiety and makes it less insensitive, resulting in the reduced incidence of actual situations. Initially, VR graded exposure therapy was found to be successful in reducing fear of spiders (51, 52), social phobia (53), and flight phobia (3, 54) after applying it to a small number of subjects. A self-training program with mobile VR individuals with acrophobia has been safely and successfully applied to reduce fear of heights (55). It can be safely applied at home and at the hospital. It can be easily interrupted or repeated depending on the situation. VR can reduce the degree of anxiety by exposing the patient to a virtual dental care scenario in an incremental manner (56, 57). Similarly, a pilot study has applied a VR headset as a fear reduction tool and pain distraction for fear of needles, where 94.1% of pediatric subjects reported an improvement after using VR during immunization (58). Recently, VR with repetitive transcranial magnetic stimulation (rTMS) over the prefrontal cortex has been applied in participants with spider phobias. It diminished activation in the left inferior frontal gyrus in functional near-infrared spectroscopy (fNIRS) during an emotional Stroop paradigm (59).

Schizophrenia

Patients with schizophrenia show anhedonia, social withdrawal, and a blunted affect, which can lead to rumination and isolation. While exposure therapy in anxiety-related disorders uses VR as a simulation tool, the so-called avatar therapy for negative symptoms of schizophrenia focuses on interactive VR. In a computer-generated virtual world, VR users are no longer simply external observers, but active participants. It is one of the key variables in understanding social environments that need to be controlled, and thus provides exciting applications to research and treatment (60). For example, interactive VR therapy has shown benefits in social skills such as role-playing (33), memory function (61), medication management skills (62), job interviews (63), and vocational training (64). Recent VR-based cognitive rehabilitation programs also manage positive symptoms in schizophrenia such as auditory verbal hallucinations (11).

Autism

Autism is characterized by a state of being trapped in one's own world. It is a childhood developmental disability. Children with autism do not interact with others. They do not have emotional ties. VR approaches for rehabilitation in autism tend to create virtual environments integrated with other equipment, facilitating cognitive processes of training such as concentration and other functional skills in everyday life. The University of Texas has developed a training program to assist in the social skills training of autistic children (65). It uses brain imaging and Electroencephalography (EEG) monitoring. It also uses avatars to put children in situations such as job interviews and meetings. They practice reading social signals and expressing socially appropriate behaviors. After completion of the program, the activity of the brain area associated with social understanding was found to be increased in participants' brain image. Smith and colleagues at the Northwestern University Psychiatry Department have reported that young adults diagnosed with autism spectrum have a higher job search rate than the comparative group at six months after receiving job interviews through VR (66). For the purpose of training outdoor activity, individuals with Autism spectrum disorder were placed in a three-dimensional city and given a set of tasks that involved taking buses through a game. A statistically significant increase in measures of knowledge of the process of riding a bus, a reduction in the electro-dermal activity, and a high success rate in their application were found (67).

Dementia and Mild Cognitive Impairment (MCI)

Lessons from the Nun study have revealed that cognitive reserve and training are also important in preventing Alzheimer's disease (68). Dementia is a broad term describing such disorders of the brain that progress over time. Basically, in evaluating cognitive dysfunction and detecting MCI, VR has been applied and has exhibited very high accuracy. Cushman et al. (69) have investigated navigational impairment of early Alzheimer's disease, using both real-world and laptop PC based virtual environments in the same subjects; 35 young normal controls, 26 older normal controls, 12 patients with mild cognitive impairment and 14 patients with early Alzheimer's disease (AD). It was found that virtual environment testing provides a valid assessment of navigational skills for aging and Alzheimer's disease (69). Also, there is a systematic review that presented a status of VR applications for diagnostic assessment and cognitive training in Alzheimer's disease and MCI. Both semi-immersive and fully-immersive VR technology can be feasible amongst individuals living within the earlier stages of dementia outside of a hospital environment (70). While much of the VR studies appear to focus on the treatment of anxiety or phobias, the population of VR applications is underdeveloped. Even though sample sizes are limited, VR-based cognitive training has shown benefits for episodic memory in Amnestic MCI and early to moderate Alzheimer's disease (71). Moreover, Moyle el al., explored the feasibility of VR in individuals with a range of cognitive impairments from mild to more severe stages of dementia (72). VR was perceived to have a positive effect on people with dementia, although a greater level of fear and anxiety

during VR were experienced compared to those in the normative sample (72). Some individuals in the earlier stages of dementia experienced boredom, and VR technology was also found to increase fear and anxiety in one study. However, it is perhaps not surprising that recent advances in VR rehabilitation applications keep pointing to the feasibility of VR training in healthy elderly persons as well as in pathological populations (73).

Stress and Pain Alleviation

Stress and pain have deleterious effects on the mind and body. In order to decrease one's attention available for conscious pain processing, VR usage for stress and pain alleviation typically provides simple forms of distraction (e.g., watching videos or playing video games). Although the physical mechanisms are not well understood, the patients focus moves away from the conscious attention on the stressful and painful condition during the occupational activity (74). While patients can learn pain-management techniques as mindfulness, several experimental results suggest that VR techniques has actual benefits for subjective pain reduction (75). For example, Oculus Rift uses DEEP, a meditation application to help users breathe deeply. The application works through a band surrounding the chest to measure breathing. In another pilot study, 44 participants attended a mindfulness conference putting on an Oculus Rift DK2 VR helmet and floated down a calm 3D computer-generated virtual river while listening to digitized DBT mindfulness skills training instructions. Participants reported significantly less sadness, anger, and anxiety but more relaxation (76). Dr. Spiegel's team at the Cedars-Sinai Hospital has given chronic patients the opportunity to get out of the hospital through VR and to enjoy the natural scenery. This could reduce a patient's stress and shorten hospital stays (77). Relaxation and meditation in various VR applications have become increasingly widespread for treating patients at home or in hospitals (78).

Studies at the University of Barcelona have shown that applying VR to depressed patients can reduce the severity of their depression and self-degradation and increase satisfaction (79). By limiting distractions from the real world and increasing the sense of presence, VR may facilitate mindfulness practice as well.

Limitations

Clearly, exposure to VR applications may result in significant discomfort for the majority of people, with symptoms of motion sickness including eye fatigue, headaches, nausea, and sweating (80, 81). VR Sickness is different from common motion sickness because motion sickness is caused by visual perception of self-motion while VR sickness does not require actual movement. A conflict between accommodation and vergence depth cues on stereoscopic displays is a significant cause of visual discomfort from VR (82). Dry eyes due to an overheated display in an enclosed space and retinal damage due to blue light are also concerns. As shown in this review, only a few large-sized and well-designed studies have been conducted in psychiatry with VR.

VR is developing to improve real-life adaptation of patients with psychiatric problems. However, patients may become preoccupied or addicted to the VR environment, similar to internet game addiction. If patients with schizophrenia have impairment on reality testing, they may have delusional thinking in the VR environment. Doctor-patient relationships and careful education before using VR are mandatory before applying VR treatments in psychiatric patients. In the near future, a guideline to apply VR treatments to patients with psychiatric illnesses should be established. VR will play a role as an alternative option for psychiatrists to use in supporting psychiatric assessments and treatments in patients.

CONCLUSION

Many studies and clinical trials have used VR as a simulation, interaction, and distraction tool for patients with psychiatric illnesses such as PTSD, anxiety, specific phobia, schizophrenia, autism, dementia, and heavy stress. VR environments show the possibility of changing their anxiety, depression, cognition, and social functions by effectively exposing them sources of fear, presenting interactive virtual environments of cognitive-behavioral approaches, and contributing to other rehabilitation applications.

In practice, patients with a psychiatric diagnosis such as depression, bipolar disorder, anxiety disorder, schizophrenia, and even alcohol use disorder share common characteristics such as anxiety, avoidance, and poor insight to their illnesses. Modern VR systems can deliver an ideal place where one can confront the problem which needs to be overcome, not only through talking with doctors, but also through virtual environments with well-controlled sensory stimuli. This may produce cognitive and behavioral changes in patients with psychiatric disorders including autism and dementia. They also have benefits in reducing chronic pain and intensive stress. However, VR needs to overcome technical hurdles such as motion sickness and dry eyes, as well as user hurdles such as preoccupation and addiction.

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All authors listed have made substantial, direct, and intellectual contribution to the work and approved it for publication.

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Risk Factors and Neuropsychological Assessments of Subjective Cognitive Decline (*plus*) in Chinese Memory Clinic

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Background: Since subjective cognitive decline (SCD) was standardized in 2014, many studies have investigated its features. However, the risk of SCD (*plus*) progressing to AD is much higher, and yet there have been few studies reporting the risk factors and neuropsychological assessment characteristics of SCD (*plus*).

Objective: To characterize SCD (*plus*) by comparing it with normal control (NC), amnesic mild cognitive impairment (aMCI), and Alzheimer Disease (AD) regarding their demographics, lifestyle, family history of dementia, multimorbidity and the neuropsychological assessments.

Methods: A total of 135 participants were recruited, including 23 NC, 30 SCD (*plus*), 45 aMCI and 37 AD. Descriptive statistics were provided. A logistic regression model was used to analyze the affecting factors of SCD (*plus*), and finally the Receiver Operating Characteristic (ROC) analysis was applied to distinguish between SCD (*plus*) and NC.

Results: (1) SCD (*plus*) group was younger than both the aMCI group and AD group. It consisted of more participants with mental work and higher body mass index (BMI) than the AD group. (2) Scores of Auditory Verbal Learning Test - Immediate recall (AVLT-IR) and AVLT-Long delayed recall (AVLT-LR) decreased in the following order: NC→SCD (*plus*)→aMCI→AD. (3) The Area Under Curve (AUC) for discriminating SCD (*plus*) and NC group was from 0.673 to 0.838.

Conclusion: Aging is an important risk factor of both NC progressing to SCD (*plus*), and SCD (*plus*) progressing to aMCI or AD. In addition to aging, lower education level and

lower BMI were significantly associated with greater odds of SCD (*plus*) progressing to aMCI or AD patients, whereas mental work was a protective factor of SCD (*plus*) progressing to AD. Finally, AVLT is a sensitive indicator of the cognitive decline and impairment in SCD (*plus*) in relative to normal controls.

Keywords: Alzheimer Disease, subjective cognitive decline, risk factors, neuropsychological assessment, objective cognitive features

INTRODUCTION

World Alzheimer Reports showed that there were 47 million people living with dementia worldwide in 2016 (Alzheimer's Disease International, 2016). This number is expected to increase to more than 131 million by 2050. The total estimated worldwide cost for dementia is US$ 818 billion, and by 2018 dementia will become a trillion-dollar disease. However, no effective modifying therapy has been validated yet, even for mild cognitive impairment (MCI) (Sperling et al., 2011).

Pre-mild cognitive impairment subjective cognitive decline (pre-MCI SCD), which has been defined as a self-experienced persistent decline in cognitive capacity in comparison with a previously normal status and objective cognitive performance within normal ranges (Jessen et al., 2014), is the first symptomatic manifestation of Alzheimer Disease (AD) and has received increasing attention (Rabin et al., 2015; Fernandez-Blazquez et al., 2016; Vogel et al., 2016). Individuals present with several specific features (e.g., age at onset of SCD $\geq$60 years; complaints about SCD within the past 5 years; the complainers feel their performance are not as good as their peers and concerning associated with SCD, etc.) associated with pre-MCI SCD would be identified as SCD (*plus*) (Jessen et al., 2014)* – one of the preclinical stages of AD [See the **appendix** for the details of clinical features of SCD (*plus*)]. To our best knowledge, the risk of progressing to AD is higher for SCD (*plus*) than for SCD (Jessen et al., 2014). Accurate identification of SCD (*plus*) is therefore fundamental and crucial for early and successful intervention, which may help slow down its progression to AD and improve the prognosis.

Previous studies on SCD demographics showed people with SCD were younger and had a higher education than patients with MCI and AD dementia (Jonker et al., 2000; Garcia-Ptacek et al., 2014). Women were reported to be more likely to have SCD than men (Jonker et al., 2000). Less physical activity, hypertension, smoking and depression were found to be associated with the increase occurrence of SCD (Paradise et al., 2011; Chen et al., 2014). Also, among workers, those with cognitively demanding work were more sensitive to the changes of cognitive decline, and were thus more likely to report SCD (Rijs et al., 2015). Moreover, Aarts et al. (2011) demonstrated that SCD was related with multiple comorbidities (e.g., diabetes mellitus, stroke/transient ischemic attack, myocardial infarction, etc.). Cerebral trauma, middle-aged obesity, marital status (unmarried and widowed), born in the countryside, low social contact, and daily drinking were regarded as the risk factors for cognitive decline (Ao and Liu, 2004; Williams et al., 2010; Deng, 2014; Hao et al., 2017). In addition, a few studies showed that lower body mass index (BMI) associated with sarcopenia, was closely linked with the development of AD (Sugimoto et al., 2016; Ogawa et al., 2018). However, all these studies focused either on SCD or pre-MCI SCD, and little is known about the risk factors for SCD (*plus*) as a different category of patients.

Subjective cognitive decline may not a demonstrate detectable objective impairment when using the standardized neuropsychological assessment (Rabin et al., 2017), but it is still unknown about whether those assessments are useful for identifying SCD (*plus*). In addition, many studies have shown the distinction between SCD and MCI or AD, by using these neuropsychological assessments, such as MoCA, CDT and AVLT (Fernaeus et al., 2014; Zhao et al., 2015; Vyhnalek et al., 2017; Wang et al., 2019). Their high sensitivity and specificity have also been reported previously, suggesting that those assessments were able to distinguish SCD from MCI and AD (Vyhnalek et al., 2014; Huang et al., 2018; Park et al., 2018; Xu et al., 2018). However, little is known about the diagnostic power of these tools in discriminating SCD (*plus*) and NC. Furthermore, according to the diagnosis framework of SCD or SCD (*plus*), like NC, their scores of objective neuropsychological assessments are within the normal range. However, the chance of SCD (*plus*) progressing to MCI or dementia was significantly higher than the normal controls. Therefore, the distinguishing features between the SCD (*plus*) and NC groups are of great significance to study, as these could be more practically important for identifying people with SCD (*plus*) at an early stage and facilitate early intervention.

Therefore, our current study aims to (1) examine the relationship between SCD (*plus*) and the following potential risk factors including: demographics, family history of dementia, comorbidities, history of cigarettes smoking and drinking, and (2) to assess the sensitivity of the standard neuropsychological assessments on detecting SCD (*plus*) by comparing its scores with normal controls (NC), amnesic mild cognitive impairment (aMCI) and AD dementia. The ultimate purpose is to characterize SCD (*plus*) in order to provide more information for its early identification and intervention.

MATERIALS AND METHODS

Ethics Statement

This study was approved by the Medical Ethics Committee of Xuanwu Hospital of Capital Medical University, Beijing, China. Written informed consent was obtained from either participants or their legally agreed surrogates.

Participants

One Hundred thirty-five right-handed, Han Chinese subjects, including 30 SCD (*plus*), 45 aMCI, and 37 AD patients were recruited from the memory clinic of the Neurology Department, Xuanwu Hospital, Capital Medical University, Beijing, China from December 1, 2010 to June 30, 2016. 23 NC subjects were recruited from the hospital by advertisements.

Assessment and Diagnosis Procedure

All of the subjects underwent a series of standardized clinical evaluations, including the Chinese version of Mini-Mental State Examination (MMSE) (Katzman et al., 1988), Montreal Cognitive Assessment (MoCA)- the Beijing version (Lu et al., 2011), Clinical Dementia Rating Scale (CDR) (Morris, 1993), World Health Organization-University of California Los Angeles Auditory Verbal Learning Test (AVLT) (Maj et al., 1994), Hachinski Ischemic Index (HIS) (Hachinski et al., 1975), Hamilton Anxiety Scale (HAMA) (Tang, 1984), and Hamilton Depression Scale (HAMD) (Hamilton, 1980).

Inclusion criteria for each group: All SCD (*plus*) subjects met the criteria for SCD (*plus*) proposed by SCD-I (Jessen et al., 2014): (a) presence of self-perceived continuous memory decline within the last 5 years, confirmed by informant report; (b) onset age $\geq$ 60 years old; (c) feeling cognitive decline worse than their peers and concerned about SCD; (d) normal performance on both MMSE, MoCA and AVLT after age and education adjustment; (e) CDR score = 0; (f) no impairment of daily life activities; and (g) HIS score $\leq$4.

The aMCI patients met the following criteria (Petersen, 2004): (a) memory complaint, preferably confirmed by an informant; (b) objective memory impairment; (c) normal or near-normal performance on general cognitive function with no or minimum impairment of daily life activities; (d) CDR score = 0.5; (e) HIS score $\leq$4; and (f) failure to meet the criteria of dementia according to DSM-IV (American Psychiatric Association, 1994).

The diagnosis of AD fulfilled standardized diagnostic criteria (McKhann et al., 1984; American Psychiatric Association, 1994; Dubois et al., 2007): (a) met the diagnostic criteria of dementia; (b) gradual and progressive decline in memory function over more than 6 months; (c) impaired episodic memory on objective testing; (d) HIS score $\leq$4; and (e) hippocampal atrophy confirmed by structural MRI.

Criteria of NC was defined as: (a) having no report of any cognition complaint; (b) normal performance on MMSE, MoCA and AVLT after age and education-adjusted; (c) CDR score = 0; and (d) no impairment of daily life activities.

Exclusion criteria for all the subjects: (a) a history of stroke (HIS >4); (b) severe depression and anxiety (HAMD >30, and HAMA $\geq$29); (c) other CNS diseases which could cause cognitive decline (e.g., brain tumors, Parkinson's disease, encephalitis, or epilepsy); (d) other systemic diseases which could cause cognitive decline (e.g., thyroid dysfunction, severe anemia, syphilis, or HIV); (e) a history of psychosis or congenital mental growth retardation; (f) cognitive decline caused by traumatic brain injury; or (g) those who could not complete neuropsychological tests or with contraindication to MRI.

Statistical Analysis

We conducted all analyses using the Statistical Package for the Social Sciences version 17.0 (SPSS Inc., Chicago, IL, United States). Descriptive statistics (sociodemographic characteristics, lifestyle, comorbidities, family history of dementia and scores of neuropsychological assessments) were calculated by percentages or median. The $\chi 2$ or Kruskal–Wallis test was used to assess group differences between SCD (*plus*) and the other three groups (NC, aMCI and AD group). For the four groups comparison, $p < 0.05$ was considered to be statistically significant, and corrected p' value ($p < 0.007$) was used in the Partitions of Pearson's chi-square statistics for *post hoc* pairwise comparisons. To examine the potential risk factors for each group in relation to the SCD (*plus*) group, we performed multiple logistic regression analysis with the removed backwards approach by including the sociodemographic characteristics, lifestyle, comorbidities and family history of dementia as the independent variables, and diagnosis as the dependent variable. In addition, odds ratios (ORs) were calculated for each variable. $p < 0.05$ was required for variables to be remained in the model. Finally, we obtained the receiver operating characteristic (ROC) curves and calculated the area under curve (AUC) of the characteristic factors that distinguish the NC and SCD (*plus*) group.

TABLE 1 | Clinical characteristics of the study sample.

Characteristics	*N* = 135 *n* (%)
Age, years	
≤75	96(71.1)
>75	39(28.9)
Gender	
Males	55(40.7)
Females	80(59.3)
Education, years	
≥12	94(69.6)
<12	41(30.4)
Job category	
Mental work	79(58.5)
Physical work	56(41.5)
BMI, Kg/m^2	
≤23.9	83(61.5)
>23.9	52(38.5)
Lifestyle	
Current smoking	13(9.6)
Current drinking	18(13.3)
Family history of dementia	22(16.3)
Comorbidities	
Hypertension	48(35.6)
Cerebrovascular Disease	24(17.8)
Heart disease	12(8.9)
Diabetes	25(18.5)
Hyperlipidemia	40(29.6)
Multimorbidity	43(31.9)

BMI, body mass index; Multimorbidity, accompanied with two or more diseases above.

RESULTS

Clinical Characteristics of the Participants

The clinical characteristics of the total sample were summarized in **Table 1**.

Comparisons Between NC, SCD (*plus*), aMCI, and AD Groups

The difference between age among the four groups was significant ($p < 0.05$). Further pairwise comparison showed that the age of SCD (*plus)* was lower than the other two groups (aMCI and AD) at the corrected test level p' [1]($p < 0.001$).

For BMI, the difference among the four groups was also significant ($p < 0.05$). For a pairwise comparison, we only found the number of people with the BMI $\leq$23.9 Kg/m^2 in NC group (39.1%) was smaller than that in the AD group, but no difference was shown between SCD (*plus*) group (46.7%) and AD group (78.4%) ($p > 0.007$).

[1]$p' = 0.05/[k(k-1)/2 + 1]$ ($k = 4$), $\alpha' = 0.007$.

A family history of dementia was presented in 26.7% of the SCD (*plus*) group. The proportion of currently smoking and drinking in SCD (*plus*) group was 10.0 and 16.7%, respectively. No significant differences among the four groups were found for family history of dementia, smoking and drinking ($p > 0.05$).

The proportion of having hypertension, cerebrovascular disease, cardiovascular disease, diabetes, and hyperlipidemia as multimorbidity in the SCD (*plus*) group was 40.0, 13.3, 6.7, 23.3, 36.7 and 30.0%, respectively, but again there were no differences between the SCD (*plus*) group and the other groups ($p > 0.05$) (**Table 2**).

Comparison of Scores of Neuropsychological Assessments Between NC, SCD (*plus*), aMCI, and AD

The scores of AVLT-First Immediate Free Recall (median AVLT-IR1 scores = 6) and AVLT-Long Delay Free Recall (median AVLT-LR = 9) of SCD (*plus*) group were lower than those of NC group (median values of AVLT-IR1 and AVLT-LR 7 and 11, respectively) ($p < 0.05$). We found no difference of the total score of MoCA between the SCD (*plus*) group and the NC group, the median scores of which was 25.5 and 28.0, respectively ($p = 0.08$).

TABLE 2 | Comparisons between NC, SCD (*plus*), aMCI, and AD groups for clinical characteristics.

Characteristics	Groups				
	NC (*n* = 23) N (%)	SCD (*plus*) (*n* = 30) N (%)	aMCI (*n* = 45) N (%)	AD (*n* = 37) N (%)	*P*#
Age, years					<0.01*,**
≤75	18(78.3)	29(96.7)	27(60.0)	22(59.5)	
>75	5(21.7)	1(3.3)	18(40.0)	15(40.5)	
Gender					
Males	12(52.2)	13(43.3)	19(42.2)	11(29.7)	0.36
Females	11(47.8)	17(56.7)	26(57.8)	26(70.3)	
Education, years					0.06
≤12	15(65.2)	16(53.3)	32(71.1)	31(83.8)	
>12	8(34.8)	14(46.7)	13(28.9)	6(16.2)	
BMI, Kg/m^2					<0.01***
≤23.9	9(39.1)	14(46.7)	31(68.9)	29(78.4)	
>23.9	14(60.9)	16(53.3)	14(31.1)	8(21.6)	
Mental workers	16(69.6)	23(76.7)	25(55.6)	15(40.5)	0.01**
Lifestyle					
Current smoking	4(17.4)	3(10.0)	4(8.9)	2(5.4)	0.51
Current drinking	5(21.7)	5(16.7)	5(11.1)	3(8.1)	0.44
Family history of dementia	1(4.3)	8(26.7)	5(11.1)	8(21.6)	0.09
Comorbidities					
Hypertension	9(39.1)	12(40.0)	13(28.9)	14(37.8)	0.72
Cerebrovascular disease	3(13.0)	4(13.3)	8(17.8)	9(24.3)	0.61
Heart disease	2(8.7)	2(6.7)	4(8.9)	4(10.8)	0.95
Diabetes	6(26.1)	7(23.3)	7(15.6)	5(13.5)	0.53
Hyperlipidemia	3(13.0)	11(36.7)	16(35.6)	10(27.0)	0.21
Multimorbidity	7(30.4)	9(30.0)	13(28.9)	14(37.8)	0.83

*In the last column of this table, p# illustrates the results for among-four-group comparison. Symbols in the brackets demonstrate whether there was difference for the pairwise comparison: *represented a significant difference between the SCD (plus) group and the aMCI group; **represented a significant difference between the SCD (plus) group and the AD group; ***represented a significant difference between the NC group and the AD group. SCD (plus), subjective cognitive decline (plus); NC, normal control; aMCI, amnesic mild cognitive impairment; AD, Alzheimer Disease Dementia; BMI, body mass index; Multimorbidity, accompanied with two or more diseases above.*

TABLE 3 | Comparison between SCD (*plus*) and NC, aMCI and AD group for scores of neuropsychological assessments.

Variables	Groups						
	SCD (*plus*) Percentile 50 (Percentile 25,75)	**NC Percentile 50 (Percentile 25,75)**	**aMCI Percentile 50 (Percentile 25,75)**	**AD Percentile 50 (Percentile 25,75)**	***P* (SCD vs. NC)**	***P* (SCD Vs. aMCI)**	***P* (SCD Vs. AD)**
AVLT-IR1	6.0(4,7)	7.0(6,9)	5.0(4,5)	2.5(1,3)	0.04	<0.01	<0.01
AVLT-IR2	9.0(7,11)	10.0(8,12)	6.0(5,7)	3.5(2,5)	0.10	<0.01	<0.01
AVLT-IR3	11.0(9,13)	12.0(10,14)	7.0(6,9)	5.0(3,6)	0.06	<0.01	<0.01
AVLT-LR	9.0(7,11)	11.0(9,14)	2.0(0,5)	0.0(0,1.75)	0.03	<0.01	<0.01
AVLT-RR	12.5(10.75,14)	13.0(10,14)	7.0(5,10)	4.0(1,6.75)	0.64	<0.01	<0.01
MMSE	28.0(27,29.25)	29.0(27,30)	24.0(21,27)	17.0(12.25,21)	0.87	<0.01	<0.01
MoCA	25.5(25,27.25)	28.0(26,28)	18.0(15,22)	11.0(8,15.75)	0.08	<0.01	<0.01
TMT	1.0(0,1)	1.0(0,1)	0.0(0,1)	0.0(0,0)	0.82	<0.01	<0.01
Duplicate-C	1.0(1,1)	1.0(0,1)	1.0(0,1)	0.0(0,0.75)	0.39	<0.01	<0.01
CDT	3.0(3,3)	3.0(3,3)	2.0(1,3)	1.0(1,1.75)	0.54	<0.01	<0.01
Naming	3.0(3,3)	3.0(3,3)	3.0(2,3)	2.0(1.25,3)	0.07	0.03	<0.01
Digit span	2.0(2,2)	2.0(2,2)	2.0(2,2)	2.0(1,2)	0.07	0.01	<0.01
Alertness test	1.0(1,1)	1.0(1,2)	1.0(0,1)	0.0(0,1)	0.41	0.01	<0.01
Subtraction 7	3.0(3,3)	3.0(3,3)	3.0(2,3)	1.5(0,2)	0.10	<0.01	<0.01
Repeat-S	1.0(1,2)	2.0(1,2)	1.0(0,1)	0.0(0,1)	0.34	0.01	<0.01
VFT	1.0(1,1)	1.0(1,1)	1.0(1,1)	0.0(0,1)	1.00	0.02	<0.01
Abstract test	2.0(1,2)	2.0(1,2)	1.0(0,2)	0.0(0,1)	0.75	<0.01	<0.01
MoCA-DR	3.0(2,4)	3.0(3,4)	0.0(0,1)	0.0(0,0)	0.17	<0.01	<0.01
Orientation	6.0(6,6)	6.0(6,6)	5.0(4,6)	2.0(1,4)	0.78	<0.01	<0.01

The p values represent the comparison between the SCD (plus) group and the other three groups (NC, aMCI, and AD). SCD (plus), Subjective Cognitive Decline (plus); NC, normal control; aMCI, amnesic Mild Cognitive Impairment; AD, Alzheimer Disease Dementia; AVLT-IR1, Auditory Verbal Learning Test- First Immediate Free Recall; AVLT-IR2, Auditory Verbal Learning Test-Second Immediate Free Recall; AVLT-IR3, Auditory Verbal Learning Test-Third Immediate Free Recall; AVLT-LR, Auditory Verbal Learning Test-Long Delay Free Recall; AVLT-RR, Auditory Verbal Learning Test-Recognition Recall; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; CDT, clock-drawing test; TMT, Trail Making Test; Duplicate-C, duplicate cube; Repeat-S, repeat sentence; VFT, verbal fluency test; MoCA -DR, Montreal Cognitive Assessment-Delay Free Recall.

All the other scores of neuropsychological assessments, including AVLT-Second Immediate Free Recall (AVLT-IR2), AVLT-Third Immediate Free Recall (AVLT-IR3), AVLT-Recognition Recall (AVLT-RR), total scores of MMSE and MoCA, and single cognitive domain scores of MoCA test -the Trail Making Test (TMT), copy cube, clock drawing test (CDT), naming, digit span, alertness test, continuous subtraction 7, repeat sentence, Verbal Fluency Test (VFT), abstract test, MoCA-Delay Free Recall (MoCA-DR) and orientation test, were higher in SCD (*plus*) group compared to those in the aMCI and AD groups ($p < 0.05$). However, no significant differences were found between SCD *(plus*) and NC group ($p > 0.05$) (**Table 3**).

Affecting Factors for NC, SCD (*plus*), aMCI and AD Groups

Our results of the multiple logistic regression analysis showed that aging, years of education, job category and BMI were affecting factors of SCD (*plus*). Aging was an important risk factor for SCD (*plus*) progressing to aMCI (OR = 0.05, 95% CI = 0.01–0.41) and AD (OR = 0.03, 95% CI = 0.01–0.39), which also showed a certain risk effect on the progression of NC to SCD (*plus*) subjects (OR = 0.10, 95% CI = 0.01–0.93) ($p < 0.05$). Mental work had a protective effect on SCD (*plus*) progressing to AD patients ($p < 0.05$), whereas lower education (OR = 4.43, 95% CI = 1.03–19.18) and lower BMI (OR = 3.73, 95% CI = 1.08–12.98) were significantly associated with greater odds of SCD (*plus*) progressing to AD patients ($p < 0.05$) (see **Table 4**).

ROC of NC and SCD (*plus*)

We used the ROC curves to evaluate the goodness of the affecting features and neuropsychological scores, respectively, on discriminating the SCD (*plus*) group from the NC group. As a variable that differed significantly between all the groups, we first used age as the factor and found its AUC was 0.592 (95% CI, 0.434–0.750), which was low. To further explore the optimal discriminating model, we continued to add more factors and we found that by using age, gender, years of education, job category, BMI, current smoking, and current drinking, the AUC reached 0.673 (95% CI, 0.524–0.823).

Based on the results of the neuropsychological assessments, we also performed ROC analysis by using scores of AVLT-LR and AVLT-IR1 as variables, and the AUCs were 0.679 (95% CI, 0.535–0.823) and 0.662 (95% CI, 0.506–0.819), respectively. Finally, we added the clinical features including the demographics and life styles as variables in the logistic regression in addition to AVLT-LR or AVLT-IR1, respectively, and we found that the AUC increased to 0.823 (95% CI, 0.708–0.938) and 0.764 (95% CI, 0.631–0.897). When combining AVLT-IR1, AVLT-LR and clinical

TABLE 4 | Affecting Factors for NC, SCD (*plus*), aMCI and AD groups.

Characteristics	NC	aMCI	AD
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age, years			
≤75	0.10(0.01–0.93)	0.05(0.01–0.41)	0.03(0.01–0.39)
>75	Ref.	Ref.	Ref.
Education, years			
≤12			4.43(1.03–19.18)
>12	Ref.	Ref.	Ref.
Job category			
Mental work			0.25(0.06–0.98)
Physical work	Ref.	Ref.	Ref.
BMI			
≤23.9			3.73(1.08–12.98)

NC, normal control; aMCI, amnesic Mild Cognitive Impairment; AD, Alzheimer Disease Dementia; OR, odds ratios; CI, confidential interval. Ref., this group was used the reference group.

variables in the regression model, the AUC increased from 0.673 to 0.838 (95% CI, 0.729–0.948) (**Figure 1**).

DISCUSSION

To the best of our knowledge, the risk of progressing to AD is higher for SCD (*plus*) than for SCD, but there have been few studies reporting its risk factors and neuropsychological assessment characteristics. This is the first study that reveals the presence of early episodic memory impairment in SCD (*plus*) population in memory clinic by fulfilling all the six items of the diagnostic framework. This study also characterized the clinical features and neuropsychological assessments of SCD (*plus*) in relative to normal controls, amnestic mild cognitive impairment (aMCI) and Alzheimer disease (AD).

We identified lower age, longer education period, and more mental work as the demographic characteristics of SCD (*plus*) group, compared with aMCI and AD group, which are in agreement with the previous studies (Mohs et al., 2001; Sando et al., 2008; Hebert et al., 2010; Iliffe and Pealing, 2010; Jefferson et al., 2011; Meng and D'Arcy, 2012; Alzheimer's Association, 2014; Beydoun et al., 2014; Garcia-Ptacek et al., 2014; Liang et al., 2018). We also showed that higher BMI was a protective factor for SCD (*plus*) progressing to AD patients, which was consistent with some of the previous studies (Barnes et al., 2009; Fitzpatrick et al., 2009; Xu et al., 2011; Gustafson and Luchsinger, 2013; Qizilbash et al., 2015). Latent AD may be accompanied by the metabolic changes that are not yet fully understood. Yet this phenomenon may be associated with the changes of body composition with aging, such as the morphological changes of fat cells and the adipose tissue compartment, diminished muscle mass, sarcopenia, and somatic frailty. For women who are affected by the reproductive aging and changes in the sex hormone milieu, it may be related to the alteration of adipose tissue. On the contrary, other researchers argued that obesity increased the risk of dementia (Beydoun et al., 2008; Profenno et al., 2010; Sellbom and Gunstad, 2012; Loef and Walach, 2013), which is also greatly correlated with other morbidities, such as hypertension and diabetes (Luchsinger and Gustafson, 2009). These inconsistencies may be attributed to the error in the measurement of adiposity. Besides, other factors (Devore et al., 2010; Littlejohns et al., 2014; Emmerzaal et al., 2015; Qizilbash et al., 2015), such as cholesterol levels, age-related regulatory changes in carbohydrate, lipid or protein metabolism, increased intake of vitamin E, anti-oxidant and vitamin D may all affect the relationship between BMI and dementia. It is also possible that the higher BMI was the result of having olfaction firstly affected in the progression of AD (Gustafson and Luchsinger, 2013).

Smoking was regarded as a risk factor of dementia (Lee et al., 2010; Beydoun et al., 2014; Zhong et al., 2015), but we found no statistical differences between all the groups, which may be due to the low percentage of smokers in our groups. Also, there was no significant correlation between alcohol consumption and cognitive impairment, which was in line with previous findings (Baumgart et al., 2015).

Earlier studies have found that hypertension in later life was a protective factor for cognitive decline (Lee et al., 2010; Beydoun et al., 2014), whereas diabetes, hyperlipidemia and cerebrovascular disease increased the risk of dementia (Honig et al., 2003; Profenno et al., 2010; Gudala et al., 2013; Roberts et al., 2014; Cooper et al., 2015). In our study, we did not find significant difference of comorbidities including hypertension, cerebrovascular disease, cardiovascular disease, diabetes and hyperlipidemia between groups, and this inconsistency might be due to the following reasons: (1) Those chronic diseases were not stratified according to the sex, disease duration and severity. A few studies showed that middle-aged individuals with hypertension and diabetes for longer than 6 years had a positive correlation with cognitive decline (Helzner et al., 2009), Sex difference in the presence of comorbidities which involve the vascular contributions to the cognitive impairment and dementia should be considered (Gannon et al., 2018); and (2) our patients did not co-present as many diseases as they were shown in one previous study, such as arthritis, prostate disease, lung disease and so on (Aarts et al., 2011).

In our study, after controlling the clinical characteristic variables, the SCD (*plus*) group showed lower scores of AVLT1 and AVLT-LR than those of the NC group ($p < 0.05$). This suggests that memory impairment has already presented in SCD (*plus*) population at the AD preclinical stage. We also showed that the combination of AVLT-IR1 and AVLT-LR improved the diagnostic accuracy of SCD (*plus*) compared to the condition when they were used separately, which indicates that AVLT may allow for distinguishing SCD (*plus*) form NC individuals. It also suggests that in order to better identify SCD (*plus*), episodic memory should be included as part of the neuropsychological assessment. Delayed recall in AVLT is considered to be the most sensitive measure of early AD (Zhao et al., 2012). However, not all studies have included this test (Yang et al., 2015). Our SCD (*plus*) individuals showed slightly worse performance on the challenging cognitive tasks than individuals without cognitive complaints (Koppara et al., 2015; Smart and Krawitz, 2015). Also, compared to no complaints, reduced episodic memory

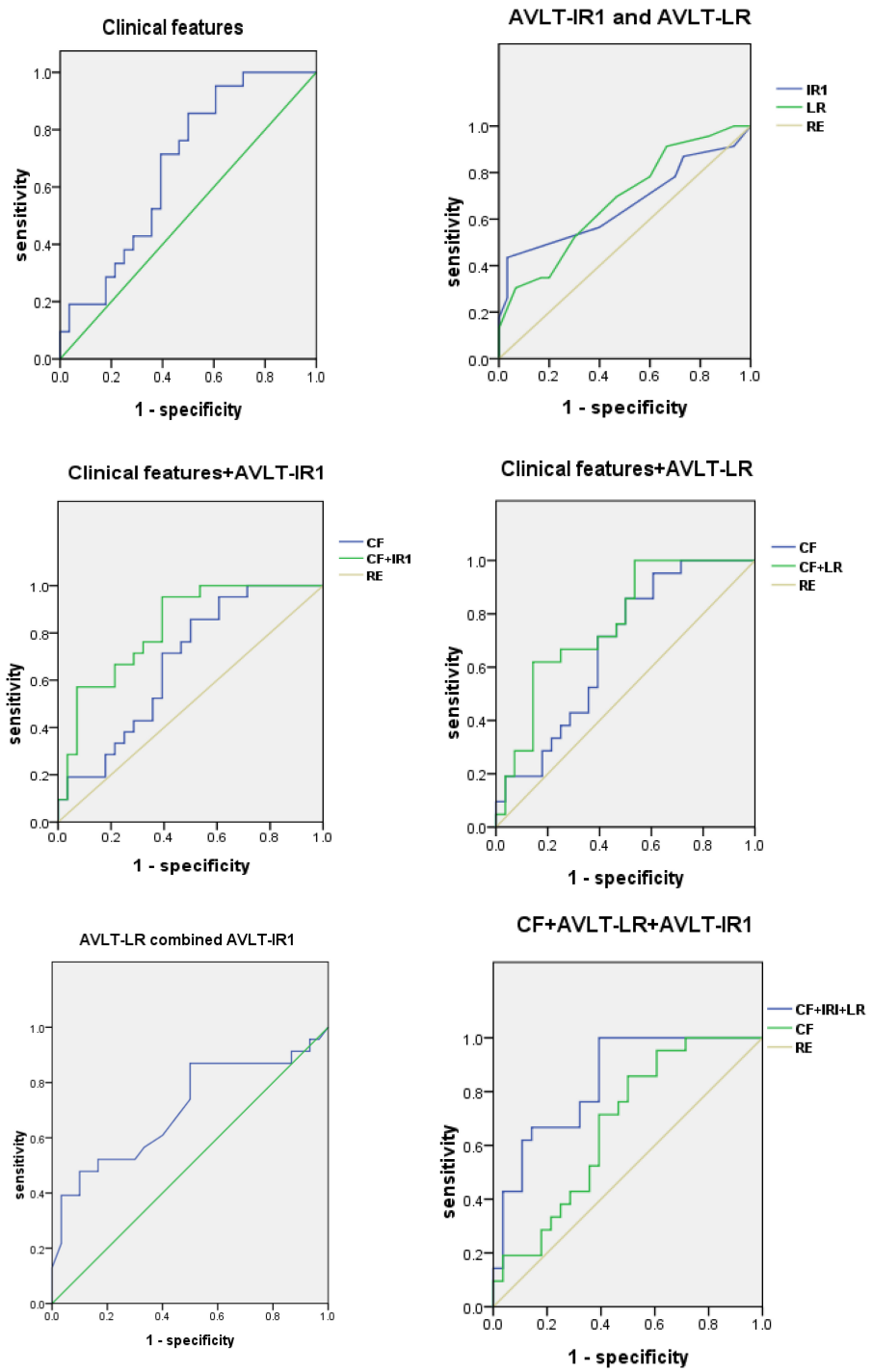

FIGURE 1 | ROCs for NC and SCD (*plus*) group. ROC curves for NC and SCD (*plus*) group using clinical features, AVLT-IR and AVLT-LR. AVLT-IR1, Auditory Verbal Learning Test-First Immediate Free Recall; AVLT-LR, Auditory Verbal Learning Test-Long Delay Free Recall; ROC, receiver operating characteristic; CF, clinical features; RE, reference.

learning effect and poorer performance on psychomotor speed and language were present in SCD participants (Kielb et al., 2017). However, a different cutoff value from what is currently used for discriminating MCI from NC may need to be provided in the future to differ SCD (*plus*) from NC with better sensitivity and reliability. For the global cognition revealed by MoCA and

MMSE, although the differences between the SCD (*plus*) and NC groups were not significant, MoCA showed a higher sensitivity of assessment compared with MMSE. Thus, MoCA may be helpful to be included in the SCD (*plus*) screening scales, but further verification is needed by follow-up studies.

In addition, our study found that except for memory impairment, the other cognitive domains also had begun to decline from the aMCI stage ($p < 0.05$). It indicates that once a patient enters the stage of MCI, other cognitive domains may also have been damaged. Deng (2014) found that 54.2% elderly in the a different cohort had cognitive impairment, and the abstract scores were lower in both the normal control and cognitive impairment groups. The memory impairment group scored lower in the domains of execution, visual space, language and delayed recall. MCI is often characterized by slight but noticeable deficits in attention, learning and memory, executive function, processing speed, and semantic language (Storandt et al., 2006; Saunders and Summers, 2011; Summers and Saunders, 2012), and the early cognitive impairment of these domain are also strong predictors of the progression from MCI to AD (Brandt et al., 2009; Klekociuk et al., 2014). In order to be sensitive to the impairment of single cognitive domain in SCD (*plus*), questionnaires designed for screening patients with cognitive impairments need to report not only the global cognition scales (such as MMSE, MoCA), but also the scores of single cognitive domains, such as language and execution etc.

The limitations of this study are: (1) our sample size is relatively small, which might be the cause of some of the negative results between groups. Further investigations with larger sample sizes are needed; (2) Our study is a cross-sectional survey and follow-up studies should be performed to further confirm the final conclusions; (3) We adopted the standardized criteria of pre-MCI SCD proposed in 2014 by Jessen (Jessen et al., 2014) given depression and anxiety maybe the early presentations of the SCD (*plus)*. We admit that using this criterion, some of the subjects would have mild to moderate anxiety and depression. However, the present study did not address this issue, which would be of interest to study further. (4) The diagnosis of SCD (*plus*) was not validated by the other tests. For instance, it lacks the completeness of Aβ-PET, APOEε4, cerebrospinal fluid tau or Aβ examinations, given that only ∼60% of the included population had genetic tested and Aβ-PET undertaken; and (5) finally, other related biomarkers and imaging approaches need to be investigated to gain more understanding of SCD (*plus*).

In summary, we characterized the SCD (*plus*) and unraveled that aging, shorter education period, physical labor work and lower BMI are risk factors for SCD (*plus*) progressing to aMCI or AD. This study may provide a reference to the inclusion criteria for the future early interventional studies and may pave the way for exploring more sensitive neuropsychological assessments for the cognitive decline in SCD (*plus*) individuals.

DATA AVAILABILITY

All datasets generated for this study are included in the manuscript and/or the supplementary files.

ETHICS STATEMENT

This study was approved by the Medical Ethics Committee of Xuanwu Hospital of Capital Medical University, Beijing, China. Written informed consent was obtained from either participants or their legally agreed surrogates.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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APPENDIX

Pre-MCI SCD

It is defined as (1) the objective cognitive performance of the individuals to be within the normal range; (2) decline of the self-perceived cognitive abilities; (3) these subtle cognitive declines should not reach the diagnosis of mild cognitive impairment (MCI) or dementia; and (4) this should not be caused by any psychiatric disorders or neurological and medical conditions.

SCD (*plus*)

In addition to meeting the diagnosis of pre-MCI SCD, SCD (*plus*) also need to meet the following criteria: onset age $\geq$60 years; complaints about SCD within the past 5 years; the complainers feel their performance are not as good as their peers and concerning associated with SCD; a confirmed cognitive decline by the informants; complains were only limited memory problems rather than other cognitive domains; and presence of the APOE ε4 genotype and biomarker evidence for a potential progression to AD.

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Classification of Early and Late Mild Cognitive Impairment Using Functional Brain Network of Resting-State fMRI

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Using the Pearson correlation coefficient to constructing functional brain network has been evidenced to be an effective means to diagnose different stages of mild cognitive impairment (MCI) disease. In this study, we investigated the efficacy of a classification framework to distinguish early mild cognitive impairment (EMCI) from late mild cognitive impairment (LMCI) by using the effective features derived from functional brain network of three frequency bands (full-band: 0.01–0.08 Hz; slow-4: 0.027–0.08 Hz; slow-5: 0.01–0.027 Hz) at Rest. Graphic theory was performed to calculate and analyze the relationship between changes in network connectivity. Subsequently, three different algorithms [minimal redundancy maximal relevance (mRMR), sparse linear regression feature selection algorithm based on stationary selection (SS-LR), and Fisher Score (FS)] were applied to select the features of network attributes, respectively. Finally, we used the support vector machine (SVM) with nested cross validation to classify the samples into two categories to obtain unbiased results. Our results showed that the global efficiency, the local efficiency, and the average clustering coefficient were significantly higher in the slow-5 band for the LMCI–EMCI comparison, while the characteristic path length was significantly longer under most threshold values. The classification results showed that the features selected by the mRMR algorithm have higher classification performance than those selected by the SS-LR and FS algorithms. The classification results obtained by using mRMR algorithm in slow-5 band are the best, with 83.87% accuracy (ACC), 86.21% sensitivity (SEN), 81.21% specificity (SPE), and the area under receiver operating characteristic curve (AUC) of 0.905. The present results suggest that the method we proposed could effectively help diagnose MCI disease in clinic and predict its conversion to Alzheimer's disease at an early stage.

Keywords: resting-state fMRI, mild cognitive impairment, feature section, functional network, classification

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is clinically characterized by dementia and cognitive decline (1). According to the World Alzheimer's Disease Report in recent years (2, 3), about 35.6 million people suffered from dementia in 2010, and global dementia care costs

more than 600 billion US dollars or approximately 1% of the global GDP. Mild cognitive impairment (MCI), commonly characterized by slight cognitive deficits but largely intact activities of daily living (4, 5), is a transitional stage between the healthy aging and dementia that can be divided into EMCI and LMCI, according to extent of episodic memory impairment (6). Research has shown that individuals with MCI tend to progress to AD at a rate of approximately 10–15% per year (7). Jessen et al. (8) showed that the risk of LMCI conversion to AD is higher than that of EMCI. Identifying potentially high-sensitivity diagnostic markers that change with disease progression may assist the physician in making a diagnosis. If it is found at an early stage of MCI, patients can reduced the number of AD incidence by nearly one-third through rehabilitation exercises and medication (9). Unfortunately, sensitive markers vary with disease progression (6), and there are currently no definitive diagnostic biomarkers and effective treatments for AD (10). Thus, early detection of EMCI individuals increasingly attaches clinical importance to potentially delaying or preventing the transition from EMCI to LMCI. Many experts study the early diagnosis of AD diseases from the aspects of neuropsychology, chemistry, and medical imaging. In clinical practice, doctors use the neuropsychological scale to diagnose and treat patients because of their simple operation, less time, and doubts. MCI patients have a certain sensitivity when they are initially tested and are widely used by clinicians (11), but they are subjectively influenced by individuals. Individual differences are relatively large, and other diagnostic methods need to be combined to give the final diagnosis. In biochemistry, the levels of Aβ and p-tau proteins in CSF are important biomarkers (12). Studies have shown that the content of amyloid has increased before clinical symptoms appear, can be used for early prediction of clinical AD disease, but is not sensitive (13). The content of p-tau protein in AD patients is significantly increased, with high sensitivity and specificity, and has certain reference value in clinical diagnosis (14), but the detection of this index is traumatic, patients have certain rejection psychology, and clinical operation is more difficult. Compared with these methods, Hinrichs et al. (15) reported that clinical and imaging data [MRI and fludeoxyglucose (FDG-PET)] can be successfully combined to predict AD using machine-learning techniques. They found that the imaging modalities had a better performance in prediction of AD compared to clinical data.

Neuroimaging research shows that MCI and AD patients have significant disruption compared with healthy control group in either the structural network or functional network (16–19). Several studies using the electroencephalogram (EEG) (20) and MRI (16, 17) have found abnormal clustering coefficients and characteristic path lengths in the brain networks of AD patients, implicating a loss of small-worldness attributes and disrupted whole brain organization network. Liu and Zhang (21) also used functional networks to detect betweenness centrality alteration in MCI and compared with AD group, showed decreased in the amygdala and rolandic operculum, and increased in the frontal gyrus, parietal gyrus, and medial temporal lobe. However, for MCI patients, changes in the brain are very subtle (19, 20); therefore, few studies have examined the characteristics of whole brain networks in different stages of MCI patients. Xiang and colleagues (22) used functional brain networks to study the abnormal brain connection in MCI and reported that the clustering coefficient in EMCI is higher than that of LMCI, while the average shortest path in LMCI is longer than that of EMCI. Although the difference was not significant, this method of analyzing functional brain network differences might provide an effective feature reference for the classification to distinguish EMCI from LMCI.

Recently, several studies have demonstrated that the features obtained from functional brain network measures and machine learning approach based on rs-fMRI contribute useful information for more accurate classification. Chen et al. (23) used large-scale network (LSN) analysis with an AUC of 95% to classify subjects with amnestic mild cognitive impairment (aMCI n = 15) and cognitively normal (CN n = 20) subjects. Challis et al. (24) proposed GP-LR models and employed SVM with 75% accuracy to distinguish healthy subjects from subjects with amnesic mild cognitive impairment. Khazaee and colleagues (25) used time series to construct brain function network, and linear SVM classifiers were used to classify AD and normal people, which obtained 100% classification accuracy. This could be due to the small sample size, and the single variable Fisher Score feature selection algorithm was used. In another study, they extracted both temporal variabilities and spatial variabilities from dynamic connectivity networks (DCNs) as features, and integrate them for classification by using manifold regularized multi-task feature learning and multi-kernel learning techniques. The method they proposed yields the accuracy of 78.8% for LMCI and EMCI classification (26). It has been shown that combination of the graph theory with machine learning approach on the basis of rs-fMRI can accurately classify patients with MCI, patients with AD, and normal subjects (22, 23).

However, most of the studies pooled EMCI and LMCI groups into a single larger MCI group (24, 25, 27), and few studies investigated utility of rs-fMRI to distinguish two groups (25). In addition, Zuo et al. (28) divided the BOLD signal into five bands: full-band (0.01–0.08 Hz), slow-2 (0.0198–0.25 Hz), slow-3 (0.073–0.0198 Hz), slow-4 (0.027–0.073 Hz), and slow-5 (0.01–0.027 Hz). Brain activity of MCI patients has significant differences in the posterior cingulate, hippocampus, and medial prefrontal regions in the slow-4 band and slow-5 band, and the classification of MCI by frequency division achieved a better classification result (29, 30). Thus, the combination of functional brain networks and frequency division provides a new direction for classifying MCI patients.

In the current study, we aim to evaluate the efficacy of a classification framework to distinguish EMCI from LMCI by using the effective features derived from functional brain network of three frequency bands during Rest States. On the basis of classification result to find high-sensitivity features, we can better understand why sensitive markers in brain region vary with disease progression. We supposed that providing appropriate treatment and cognitive training for patients' high-sensitivity brain region at different stages of the disease might be preventing the progression of AD transformation.

Firstly, we preprocessed the signal and divided it into three frequency bands (full-band: 0.01–0.08 Hz; slow-4: 0.027–0.08 Hz;

slow-5: 0.01–0.027 Hz) at Rest. Then, we constructed functional brain network by calculating Pearson's correlation coefficients between time series of all pairs of the brain regions and thresholded it to an undirected binary network. Several graph-theoretic parameters (global efficiency, local efficiency, characteristic path length, clustering coefficient, and small-worldness) were selected to measure the characteristics of functional brain networks. Nodal characteristics were examined at a high discriminative range of sparsity from 8 to 20%. At the feature selection step, we employed three different algorithms for selecting optimal feature. To obtain unbiased results, support vector machine (SVM) classifiers with nested cross validation were used for classification. Finally, we compared the performances of three feature selection methods from classification results. We supposed that classification results may be influenced by different bands and the classification results may be the best in the slow-5 band.

MATERIALS AND METHODS

Participants

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (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 demographic data of the datasets are listed in **Table 1**. This study included 33 early MCI (EMCI) patients (average age 71.69 years, 19 female) and 29 late MCI (LMCI) patients (average age 70.73 years, 13 female). In the ADNI project, MCI diagnostic criteria included 1) Mini-Mental State Examination (MMSE) scores between 24 and 30, 2) a memory complaint, objective memory loss measured by education adjusted scores on the Wechsler Memory Scale Logical Memory II, 3) a Clinical Dementia Rating (CDR) of 0.5, and 4) absence of significant levels of impairment in other cognitive domains, essentially preserved activities of daily living, and an absence of dementia. As shown in ADNI project, the MCI stage was divided into EMCI and LMCI. Detailed diagnostic criteria of EMCI and LMCI: Both are characterized by evidence of AD biomarker abnormalities, with EMCI patients showing milder cognitive deficits. In terms of neuropsychological criteria, EMCI is defined as a performance 1–1.5 SD below the mean in one episodic memory test, identifying intermediate level of subtle memory impairment between normal cognition and MCI (31). In **Table 1**, we listed the p values of a Chi-Square test of gender and a two-sample t-test of age, CDR, and MMSE. We can see that gender, age, and MMSE have no signification differences for EMCI vs. LMCI.

TABLE 1 | Demographic data of EMCI vs. LMCI subjects.

Variable	EMCI n=33	LMCI n=29	p-value
Gender (M/F)	14/19	16/13	0.316
Age	71.69±5.74	70.73±5.90	0.519
CDR	0.5	0.5	1
MMSE	28.12±1.65	27.17±2.20	0.058

Values represent mean ± SD. MMSE, Mini-Mental State Examination; CDR, Clinical Dementia Rating. Chi-Square test was used for gender comparison. Two-sample t-test was used for age, CDR, and MMSE comparison. P > 0.05 indicates two groups have no significant differences.

Data Acquisition

All subjects underwent structural and functional MRI scanning on 3T Philips scanner according to the ADNI acquisition protocol (32). The structural images were acquired with T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) sequences (170 slices; TR = 3,000 ms; TE = 30 ms; matrix = 256 × 256; voxel size = 1.2 × 1.0 × 1.0 mm^3; flip angle = 9°). rs-fMRI scans were acquired with a T2*-weighted echo planar imaging (EPI) sequence with the following scanning parameters: 48 slices; TR = 3,000 ms; TE= 30 ms; matrix = 64 × 64; voxel size = 3.313 × 3.313 × 3.313 mm^3; flip angle = 80°.

Preprocessing

rs-fMRI data preprocessing was performed using software MATLAB 2013a (MathWorks, Inc, https://www.mathworks.com) and Data Processing Assistant for Resting-State Functional MR Imaging (DPARSF) (33) toolbox and Statistical Parametric Mapping software (SPM8) (34) package (http://www.fil.ion.ucl.ac.uk/spm) and Resting-State fMRI Data Analysis Toolkit (35) (REST; http://restfmri.net) for each subject. The preprocessing steps were as follows:

(1) For signal stabilization and to allow the participants to adapt to the environment, the first 10 EPI volumes of the fMRI images were discarded.
(2) Slice-timing correction for interleaved acquisition.
(3) Realignment for head movement compensation by using a six-parameter rigid-body spatial transformation. None of the subjects were excluded on the basis of the criterion with head motion limited to less than 2 mm or 2°.
(4) Each of structural MRI images was coregistered to the mean functional image by using a linear transformation, and the transformed structural images were segmented into grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) by using a unified segmentation algorithm. The functional images were normalization to Montreal Neurologic Institute (MNI) space.
(5) Spatial smoothed with 6 mm FWHM Gaussian kernel and linear detrending were implemented as well.
(6) The global mean signal, six head motion parameters, CSF, and WM signals were also removed as nuisance covariates to reduce the effects of motion and non-neuronal blood oxygenation level-dependent (BOLD) fluctuations (36, 37).
(7) Low frequency signals were divided into full-band (0.01–0.08 Hz), slow-4 (0.027–0.08 Hz), and slow-5 (0.01–0.027 Hz).

Functional Network Construction

The nodes of the brain network were defined by parcellation of the whole brain into 90 distinct regions using the automated anatomical labeling (AAL) atlas, which is a gross functional subdivision of the cortex (38). The time series of voxels within each of the 90 ROIs was averaged, and the resulting signal was used as the node. The edges were constructed by calculating Pearson's correlation coefficients between time series of all pairs of the brain regions. We applied Fisher's r-to-z transform on raw undirected connectivity matrix of the three bands to improve the normality of the partial correlation coefficients (18, 39). By definition, this matrix is symmetric with a zero diagonal (no self-connections) (40). To determine the available edges, each individual's brain network sparsity is thresholded as a binary matrix, where the edges are 1 if the weights of the two ROIs are larger than a given threshold, and 0 otherwise. The threshold represents the network connection cost, defined as the ratio of the suprathreshold connections relative to the total possible number of connections in the network (41). There is no straightforward rule for the definition of the single sparseness threshold, and different sparsenesses lead to different experimental results (17, 37). In this study, each network was examined for the range of costs from 8% to 20%, at 1% intervals. We performed a search over different thresholds to find the optimal threshold value (42). In order to generate effective network characteristics, statistically significant differences in network parameters between the two groups of patients under different sparsity levels were calculated.

Graph Theory Parameters

All graph theory parameters were computed and analyzed using Matlab 2013a (MathWorks, Inc) scripts and matlab_bgl (https://github.com/dgleich/matlab-bgl)

The undirected connectivity matrix in three bands for each subject was used to calculate different graph metrics. To obtain efficient features and avoid feature largely redundancy, we first computed five global graph measures on the undirected graphs. The global graph measures are as follows: global efficiency, local efficiency, characteristic path length, clustering coefficient, and small-worldness (43). We performed two sample T test on five graph metrics of two groups subjects. In **Supplementary Figures 1**, **2**, and **3**, results showed that global efficiency, local efficiency, clustering coefficient, and characteristic path length had significant differences in slow-5 band. Although there are no obvious differences in slow-4 and full-band, the trend is similar to slow-5 band.

Feature Extraction

In feature extraction section (**Figure 1A**), 270 nodal features [nodal path length (NL), nodal degree (ND), and betweenness centrality (BC)] were employed for subsequent analysis. For ND, BC, and NL, we utilize 270 features in each band, a total of $270 \times 3 = 810$ features. In brief, for a given node i, NL, ND, and BC were defined as follows:

$$L_i = \frac{\sum_{j \neq i \in V} L_{ij}}{(V-1)} \quad (1)$$

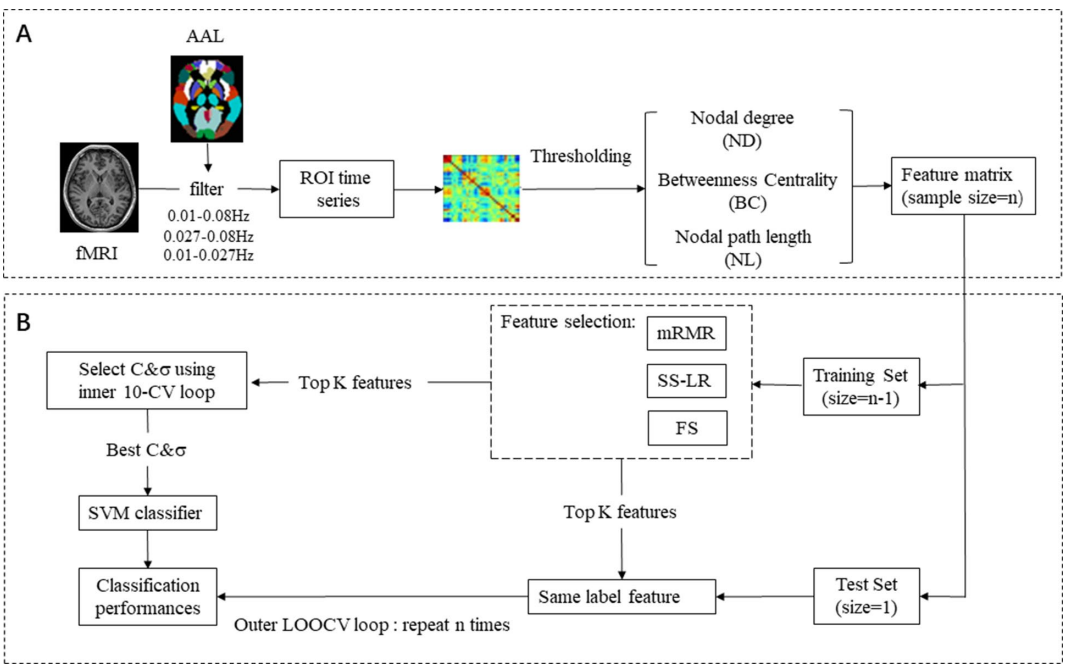

FIGURE 1 | EMCI and LMCI classification framework. **(A)** Raw data preprocessing, feature extraction, and feature selection process. **(B)** Classification: SVM classifier with nested cross validation is implemented for classification.

$$K_i = \sum_{j \in V} b_{ij} \tag{2}$$

$$B_i = \sum_{i \neq j \neq m \in V} \frac{S_{jm}(i)}{S_{jm}} \tag{3}$$

where L_{ij} represents the minimum number of edges between node i and j, V is the size of a graph, b_{ij} is the connection status between the node i and j, S_{jm}, represents the number of shortest path lengths between node m and j, and $S_{jm}(i)$ represents the number of shortest paths through the node i between node m and j. Intuitively, path length L_i measures the speed of the message that passes through a given node, and the degree of an individual node K_i is equal to the number of links connected to that node, and the greater the B_i is, the more important the node i is to the information communication in the network, thus reflecting the level of interaction in the network.

Feature Selection

As shown in **Figure 1A**, we selected 270 features from three types of network features (NL, ND, and BC) for three frequency bands (slow-4, slow-5, full-band) of each subject, respectively. In particular, we took integrate feature sets from three bands into a new feature named all band for subsequent analysis. There is no doubt that feature selection is a wonderful choice that degrades redundancy in feature, reduces training-testing time, and improves classification performance. Here, three sorts algorithm were applied to feature selection.

Minimal Redundancy Maximal Relevance Feature Selection Algorithm (mRMR)

Here, we utilized mRMR for feature selection that was first proposed by Ding and Peng (44) in 2005. mRMR can commendably solve tradeoff problem between feature redundancy and relevance that uses mutual information as a feature correlation measure factor (45). Given two random variables X and Y, Mutual information between them is defined as:

$$I(X,Y) = \iint p(x,y) \log \frac{p(x,y)}{p(x)p(y)} dx\, dy \tag{4}$$

where $p(x)$ and $p(y)$ refers to probabilistic density functions and p(x, y) is their joint probability density function.

Max-Relevance is to search features satisfying that is defined as:

$$\max D(S,c), D = \frac{1}{|S|} \sum_{x_i \in S} I(x_i;c) \tag{5}$$

S refers to feature set with m features $\{x_i\}$ and c is the class. The relevance of a feature set S for the class c is defined by the average value of all mutual information values between the individual feature x_i and the class c

Min-Redundancy is defined as:

$$\min R(S), R = \frac{1}{|S|^2} \sum_{x_i, x_j \in S} I(x_i, x_j) \tag{6}$$

Formula is used to select mutually exclusive features. The criterion combining the above two constraints is called "minimal-redundancy-maximal-relevance" (mRMR). The mRMR is defined as:

$$mRMR = \max_S \left\{ \frac{1}{|S|} \sum_{x_i \in S} I(x_i;c) - \frac{1}{|S|^2} \sum_{x_i, x_j \in S} I(x_i, x_j) \right\} \tag{7}$$

Sparse Linear Regression Feature Selection Algorithm Based on Stationary Selection (SS-LR)

Given a data set $T = (X, Y)$, where $X = (x_1, x_2, \ldots, x_n)^T \in R^{n \times m}$ is the sample, $Y = (y_1, y_2, \ldots, y_n)^T \in R^{n \times 1}$ is its associated sample real label, n is the number of samples, and m is the number of features of each sample. The model of linear regression can be defined as:

$$f(X) = Xw \tag{8}$$

where $w = (w_1, w_2, \ldots, w_n) \in R^{m \times 1}$ is the coefficient in the linear regression, and $f(X)$ is the prediction label vector obtained by discriminating the unknown sample. Let $L(w)$ be the loss function of linear regression, and then the function is as shown in Equation (9):

$$L(w) = \min_w \frac{1}{n} || f(X) - Y ||_2^2 \tag{9}$$

In order to control the complexity of the model, an L_1 regularization term is usually added after the loss function, and the expression after regularization is added:

$$L(w) = \min_w \frac{1}{n} || f(X) - Y ||_2^2 + | \lambda | w ||_1 \tag{10}$$

where $|| w ||_1 = \sum_{i=1}^{m} w_i$, $\lambda > 0$ is a regularization parameter in control of the model. As λ increases, the sparseness of the function becomes larger, that is, in front of some feature attributes. The coefficient becomes 0, that is, linear regression with L_1 regularization can be used for feature selection. In this paper, the SLEP package (46) was used to solve sparse linear regression. To solve the problem of proper regularization, we employed subsampling or bootstrapping to apply the stability selection for robust feature selection (47). In this study, the range is $0.05 < \lambda < 0.3$, and the step size is 0.005.

Fisher Score

Fisher Score is a univariate feature selection algorithm. The feature with the identification criteria should satisfy the variance of the features in the selected sample of the same category as small as possible. On the contrary, the variance between the features in the different categories of samples should be as

large as possible. It is helpful for high classification accuracy of subsequent prediction results. Suppose m_i represents the average of the i-th feature in all samples, m_{1i} represents the average of the i-th feature in the one sample, and m_{2i} represents the average of the i-th feature in another sample. The Fisher Score value for each feature in a two class problem is defined as (48):

$$FS(i) = \frac{n_1(m_{1i} - m_i)^2 + n_2(m_{2i} - m_i)^2}{\left(n_1\sigma_{1i}^2 + n_2\sigma_{2i}^2\right)} \quad (11)$$

In formula, n_1 is the number of samples in the first type of sample, n_2 is the number of samples in the second type of sample, and σ_{1i}^2 is expressed as the i-th feature in the first type of sample. The variance in σ_{2i}^2 is expressed as the variance of the i-th feature in the second type of sample.

SVM Classifier

After the feature selection stage, the support vector machine (SVM) algorithm was applied to classification that is supervised machine learning algorithm using the LIBSVM toolbox (49), with radial basis function (RBF) and an optimal value for the penalized coefficient C (a constant determining the tradeoff between training error and model flatness). The RBF kernel was defined as follows:

$$K(X_1, X_2) = exp\left(-\frac{||X_1 - X_2||}{2\sigma^2}\right) \quad (12)$$

where x_1 and x_2 are two eigenvectors, and σ is the width parameter of the REF kernel. The classification framework flow chart is shown in **Figure 1B**. We used nested cross-validation (CV) to obtain unbiased estimates and select the optimal SVM model. On the training set, the optimal hyperparameters (C and σ) by a grid-search and a 10-fold CV (inner loop) was employed. For the outer loop, the leave-one-out cross validation (LOOCV) was used and repeated N times (N = 62). We selected one sample as the validation set and the remaining samples as feature selection and classifier training set for each fold of the outer CV. This operation was repeated until all subjects used once as test sample. Finally, we used the held-out sample to evaluate the performance of the training classifier. Area Under Curve (AUC) is defined as the area enclosed by the coordinate axis under the ROC curve. The larger the AUC score, the more likely the current classification algorithm is to rank the positive samples in front of the negative samples, which is a better classification. Most researchers have now adopted AUC for evaluating the predictive capability of classifiers since AUC is a better performance metric compared to accuracy (50).

To evaluate the performance of the classification results, these established measures were defined as follows:

$$Sensitivity = \frac{TP}{TP + FN},$$
$$Accurary = \frac{TP + TN}{TP + TN + FP + FN}, \quad (13)$$
$$Specificity = \frac{TN}{TN + FP}$$

where TP, TN, FP, and FN represent true positive, true negative, false positive, and false negative, respectively. According to traditional rules, we considered a correctly predicted EMCI as a true positive and LMCI as a true negative (51).

RESULTS

Classification Results

In the absence of a specific threshold value, the features of the four frequency bands (slow-4, slow-5, full-band, and all band) are selected by the mRMR, SS-LR, and FS in the Cost = 8–20%. Through a series of classification results with threshold, the AUC scores in the slow-5 band is significantly higher than that in the other frequency bands. By comparison, we found that the classification results in the slow-5 band are the best and stable under threshold value of Cost = 15%. The following results are analyzed and discussed in the threshold of Cost = 15%. The receiver operating characteristic (ROC) curves and classification results are depicted in **Figure 2** and **Table 2**.

For the mRMR algorithm model, the all band achieved a classification accuracy of 82.26% (sensitivity = 72.41%, specificity = 90.91%, AUC = 0.865). The slow-5 resulted in a higher accuracy of 83.82% (sensitivity = 86.21%, specificity = 81.82%, AUC = 0.905). Specifically, we obtained slightly lower levels of accuracies for full-band and slow-4 (40.32% and 51.61%, respectively) compared to the classification of all-band vs. slow-5. For the SS-LR algorithm model, the all-band achieved a higher accuracy of 67.74% (sensitivity = 65.52%, specificity = 69.75%, AUC = 0.789). The slow-5 resulted in accuracy of 64.52% (sensitivity = 58.62%, specificity = 69.70%, AUC = 0.713). For the FS algorithm model, the all-band achieved a classification accuracy of 54.84% (sensitivity = 43.86%, specificity = 63.64%, AUC = 0.579). The slow-5 resulted in a higher accuracy of 58.06% (sensitivity = 44.83%, specificity = 69.70%, AUC = 0.569).

To prove the effect of the number of selected features, we used the top K features (K = 1, 2, ..., 30) for classification. The classification performances and AUC scores are shown in **Figure 3**, respectively. The AUC curves appeared stable after the top 8 features, and the best classification results are depicted in the slow-5 band and all band. The AUC scores of slow-5 band and all band are higher than those in the full-band and slow-4 band. For the slow-5 band, the AUC scores increased as the number of selected features increased, and the AUC curve of the mRMR algorithm is highest, followed by SS-LR, and the lowest is FS. In all band, the highest among AUC curves is mRMR, and SS-LR and FS are comparable. The AUC curves for the three algorithms in the slow-4 and full band are relatively low and relatively messy, which cannot be distinguished by observation. In summary, it can be seen from the classification results of three feature selection algorithms that suitable algorithm may improve the classification effect.

Comparing Classification Results Based on Different Feature Selection Methods

In order to compare whether the classification effects of the classifiers under the different feature selection algorithms are

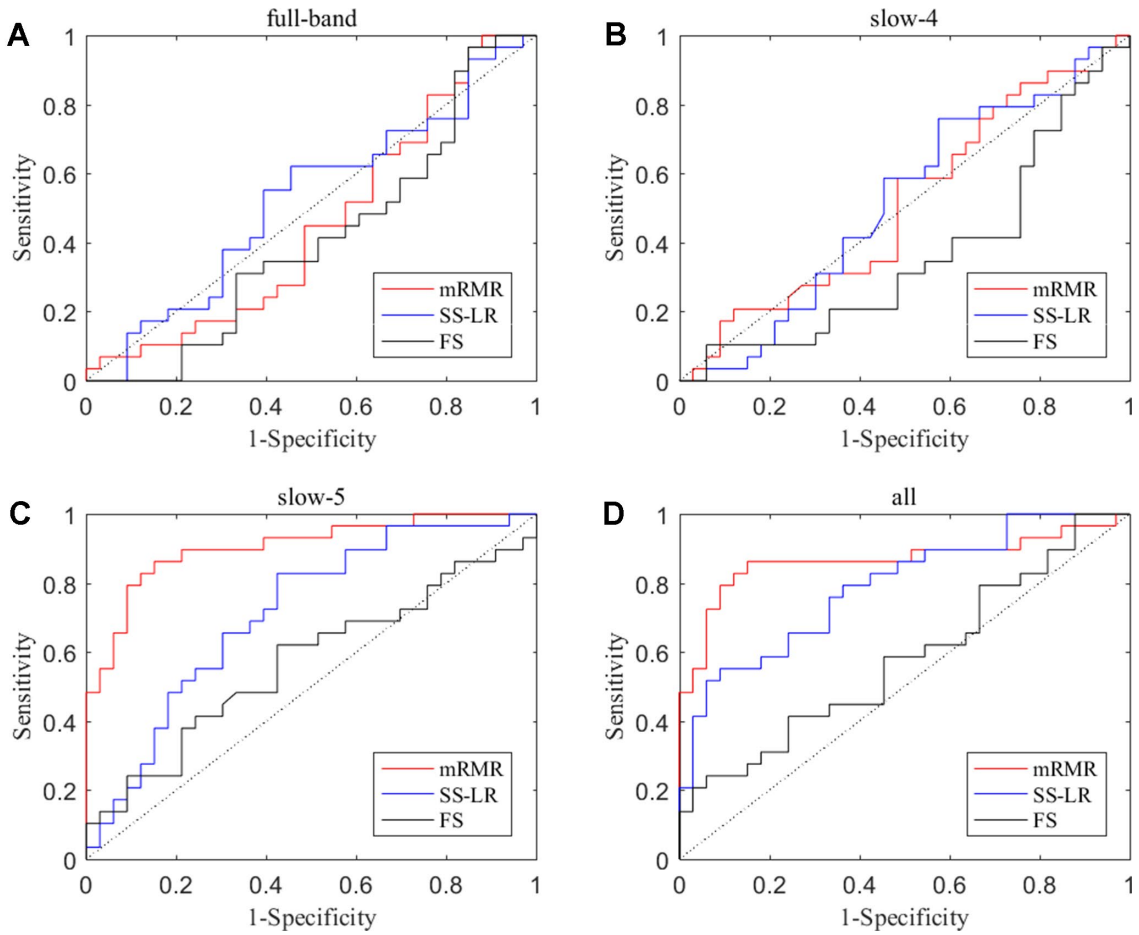

FIGURE 2 | ROC curves for the three algorithms using the top 10 nodal features **(A)** full-band, **(B)** slow-4 band, **(C)** slow-5 band, and **(D)** all band.

TABLE 2 | Classification results performance of different methods using the top 10 features.

Frequency band	mRMR				SS-LR				FS			
	ACC (%)	SEN (%)	SPE (%)	AUC	ACC (%)	SEN (%)	SPE (%)	AUC	ACC (%)	SEN (%)	SPE (%)	AUC
Full-band	40.32	27.59	51.52	0.454	53.23	44.83	60.61	0.523	48.39	34.48	60.61	0.411
Slow-4	51.61	24.14	75.76	0.512	50.00	41.38	57.58	0.512	37.10	34.48	39.39	0.363
Slow-5	83.87	86.21	81.82	0.905	64.52	58.62	69.70	0.713	58.06	44.83	69.70	0.569
All	82.26	72.41	90.91	0.865	67.74	65.52	69.75	0.789	54.84	43.86	63.64	0.579

ACC, accuracy; SEN, sensitivity; SPE, specificity.

significantly different, the McNemar test is used to compare the classification results of two different feature selection algorithms respectively. All statistics were computed with Matlab2013a platform.

When the number of features is K=10, the classification results and the p value obtained by using the mRMR and SS-LR algorithms are shown in **Tables 2** and **3**, and **Figure 4** shows the AUC scores with the number of features under the mRMR and SS-LR algorithm. As shown in **Table 3**, we compared the results of the four frequency bands using the mRMR and SS-LR feature selection algorithms, and only the classification results of the slow-5 band showed significant differences ($p = 0.006$). The AUC scores of mRMR were significantly higher than SS-LR (**Table 2**). Using the mRMR algorithm, the slow-5 band achieved the best AUC scores (AUC = 0.905), while the all band performed slightly lower (AUC = 0.865), and full-band and slow-4 band classification results both performed poor. Using the SS-LR algorithm, the classification result shows that the all band obtained the best results (AUC = 0.789), while the slow-5 band performed slightly lower (AUC = 0.713), with poor performance in full-band and slow-4 band. From **Figure 4**, the classification results of the two algorithms in full-band and slow-4 band showed almost

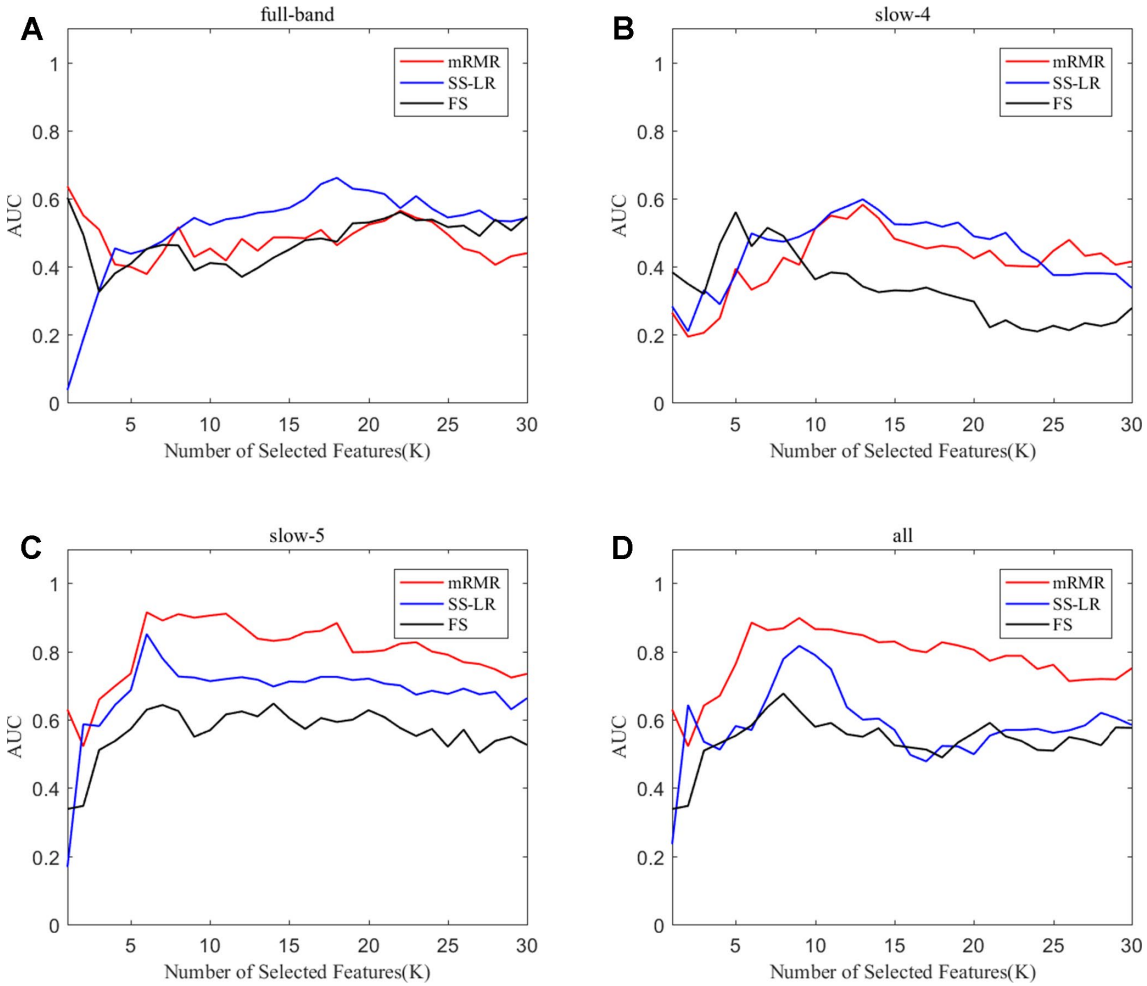

FIGURE 3 | Subgraphs **(A)**, **(B)**, **(C)**, and **(D)** represent AUC curves with the number of features K of full-band, slow-4, slow-5, and all band.

no significant differences with the K value increase and both of the AUC scores are relatively low, and can hardly be classified correctly. The classification result obtained by using the mRMR algorithm in the slow-5 band is obviously better than that of the SS-LR algorithm. In the range of 6<K<11, the mRMR curve tends to be flat, while as the K value increases, the RMR curve shows a gentle decline. The SS-LR curve tends to be flat over the entire K value range. The classification result of the mRMR algorithm in all band is significantly better than the SS-LR algorithm, and the curve of the mRMR algorithm is flatter than the curve of the SS-LR algorithm.

We compare the classification performance of the mRMR algorithm and the FS algorithm, and the results are shown in **Table 3** and **Figure 5**. For the slow-5 band and all band in **Table 3,** the classification results obtained by the mRMR algorithm and the FS algorithm showed significant differences, and the difference in all band is relatively large ($p = 0.00048$). We found no significant difference between the two algorithms in the full-band and slow-4 band. Using the mRMR algorithm, the AUC scores of the slow-5 band were higher, the all band were second, and the full band and slow-4 band were the worst. In four frequency bands, the classification results obtained by the mRMR algorithm were better than that of FS. As can be seen from **Figure 5**, in the full-band, the AUC scores obtained by the two algorithms have no significant difference within the all range, and there were significant differences in the slow-4 band within the several range (K = 17,22,25,26,27). In the slow-5, the AUC scores obtained by the mRMR curve was significantly larger than the AUC scores of the FS curve, and the mRMR curve shows a downward trend with the K value increase, while the FS curve tends to be stable. In the all band, the AUC scores obtained by the mRMR curve were significantly larger than FS, and both curves show a gentle downward trend.

As shown in **Table 3**, the classification performance obtained by the two algorithms has no significant difference in each frequency band, but the classification results obtained by the SS-LR algorithm was higher than the FS algorithm. As can be seen from **Figure 6**, there were significant differences in AUC scores in the full-band (K = 1,2,13,14,15,16), slow-4 (K = 14,17,18, ..., 25), and slow-5 (K = 6) band, and there was no

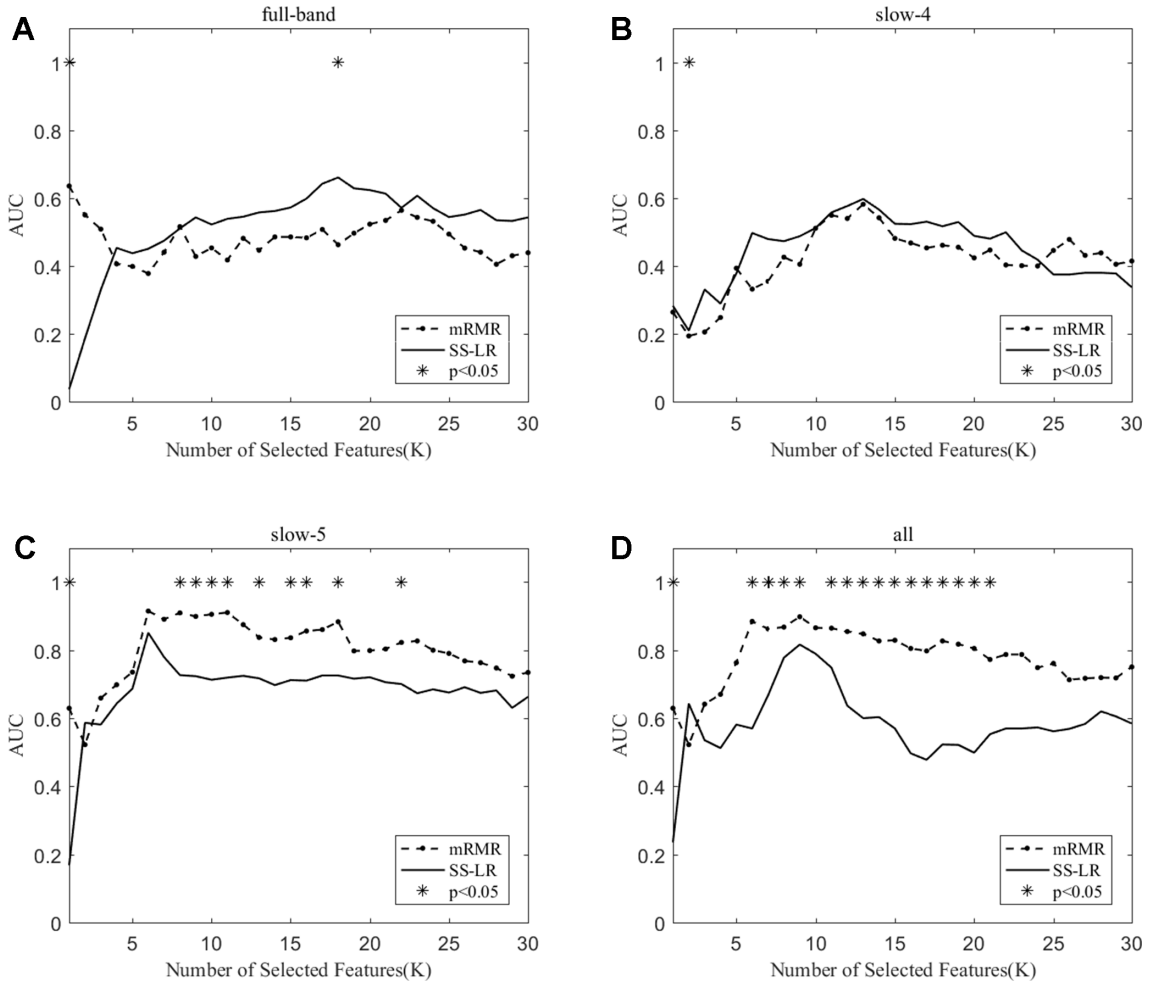

FIGURE 4 | The AUC with the number of features under the mRMR and SS-LR algorithms; * indicates a significant difference in the classification results under the two algorithms.

TABLE 3 | Comparison of classification results between different feature selection methods.

Frequency band	Sig. (mRMR VS SS-LR)	Sig. (mRMR VS FS)	Sig. (SS-LR VS FS)
Full-band	0.1356	0.3827	0.6056
Slow-4	1.000	0.1508	0.0990
Slow-5	0.006	0.0014	0.4795
All	0.0665	0.00048	0.0990

The "Sig." column gives the p-value. Results with Sig. value < 0.05 are treated as nominally significant.

significant difference in all band. Among the four frequency bands, the AUC scores are relatively higher in the slow-5 band than that in the other three bands. In the slow-5 band, the trend of the two curves was relatively flat, and the waveforms of the two curves vary in other frequency bands. It can be seen from the classification results of different frequency bands that dividing the frequency band may improve the classification effect (52–56).

In brief, the classification results obtained by using the mRMR algorithm in the slow-5 band was the best, followed by the classification result obtained by using the mRMR algorithm in all band, while the classification results obtained by using the two algorithms in the full-band and slow-4 band are relatively poor. Hence, the next work is only for discussion and analysis of slow-5 and all band.

Highly Sensitive Characteristic

This section lists the top 10 features in slow-5 band and all band obtained by the mRMR algorithm. Details on the specific characteristics of the selected features, the location and number of the AAL brain regions, and the number of selected times can be found in **Tables 4** and **5**. The features selected using the mRMR algorithm contain all the attributes, where the nodal path length (NL) attribute contains five features, and the betweenness centrality (BC) attribute contains three features, and nodal degree (ND) attribute contains two features. We found that the nodal path length attribute contributed 50% to identifying different stages of MCI.

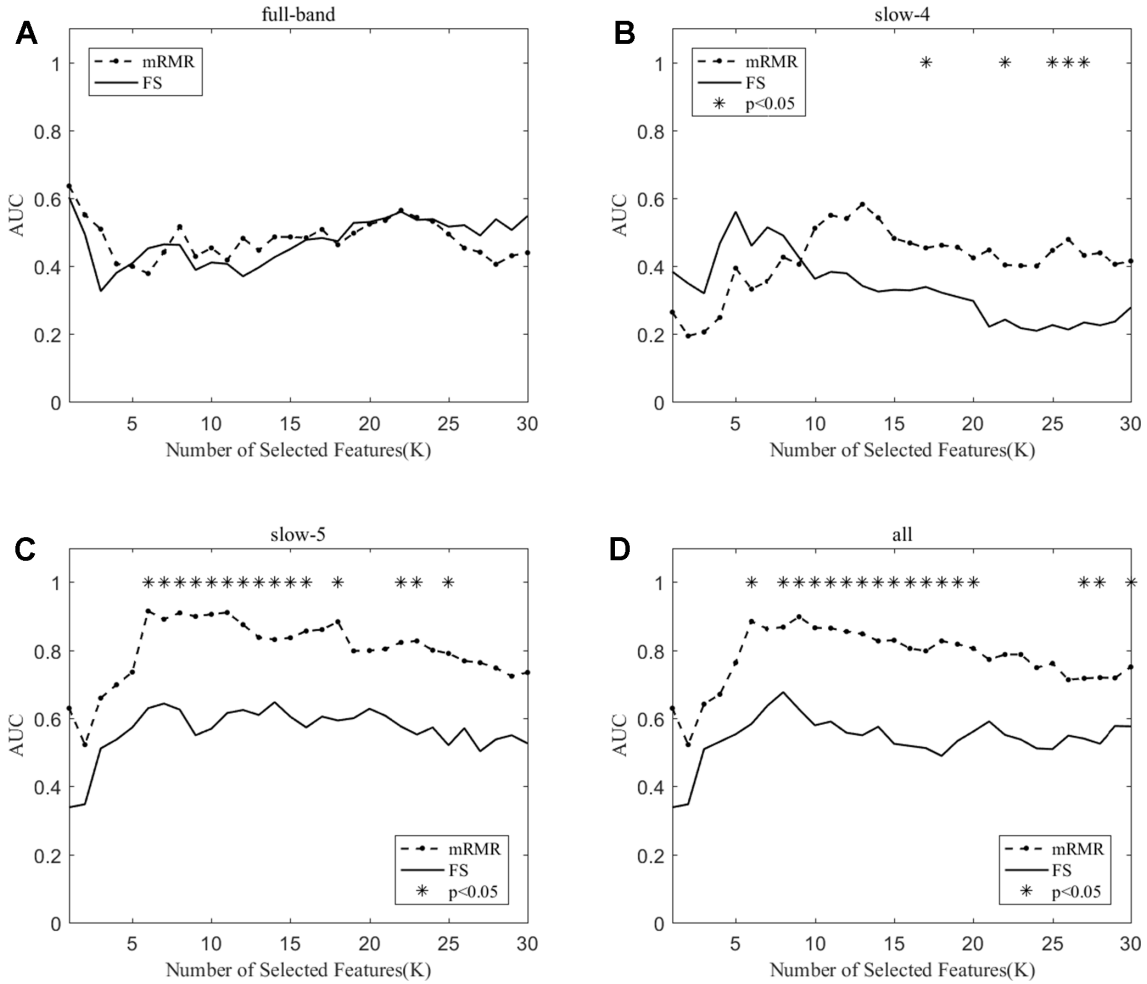

FIGURE 5 | The AUC with the number of features under the mRMR and FS algorithms; * indicates a significant difference in the classification results under the two algorithms.

The features selected (listed in **Table 4** and **Figure 7**) show roughly similar features to two frequency bands and include the left middle temporal gyrus (l-MTG), the right inferior temporal gyrus (r-ITG), the left superior temporal gyrus (l-STG), and the right caudate nucleus (r-CAU), left heschl gyrus (l-HES), left inferior occipital gyrus (l-IOG), left rolandic operculum (l-ROL), left cuneus (l-CUN), right olfactory cortex (r-OLF), and the left precentral gyrus (lPreCG). These seven brain regions were 100% selected 62 times, and three brain regions were located in the temporal lobe region. The remaining three brain regions were also selected at a frequency of more than 80%.

In addition, we also list the features selected by the mRMR algorithm in the all band. The features of all band are combined by the full-band, slow-4, and slow-5 band. As can be seen from **Table 5**, except for one nodal path length attribute feature comes from the full-band band, other features are from the slow-5 band, and these features from the slow-5 band are consistent with the features selected separately from the slow-5 band. The features of the slow-4 band are not selected, and most of the features are selected from the slow-5 band, indicating that the information in the slow-5 band that distinguishes between EMCI and LMCI is highly sensitive characteristic.

DISCUSSION

In this paper, we employed the method of constructing brain function network to classify EMCI and LMCI in the case of sub-band. Although the all band contains all features of the three frequency band, the best classification effect was achieved in the slow-5 band (ACC=83.87%, AUC=0.905) by using the feature selection method of mRMR (**Table 2**). It can be seen that the analysis in brain function network properties of the two groups in **Supplementary Figures 1**, **2**, and **3**, there are significant differences in the network attributes of the two groups in the slow-5 band, so that both of highly sensitive features and best classification results in the slow-5 band can be inferred. These results suggest that low frequency obtained by division frequency might achieve a better classification result. In addition, compared with the SS-LR and FS feature selection algorithms, the features

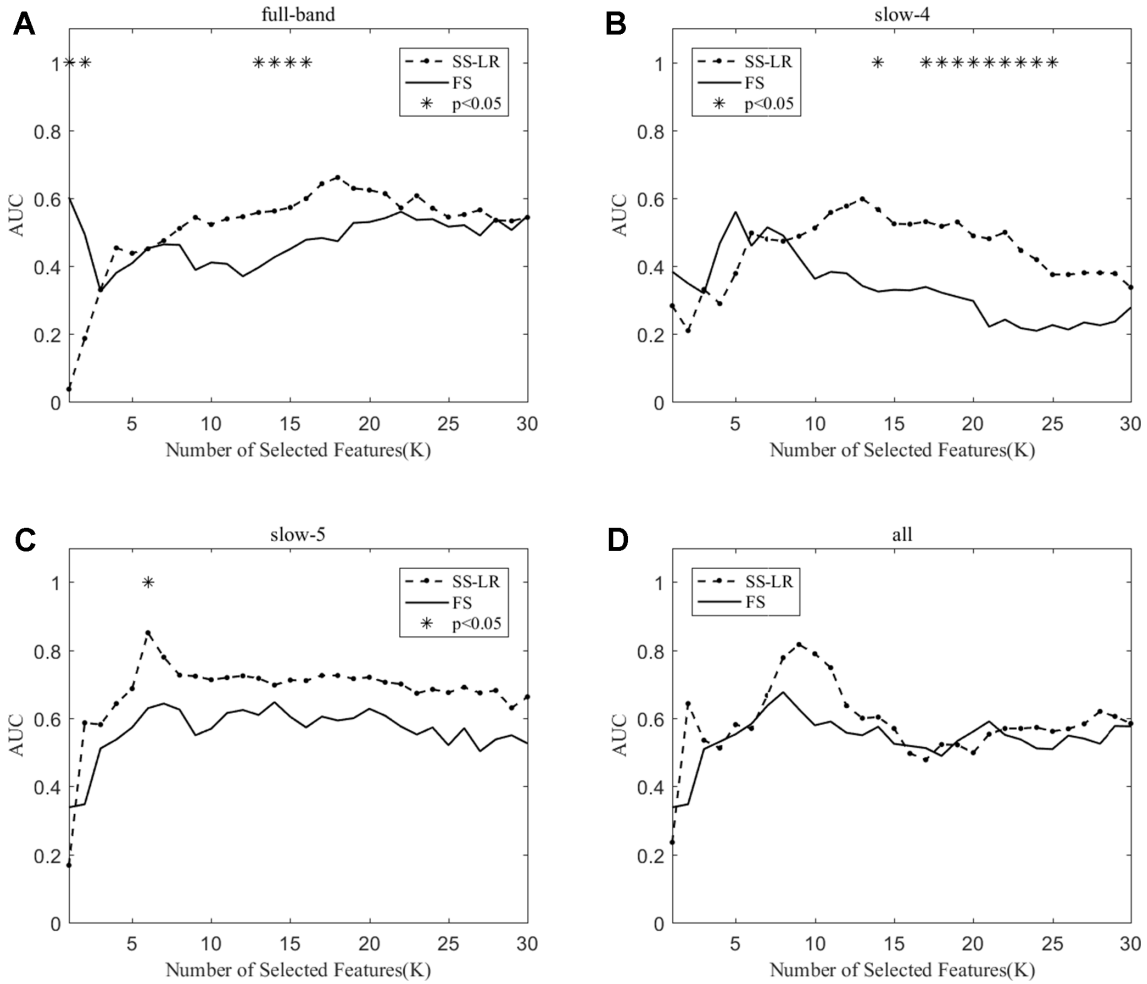

FIGURE 6 | The AUC with the number of features under the SS-LR and FS algorithms; * indicates a significant difference in the classification results under the two algorithms.

TABLE 4 | Distribution of features selected using the mRMR algorithm in the slow-5 band.

Networks attribution	Number	Region (AAL)	Selected times	Frequency (%)
ND	85	Left Middle temporal gyrus	62	100
BC	90	Right Inferior temporal gyrus	62	100
BC	83	Left Superior temporal gyrus	62	100
ND	72	Right Caudate nucleus	62	100
NL	79	Left Heschl gyrus	62	100
NL	53	Left Inferior occipital gyrus	62	100
NL	17	Left Rolandic operculum	62	100
BC	45	Left cuneus	61	>80
NL	22	Right Olfactory cortex	54	>80
NL	1	Left Precentral gyrus	53	>80

selected by the mRMR algorithm have higher classification performance and the classification effect is more stable with the number of features increases. It suggests that selecting the appropriate feature selection method for the data set can help improve the classification accuracy. From the demographic data of the two groups (**Table 1**), there is no significant difference between MMSE and CDR, which indicates that the neuropsychological scale could not distinguish the patients with EMCI and LMCI in the clinic. Our classification framework demonstrates that efficient feature extraction and selection can effectively improve the classification of EMCI and LMCI.

As shown in **Supplementary Figures 1**, **2**, and **3**, we used graph theory to calculate and analyze brain network functional differences between EMCI and LMCI. The results show that there are no significant differences in functional network properties between EMCI and LMCI in the slow-4 band. In the full-band, the global efficiency of LMCI is significantly higher than EMCI in a small part of the threshold, while the characteristic path length of LMCI is significantly longer than that of the small

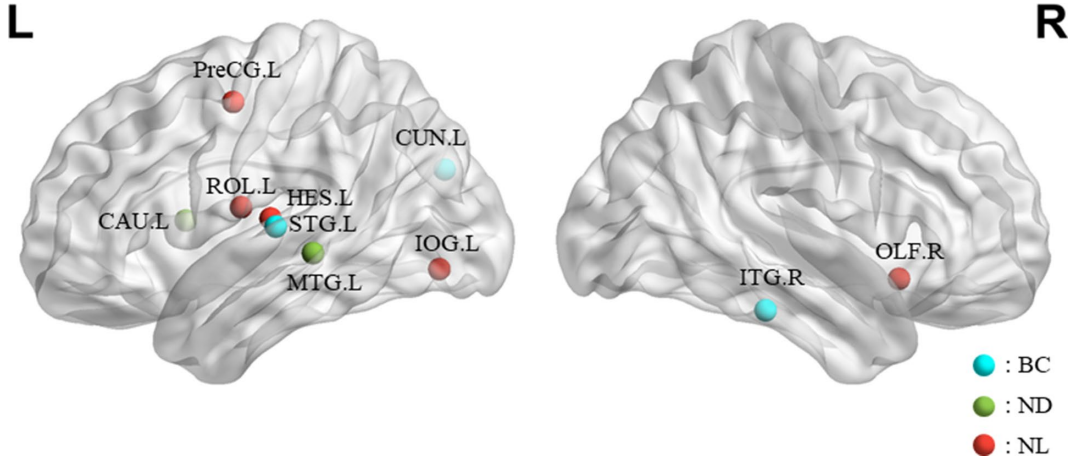

FIGURE 7 | The location and networks attribution of top 10 brain regions, listed in **Table 4**, which might be affected in early stage of MCI in sagittal views. The blue ball represents BC, the red ball represents NL, and the green ball represents ND.

TABLE 5 | Selected feature distributions in the integrated all band using the mRMR algorithm.

Networks attribution	Frequency band	Number	Region (AAL)	Selected times
NL	Full-band	53	Inferior occipital gyrus	62
ND	Slow-5	85	Left Middle temporal gyrus	62
BC	Slow-5	90	Right Inferior temporal gyrus	62
BC	Slow-5	83	Left Superior temporal gyrus	62
ND	Slow-5	72	Right Caudate nucleus	62
NL	Slow-5	53	Left Inferior occipital gyrus	62
NL	Slow-5	79	Left Heschl gyrus	61
NL	Slow-5	17	Left Rolandic operculum	61
BC	Slow-5	45	Left cuneus	60
NL	Slow-5	22	Right Olfactory cortex	23

part of the threshold. In the slow-5 band, the global efficiency, the local efficiency, and the average clustering coefficient of LMCI are significantly higher than those of EMCI, respectively. Similarly, the LMCI characteristic path length is significantly longer than EMCI under most threshold values. Consistent with our findings, it has been shown that LMCI converters and EMCI converters showed a decreased path length and mean clustering compared with the MCI stables. Specifically, EMCI converters showed a decreased clustering coefficient, transitivity, modularity, and small-worldness compared with the LMCI converters in the Cost = 5–17% threshold range (57). These findings align with Zhou's report (16) that MCI converters experience the worst local efficiency during the converting period to AD; however, the stables have highest local and global efficiency. They suggested that the abnormal brain network indicates a compensatory mechanism of local and global efficiency in these MCI stables.

As listed in **Tables 2** and **3**, the classification results show that the features selected by the mRMR algorithm have higher classification performance than those selected by the SS-LR and FS algorithms. For the mRMR algorithm, the classification results obtained in slow-5 band is more stable than that of slow-4 and full-band. As shown in **Table 6**, the results of constructing brain function network classification EMCI and LMCI in slow-5 band is better than that of other studies constructing brain network (26, 52, 58–62). Meanwhile, most previous methods (63–66) obtained accuracy <70% that constructed brain networks only considered structural feature. In brief, this study provides a valuable insight into the prediction of EMCI and LMCI conversion, and revealed that graph measures of resting-state fMRI are a potential predictor for classification. Our results suggested that brain activity in the slow-5 band carries more disease information and the top 10 selected features have high sensitivity for more efficient classification, compared with the slow-4 band and the full band. High sensitivity of functional network features, the frequently band segmentation of the signal, and the choice of the feature selection algorithm are critical to the classification.

Previous studies demonstrated connection abnormalities in the temporal lobe region in patients with AD (15, 17). Liu et al. (67) also reported decreased complexities in lPreCG, STG, and MTG in familial AD. In agreement with these studies, we found that the temporal lobe region may be affected during the early stage of MCI. Specifically, we found that the betweenness centrality in the right inferior temporal gyrus (r-ITG) and the left superior temporal gyrus (l-STG) and the nodal degree in the left middle temporal gyrus were discriminative for separating EMCI from LMCI (**Tables 4** and **5**). The MTG has the highest selectivity in the feature selection section. These results are consistent with other reports that MTG is the most important brain regions in the AD lesion (68, 69). The MTG is located in the default network in the resting state network. Studies (70, 71) have shown that the default network in the resting state network of AD patients is abnormal compared to the normal elderly. Other studies have shown that a large amount of Aβ deposition is found

TABLE 6 | Classification performance of different methods to distinguish different stages of MCI.

Article	Method	Cohort	ACC (%)	SEN (%)	SPE (%)	AUC
This paper	Proposed	EMCI/LMCI (33/29)	83.87	86.21	81.21	0.905
Biao Jie (26)	Spatio-temporal interaction patterns of dynamic connectivity networks	EMCI/LMCI (56/43)	78.8	74.4	82.1	0.783
Seyed Hani Hojjatia (52)	Graph theory and machine learning approach (mRMR, FS)	MCI-C/MCI-NC(18/62)	91.4	83.24	90.1	N/A
Mohammed Goryawala (58)	fMRI volumes and neuropsychological scores	EMCI/LMCI (114/91)	73.6	74.3	72.7	N/A
Heung-Il Suk (59)	93 features from a MR image and the same dimensional features from a FDG-PET image.	MCI-C/MCI-NC (43/56)	74.04	58	82.67	0.696
Zhang and Shen (60)	MRI, PET and cognitive scores, Leave-one-out cross-validation	MCI-C/MCI-NC (38/50)	78.4	79.0	78.0	0.768
Moradi et al. (61)	MRI, age and cognitive measures 10-fold cross-validation	sMCI/pMCI (100/164)	81.72	86.65	73.64	0.902
Ardekani et al. (62)	Hippocampal volumetric integrity (HVI) from structural MRI scans RF with 5,000 trees	sMCI/pMCI (78/86)	82.3	86.0	78.2	N/A

The best multivariate predictors of MCI conversion are shown for each study. ACC, accuracy; SEN, sensitivity; SPE, specificity; AUC, area under the curve; FDG-PET, fluorodeoxyglucose positron emission tomography; RF, Random forest.

in the temporal lobe region, indicating that this brain region is an important region in the development of AD disease (14). All of these results suggest that changes in the structure and function of the MTG region are more sensitive to the development of AD disease. Some of other sensitive brain regions, such as l-CUN and r-ITG, were also reported in previous study using PE method to analyze the complexity of the same ADNI dataset (72). Studying the structural and functional network results of AD suggests that cognitive impairment in patients may be caused by abnormal connections between different brain regions in the temporal lobe (70, 73). The area of the ITG plays an important role in maintaining language fluency (74). Hojjati and colleagues (52) demonstrated capability of rs-fMRI to predict conversion from MCI to AD by identifying affected brain regions (i.e., l-CUN, l-ROL, l-STG, r-CAU, r-ITG) underlying this conversion, and they proposed the ITG is an essential area in the verbal fluency circuit. Therefore, they suggested that these results might be indicative of disruption in communication between the ITG and other regions involved in this cognitive function in early stage of AD. For the caudate nucleus (CUN) region, Persson's study found that larger caudate nucleus volume in AD patients and further discussed this region possibly serving as a mechanism for temporary compensation (75). Consistent with this structural MRI finding, our results revealed the functional connection abnormalities of r-CAU in early AD. Niu et al. (69) revealed significant differences in the OLF.R, l-IOG, l-MTG, and other brain regions on multiple time scales for four stages of AD. Khazaee and colleagues (19) suggested that patients with AD experience disturbance of l-ROL, r-ITG, and l-STG in their brain network as AD progresses. Our findings converge nicely with what has been suggested by the previous MRI studies (76–78), and these selected brain regions have been shown to be related with MCI conversion.

In summary, the highly sensitive characteristic found that the features selected using the mRMR algorithm in the integrated all band and slow-5 band are overlapping, indicating that the information contained in the slow-5 band is more distinguishable. Moreover, selected brain regions carry more disease information with highly sensitive characteristic leading to more efficient classification. The important role of temporal lobe in MCI disease has been widely recognized. We suggested that the other regions (Right caudate nucleus, Left Heschl gyrus, Left Inferior occipital gyrus, Left Rolandic operculum, etc.) deserve researchers pay attention to explore the role of these brain regions in the MCI disease.

CONCLUSION

In this study, we investigated the efficacy of a classification framework to distinguish individuals with EMCI and LMCI by using the effective features derived from functional brain network of three frequency bands during Resting States. Without requiring other new biomarkers, our approach shows that the functional network features selected by mRMR algorithm improves the discrimination between EMCI and LMCI, compared with those selected by the SS-LR and FS algorithms. Moreover, the selected brain regions and frequency band are interpretable and consistent with previous studies. By comparing classification results, we found that the selected slow-5 band shows more stable and better performances compared with other bands. Ultimately, such a classification framework for the whole brain overall organization could substantially extend our understanding on the classification of MCI, shedding light on the novel potential diagnostic markers (highly sensitive features) located brain regions. This study has several limitations. A larger sample size and the consideration of including other degrees of severity in AD series and dementias in future work are essential to evaluate the variability and stability of functional networks for classification results. Another limitation related to network characteristics is the construction of undirected networks, ignoring the direction of information dissemination. Moreover, other findings indicated that any comparison of network parameters across studies must be made with reference to the spatial scale of the nodal parcellation (79); hence, we will evaluate the results of Power-264 brain regions for our method. The multimodality classification approach yields

statistically significant improvement (at least 7.4%) in accuracy over using each modality independently (39). Further studies are needed to integrate information from structural and functional connectivity networks for improving classification performance.

DATA AVAILABILITY

Publicly available datasets were analyzed in this study. This data can be found here: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply.

AUTHOR CONTRIBUTIONS

LL helped in calculation and manuscript writing. TZ was in charge of the data analysis and manuscript writing. ZZ and CZ helped in speeding up the data analysis. JZ and ZJ corrected the manuscript. All authors reviewed the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2019.00572/full#supplementary-material.

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Psychological Resilience Enhances the Orbitofrontal Network in the Elderly With Mild Cognitive Impairment

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Background: It has been suggested that maintaining the efficient organization of the brain's functional connectivity (FC) supports neuroflexibility under neurogenerative stress. This study examined psychological resilience-related FC in 112 older adults with mild cognitive impairment (MCI).

Methods: Using a resting-state functional magnetic resonance imaging (fMRI) approach, we investigated reorganization of the orbitofrontal gyrus (OFG)/amygdala (AMG)/hippocampus (HP)/parahippocampal gyrus (PHG) FC according to the different levels of resilience scale.

Results: Compared with the low resilient group, the high resilient group had greater connectivity strengths between the left inferior OFG and right superior OFG ($P < 0.05$, Bonferroni corrected), between the right inferior OFG and left PHG ($P < 0.05$, Bonferroni corrected), and between the right middle OFG and left PHG (false discovery rate < 0.05).

Conclusion: Psychological resilience may be associated with enhancement of the orbitofrontal network in the elderly with MCI.

Keywords: resilience, functional connectivity, fMRI, orbitofrontal cortex, elderly

INTRODUCTION

Pathology processes of major neurocognitive disorder begin before the onset of clinical symptoms. However, many patients remain free of symptoms for a considerable period despite a significant neurodegeneration and brain volume loss The concept of brain "resilience" has emerged to explain individuals' ability to tolerate disease-related pathology in the brain without developing clinical symptoms or signs (1). Of the many aspects of brain resilience, interest in psychological resilience and its mechanism has increased in terms of major neurocognitive disorder prevention.

To address this issue, it is required to assess functional network in brain. Network resilience derives from the efficient arrangement of connections between brain regions (2, 3). It has been suggested that maintaining the efficient organization of the brain's functional connectivity (FC) supports neuroflexibility under neurogenerative stress (3–5). For instance, brain regions' FCs associated with negative emotional processing and regulation, and self-referential function could be modulated and affected by antidepressant treatment (6).

More specifically, it is worth noting the relations between the orbitofrontal gyrus (OFG)-related functional network and psychological resilience (2). OFG functional activity is known to play a mediating role in subjective well-being (7). It was also reported that resilient group had greater connectivity between the OFG and amygdala (AMG) (8). Feng et al. suggested that patients with depression showed weaker functional connectivity links between the medical OFG and the parahippocampal gyrus (PHG)/medial temporal lobe, which are involved in pleasant feelings and rewards with memory systems (9).

Considering this background, the present study was designed to examine psychological resilience-related FC in the elderly with mild cognitive impairment (MCI) accompanied by depression and anxiety symptoms. Using a resting-state functional magnetic resonance imaging (fMRI) approach, we investigated linear trends of the OFG/AMG/hippocampus (HP)/PHG FC according to the level of resilience scale. In addition, given the modulatory roles of psychological resilience, we examined whether these FCs were associated with depression, anxiety, and cognitive functions.

METHODS

Participants

We recruited participants over the age of 60 with MCI accompanied by depression and anxiety symptoms from the geriatric community mental health center in Suwon, Republic of Korea. One hundred twelve subjects with a mean age of 73.78 ± 5.76 years (76.80% women) were recruited. All participants were diagnosed with depressive disorder by psychiatrists a year ago at the time of study enrollment and had taken antidepressants. Inclusion criteria were (a) MCI criteria proposed by Petersen et al. (10), (b) Clinical Dementia Rating (CDR) of 0.5 (11), (c) Clinical Global Impression-Severity (CGI-S) score below 4 points and not worse than 1 year ago, and (d) the use of antidepressants and anxiolytics at stable dosage for at least 6 weeks prior to study entry without any recommendation for changes in medication. Given the characteristics of older adults from geriatric community mental health center, participants might have chronic or residual affective symptoms, but they were clinically stable on affective symptoms. We excluded those who met the following criteria: (a) a history of severe psychiatric disorder (mental retardation, schizophrenia, bipolar disorder, and other dementia); (b) a history of neurological disorder, such as brain tumor, intracranial hemorrhage, subarachnoid hemorrhage, epilepsy, hydrocephalus, encephalitis, metabolic encephalopathy, or other neurologic conditions that could interfere with the study; (c) a history of significant hearing or visual impairment; and (d) a history of physical illnesses that could interfere with the study.

Psychological Resilience Measurement

The Brief Resilience Scale (BRS) is a simple measurement consisting of six questions. Three questions are positive, and three are negative. Each score is given 1 to 5, and negative scores are added inversely. The higher the total score, the more psychological the resilient state. This scale was validated for Korean population (Cronbach's alpha = 0.6, test–retest reliability = 0.62) (12, 13). In order to ensure sufficient number of neuroimaging analysis for each group, BRS was treated as a categorical variable based on tertiles. Subjects were divided into three groups based on BRS: from the lowest to 12 points was referred to as *2 group* ($n = 62$); from 13 to 23 points was *1 group* ($n = 21$); 24 points or more was *0 group* ($n = 29$).

Measurement of Other Clinical Variables

Depressive symptoms were measured using the Montgomery–Asbergo Depression Rating Scale (MADRS) (14, 15). The MADRS consists of 10 items of depressive symptoms in seven stages from zero to six points. Beck Anxiety Inventory (BAI) was used to evaluate anxiety symptoms. The BAI is a self-rating tool to distinguish anxiety from depression. It has a total of 21 questions and is rated 0–3 for each question (16). Both scales indicate that depression or anxiety increases as scores increase. Cognitive functions were assessed using the Mini Mental State Examination (MMSE), Stroop Test-color reading, Seoul Verbal Learning Test (SVLT)-delayed recall, Digit Span-backward, and CDR (17).

MRI Data Acquisition and Preprocessing

Resting-state fMRI (Rs-fMRI) was performed at the beginning and end of the study at Ajou University Hospital. All MRI acquisitions were performed with a 3.0-Tesla Philips scanner (Intera Achieva, Philips, Medical Systems, Best, The Netherland) located at Ajou University Hospital. For resting-state fMRI, gradient echo-planar imaging (EPI) sequence was collected (repetition time (TR) = 2,000 ms, echo time (TE) = 30 ms, flip angle = 90°, field of view (FOV) = 220 × 220 mm^2, voxel size = 2.75 × 2.75 × 3 mm^3, volumes = 176). Rs-fMRI data were acquired while participants lying down and resting with eyes closed, without focusing on any specific thoughts, and without sleeping. High-resolution T1-weighted images were acquired from each subject using a magnetization-prepared rapid acquisition gradient echo (MPRAGE) pulse sequence (TR = 2,000 ms, TE = 4 ms, flip angle = 8°, FOV = 220 × 220 mm^2, voxel size = 1 mm^3).

Clinical Data Analyses

Descriptive statistics were used to explore the data. Categorical variables between resilience groups were compared using the chi-square test, while continuous variables were compared using an analysis of variance. SPSS software version 22.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

fMRI Data and FC Analyses

Resting-state fMRI data preprocessing was conducted using statistical parametric mapping (SPM12, http://www.fil.ion.ucl.ac.uk/spm/, Wellcome Trust Centre for Neuroimaging, London, UK) (18). After the first five scans were discarded due to some stability issues, all EPI data were preprocessed by correcting for the delay in the acquisition time between different slices and correcting for head motion by realignment of all consecutive volumes to the first image of the session. The realigned images were co-registered to T1-weighted images, which were used to spatially normalize functional data into a template space using nonlinear transformation. We did not conduct spatial

smoothing on the resting-state fMRI data to avoid inflation of local connectivity and clustering.

For the current study, we selected 12 regions of interest (ROIs) as the bilateral inferior/middle/superior OFG, HP, PHG, and AMG (**Figure 1A**), which were defined using automated anatomical labeling (AAL) atlas (19). Regional mean fMRI time series, extracted from the 12 regions, were temporally processed through (a) regressing out effects of six rigid motions and their derivatives, and three principal components of the white matter and the cerebrospinal fluid mask segmented using SPM12; (b) spike detection and despiking based on four times of the median absolute deviation; and (c) band-pass filtering (0.01–0.1 Hz) (20–23). Finally, we estimated inter-regional FCs among 12 regions using Pearson correlation coefficients, which were converted into *z*-scored maps with Fisher's *r*-to-*z* transformation.

This study is aimed to investigate where individual FC shows linearly increasing or decreasing trend according to BRS scales. For this purpose, we used a general linear model, in which we designed the first three regressors (BRS 2, 1, and 0 groups) indicating different groups and the next three regressors (age, sex, and education year) including nuisance covariates (**Figure 1B**). With this design matrix, the linear trend for each FC was examined using two contrast vectors, that is, C = [−1 0 1 0 0 0] for check increasing FC and C = [1 0 −1 0 0 0] for check decreasing FC. In order to exclude the effect of changes in brain connectivity caused by depressive and anxiety symptoms, the same analyses were conducted in groups with scores of MADRS (≥34, $N = 52$; 20 to 33, $N = 48$; ≤19, $N = 12$) (24) sand BAI (≥32, $N = 20$; 27 to 32, $N = 11$; 22 to 26, $N = 15$; ≤21, $N = 66$) (25).

To detect FCs showing significant trend, we applied three threshold levels of false discovery rate (FDR) < 0.05, FDR < 0.2, and $P < 0.05$ (Bonferroni corrected) for multiple-comparison correction with the number of connections. Note that FDR control levels in the range of 0.1~0.2 are originally known to be acceptable for multiple-comparison correction (26).

For FCs exhibiting significant linear trends, we further investigated whether such trends of connection strengths are related to MADRS, MMSE, and BAI scores or not. This study was conducted using a newly defined design matrix, where these clinical variables were separated for each group (BRS 2, 1, and 0 groups) and three nuisance covariates were included as well (**Figure 3A**). All analyses for resting-state fMRI were performed using MATLAB-based custom software.

RESULTS

Clinical Characteristics of Participants

Demographic information and clinical data are summarized in **Table 1**. There were statistical differences in MADRS and BAI scores according to resilience groups.

Resilience and OFG/AMG/HP/PHG FC

Compared with the low resilient group (BRS 2 group), the high resilient group (BRS 0 group) had greater FC strength, as follows: the left inferior OFG and right superior OFG ($P < 0.05$, Bonferroni corrected), the right inferior OFG and left PHG ($P < 0.05$, Bonferroni corrected), and the right middle OFG and left PHG (FDR < 0.05). However, we did not find any reduced FC strength in the high resilient group compared with the low resilient group. See **Figure 2** for more details and a complete list of our results.

Meanwhile, no changes in OFC FC were found according to the group of MADRS score. It was also observed that only FC between the left middle OFG and left HG increased in group with low BAI score (FDR < 0.2).

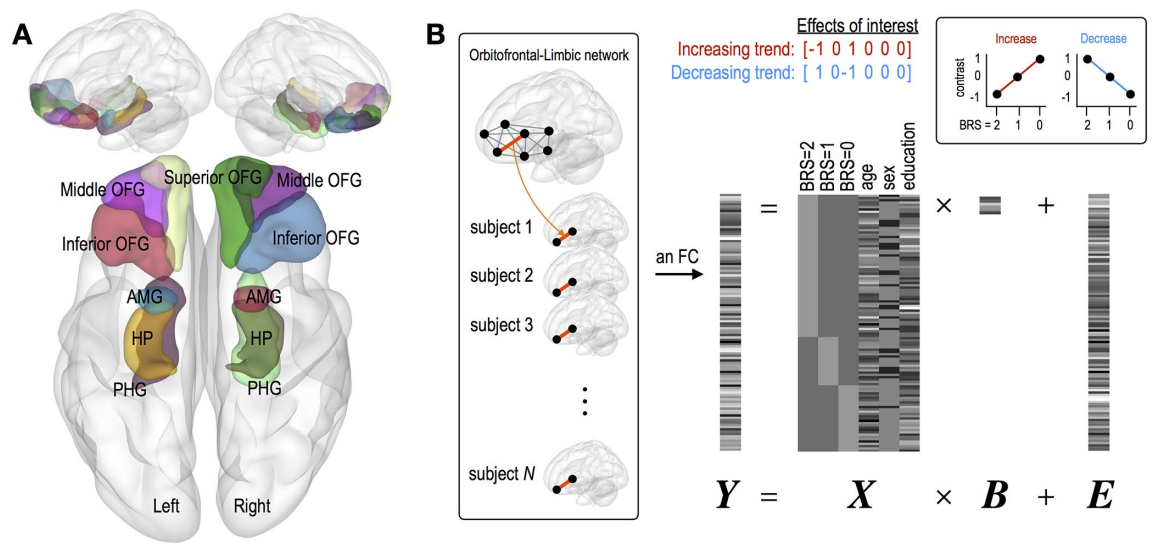

FIGURE 1 | Description of brain regions of interest and a general linear modeling used in the current study. **(A)** Twelve regions of interest consist of the bilateral inferior/middle/superior OFG, HP, PHG, and AMG. **(B)** A general linear modeling where individual FC is tested with two contrast vectors representing linear increasing and decreasing trend separately. Variables of age, sex, and education were *z*-scored. Abbreviation: OFG, orbitofrontal gyrus; HP, hippocampus; PHG, parahippocampal gyrus; AMG, amygdala.

TABLE 1 | Demographic and clinical information.

Variable	Resilience level			χ^2 or *F*	*P*-value
	High (BRS 0) (*n* = 29)	Moderate (BRS 1) (*n* = 21)	Low (BRS 2) (*n* = 62)		
Age (years)	74.79 ± 5.43	74.81 ± 5.31	72.95 ± 6.01	1.44	0.243
Sex (female)	19 (65.50)	15 (71.40)	52 (83.90)	4.15	0.126
Education (years)	7.14 ± 4.32	5.88 ± 4.78	5.70 ± 3.93	1.19	0.307
BRS	24.00 ± 0.01	18.48 ± 2.84	11.52 ± 1.65	538.95	< 0.001
MADRS	27.38 ± 10.38	31.90 ± 6.55	32.47 ± 8.43	3.52	0.033
BAI	14.14 ± 9.03	19.05 ± 10.92	21.94 ± 10.54	5.73	0.004
MMSE	24.03 ± 3.49	22.57 ± 2.60	23.37 ± 3.79	1.06	0.352
CGI-S	3.40 ± 0.72	3.76 ± 0.54	3.70 ± 0.61	2.85	0.062
SVLT-delayed recall (z score)	−1.06 ± 1.44	−0.43 ± 1.02	−0.92 ± 1.14	1.75	0.179
Stroop Test—color reading (z score)	−0.49 ± 1.36	−1.44 ± 1.50	−0.79 ± 1.44	2.49	0.088
Digit Span-backward (z score)	−0.54 ± 1.09	−1.14 ± 1.25	−0.59 ± .97	2.47	0.089

Values are mean ± standard deviation or n (%). BRS, Brief Resilience Scale; MADRS, Montgomery–Asberg Depression Rating Scale; BAI, Beck Anxiety Inventory; MMSE, Mini Mental State Examination; CGI-S, Clinical Global Impression-Severity; SVLT, Seoul Verbal Learning Test.

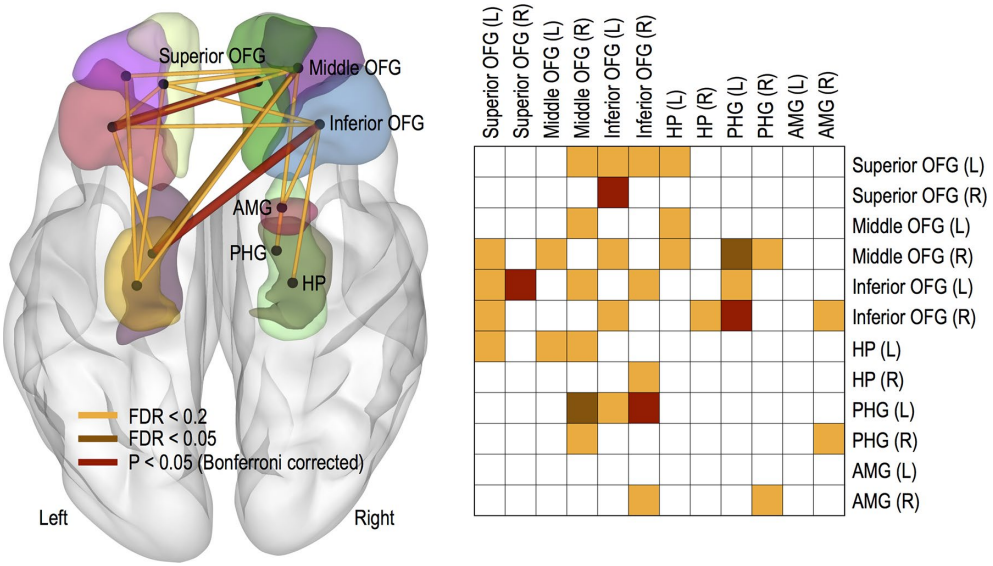

FIGURE 2 | Functional connections showing significant increasing trends. Thicker links represent more significant connections and color-coded differently for three threshold levels of FDR < 0.05, FDR < 0.2, and *P* < 0.05 (Bonferroni corrected). Abbreviation: OFG, orbitofrontal gyrus; HP, hippocampus; PHG, parahippocampal gyrus; AMG, amygdala; L, left; R, right.

Different Associations Between Cognitive/Depression/Anxiety Symptoms and OFG/AMG/HP/PHG FC According to Resilience Group

MMSE and MADRS scores were significantly positively correlated with FC strength between the left inferior OFG and right superior OFG (MMSE, $P = 0.0103$; MADRS, $P = 0.0188$) in the high resilient group (**Figure 3B**). However, we found significant negative correlations between BAI score and connectivity strength between the left inferior OFG and right superior OFG ($P = 0.0439$), the left superior OFG and right middle OFG ($P = 0.0397$), the left inferior OFG and right superior OFG ($P = 0.038$), and the left superior OFG and left HP ($P = 0.0091$) in the high resilient group (i.e., BRS 0 group) (**Figure 3B**).

Other cognitive function tests were significantly positively correlated with FC strength in the high resilient group, as follows: the right superior OFG and left HP (Stroop Test, $P = 0.007$), the right superior OFG and right HP (Stroop Test, $P = 0.0003$), the left superior OFG and left HP (Digit Span, $P = 0.0179$), and the right superior OFG and left inferior OFG (Digit Span, $P = 0.024$) (**Figure 4**).

DISCUSSION

The main finding is that psychological resilience may be associated with increased orbitofrontal network in the elderly with MCI. Brain circuits with greater FC strength in the high resilient group involved the OFG and PHG, which are implicated in the reward-related memory system (9). We also observed enhanced

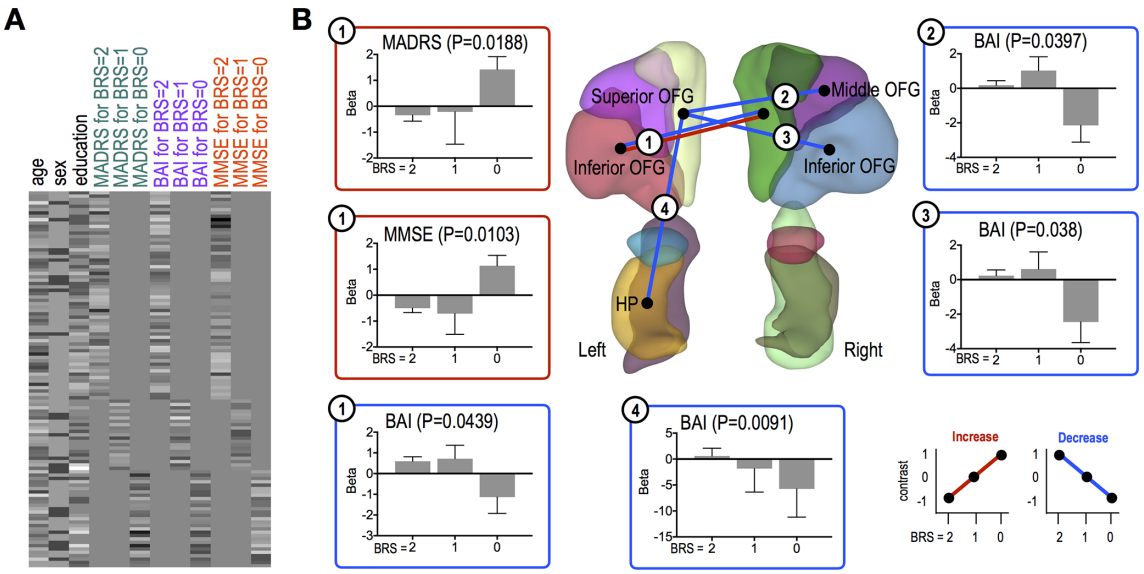

FIGURE 3 | Functional connections showing significant association trends with clinical scores. **(A)** A design matrix used in association study with clinical scores. All variables were *z*-scored before separating to each group (BRS = 2, 1, and 0). **(B)** Functional connections showing significant trends for associations between the connections and clinical scores. In each bar plot, beta values on the vertical axis represent regression coefficients, and error bars imply standard error of the betas. Red and blue lines/boxes represent FCs and variables exhibiting significantly increasing and decreasing trends, respectively. Abbreviation: OFG, orbitofrontal gyrus; HP, hippocampus; PHG, parahippocampal gyrus; AMG, amygdala.

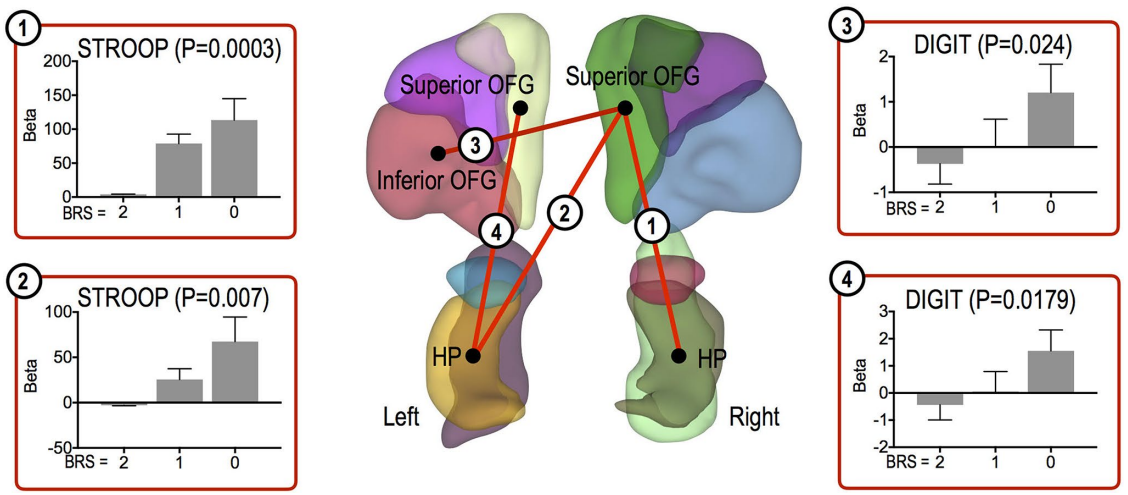

FIGURE 4 | Functional connections showing significant association trends with cognitive function test scores. Functional connections showing significantly increasing trends for associations between the connections and cognitive scores. In each bar plot, beta values on the vertical axis represent regression coefficients, and error bars imply standard error of the betas. Abbreviation: OFG, orbitofrontal gyrus; HP, hippocampus.

interconnectivity between OFG subregions as the resilience level increased.

Recent literature indicated that activation of the brain's reward system could mitigate subsequent stress responses in humans, suggesting reward pathways as a mechanism for promoting psychological resilience (27). It was proposed that the connections between the medial OFG and HP/PHG provided a route for reward/emotion-related information (28). Therefore, based on our findings, it could be assumed that these FCs are involved in rewards system through positive emotional memory, which could be associated with psychological resilience under stress.

Meanwhile, enhanced interconnectivities between OFG subregions in proportion to the degree of resilience were found in this study. Previous neuroimaging studies have reported medial OFG/reward and lateral OFG/non-reward and punishment gradient consistently. Some studies also observed elevated lateral OFG activity in the low resilience state such as depression, as well as reduced interconnectivity of the medial OFG (29–31). The theory proposed that lateral OFG/non-reward system might be more easily

triggered, and this triggered negative cognitive states, which in turn had positive feedback top-down effects on the OFG/non-reward system. The reward and non-reward systems were likely to operate reciprocally in facilitating the medial OFG/reward system, and they might operate by inhibiting the overactivity in the lateral OFG non-reward/punishment system (9, 31, 32). So increased resilience might be associated with reciprocal interconnectivity between the lateral OFG-related non-reward system and the medial OFG-related reward system.

In addition, given the modulatory roles of psychological resilience, we could find significant positive (i.e., MMSE, Stroop Test, and Digit Span) or negative (i.e., BAI) correlations between clinical symptoms and that resilience is related to the OFG connectivity strength in patient with MCI. Orbitofrontal network might be involved in subjective well-being and active stress coping mediated by psychological resilience (7). Chronic stress was known to have an effect on the transition from MCI to dementia, (33, 34). So maintaining the efficient organization of OFG FC supported neuroflexibility under stress, which might be the intervention strategy for preventing dementia. In actuality, our findings suggested that OFG/HP connectivity and interconnectivities between OFG subregions might be associated with executive/attentive function and anxiety symptoms.

However, contrary to expectations, MADRS scores were positively correlated with FC strength between the OFGs in the high resilient group. This was because despite the working of the resilience related to brain function, older adults with chronic or residual depressive symptoms might be included in this study. Given the characteristics of older adults from geriatric community mental health center, our subjects had relatively chronic and severe depressive symptoms compared with anxiety symptoms or cognitive impairment. Our findings on MADRS score might rather show that high stress levels were accompanied by dynamic brain functions in circuits representing the stress reaction and adaption. In this respect, individuals who failed to show such neuroflexibility in this OFG network could have a high risk of developing dementia. In fact, chronic depression has been well known as a risk factor for dementia (35).

There were several limitations. This study was conducted with a relatively small sample size and a high percentage of female participants. It has been reported that brain FC density might be different according to gender (36, 37). Furthermore, subjects with affective symptoms were included, so this aspect might need to be taken into account to interpret these results as an MCI study (31). These symptoms might interfere with both psychological resilience and cognitive impairment independently. However, independent analyses of depressive and anxiety symptom groups showed that increased OFG FC associated with resilience might be irrespective of brain connectivity related to affective symptoms.

CONCLUSION

We demonstrate that psychological resilience may be associated with the orbitofrontal network in the elderly with MCI. Interventions during the pre-symptomatic period of neurocognitive disorder could be effective if they promote the resilience of the brain's intrinsically efficient arrangement of functional network connections. Understanding of the resilience system modulation of stress responding might be an exciting avenue for future research.

DATA AVAILABILITY

The datasets for this study will not be made publicly available because due to ethical restrictions, data are available upon reasonable request.

ETHICS STATEMENT

The IRB committee of Ajou University Medical Center approved all protocols of the study (IRB-15-137).

AUTHOR CONTRIBUTIONS

Conceived and designed the study: SS, HR, HL, CH. Performed the study: SS, HK, JC, CH. Analyzed the data: BP, JS, N-RK, SS. Wrote the paper: SS, BP.

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SYSTEMATIC REVIEW
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A Systematic Review of Evidence for a Role of Rest-Activity Rhythms in Dementia

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Background: Rest-activity rhythm (RAR) disruption may be a risk factor for dementia that can be objectively measured with wearable accelerometers. It is possible that risk monitoring and preventive interventions could be developed targeting RARs. To evaluate whether current evidence supports these applications, we systematically reviewed published studies linking RARs with dementia, its course, and mechanisms.

Methods: Entering pre-defined search terms in PsycINFO, MEDLINE, and PubMed databases returned 192 unique titles. We identified 32 articles that met our primary inclusion criteria, namely, that they examined objective RAR measures in the context of dementia, cognition, or brain biomarkers.

Results: Cross-sectional studies consistently found that people with dementia had less stable (5/6 studies), more fragmented (4/6 studies), lower amplitude rhythms (5/5 studies), that had a worse fit to 24-h models (3/3 studies). Findings from studies relating RARs to cognitive test performance (rather than diagnostic status) were more nuanced. RAR fragmentation was associated with neurodegeneration biomarkers in 2/2 studies; and 1/1 study found 24-h model fit related to hippocampal hyperactivation. Although 2/2 studies found RARs related to markers of cerebrovascular disease, the specific RARs and cerebrovascular disease measures were not consistent. Longitudinal studies (3/3 articles) reported that lower amplitude and worse 24-h rhythm fit predicted future cognitive impairment and executive function. However, interventions aimed at modifying RARs had mixed effects (e.g., 0/4 studies demonstrated effects of morning light on 24-h model fit; evening light was associated with improved 24-h fit in 2/2 studies reporting); these effects may be more evident in subgroups.

Conclusions: Consistent evidence shows that dementia is associated with disrupted RARs. Importantly, recent studies have shown that RAR disruption is associated with dementia biomarkers and, prospectively, with the risk of cognitive impairment. Interventions mostly tried using bright light to modify RARs in people who already have dementia; these studies produced modest effects on RARs and did not show modification of dementia's course. Altogether, these findings suggest studies are needed to understand how RARs

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relate to changes in brain health earlier in the disease process. Better understanding of the biopsychosocial mechanisms linking RARs with future dementia risk can help further target intervention development.

Keywords: rest-activity rhythms, sleep-wake rhythms, actigraphy, dementia, cerebrovascular disease, neurodegeneration

INTRODUCTION

The first case report documenting rest-activity rhythm (RAR) disruption in people with dementia was published in 1986 (1). This confirmed observations of clinicians and caregivers but had the advantage of objectively specifying the activity patterns that characterized people with dementia. RAR characteristics including regularity, fragmentation, amplitude, and fit to 24-h models can be objectively quantified by applying a variety of methods to several days of continuous accelerometer recordings (see brief description of RAR methods in **Figure 1**).

Almost three decades later, literature on relationships of RARs with dementia and cognition continues to grow. Published research currently includes observational, biomarker, and intervention studies (**Figure 2**). Now that consumer-friendly accelerometer technology is increasingly available, clear evidence for a role of RARs in dementia's course could lead to useful new clinical applications. Specifically, risk stratification approaches could be designed to detect RAR characteristics that mark or hasten dementia risk. Preventive interventions could also be developed targeting RARs to protect brain health and cognition.

But, the likelihood that these clinical applications will succeed, and what specifically they should target, depends on knowing 1) what aspects of RARs affect the course of cognitive aging and its underlying mechanisms, 2) whether these aspects of RARs are modifiable, and 3) if doing so improves cognitive aging. To identify gaps between current knowledge and potential clinical applications of wearable technology targeting RARs, we systematically reviewed evidence relating RARs, brain health, and cognition.

METHODS

Target article inclusion criteria: We included articles that reported results from data-based human subject research studies with more than 20 participants (i.e., we excluded review articles, animal studies, small pilot studies, and case reports). In addition, studies were included only if they examined cognition, a biomarker related to cognition in aging, Alzheimer disease, or a related dementia (except for Parkinson's due to differences in the biological mechanisms and low number of Parkinson's articles). To be included, articles were required to have quantified 24-h RAR variable(s) from objectively measured activity time series data. We only included articles that were written in English.

Article search and selection process (**Figure 3**)*:* We searched PsycINFO, MEDLINE, and PubMed databases using pre-specified terms [("sleep-wake rhythm" or "rest-activity rhythm" or "activity rhythm")) AND ("Alzheimer's" or "dementia" or "cognition" or "cognitive" or "neurodegenerative" or "cerebrovascular")]. To minimize bias and errors in article selection, two raters (SFS and CC) independently reviewed the title, abstract, and text

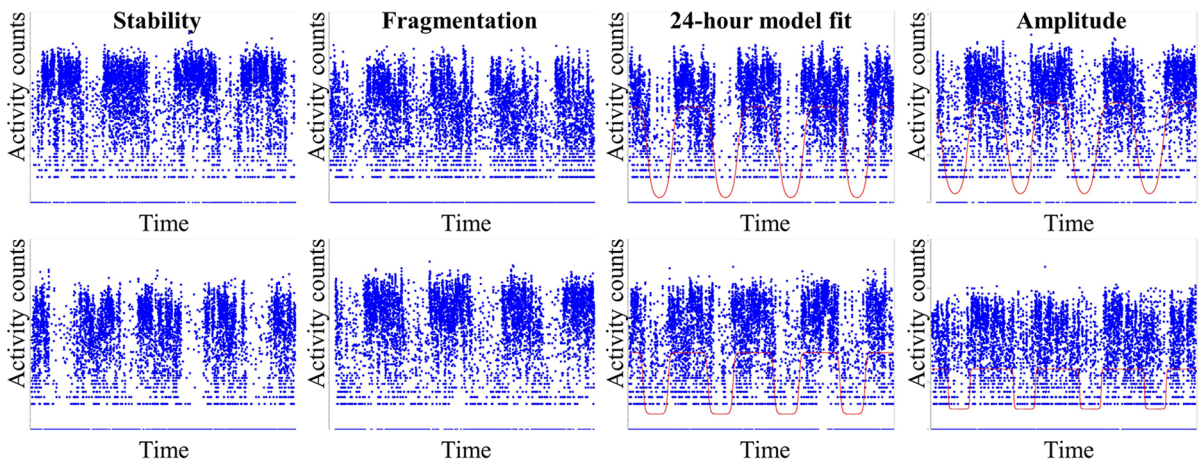

FIGURE 1 | Commonly used rest-activity rhythm (RAR) measures. The top row represents high values on the given metric and the bottom row represents low values. From left to right: note stability, measured as nonparametric inter-daily stability, indicates how much the typical 24-h profile varies from day to day; fragmentation, measured as nonparametric intra-daily variability, indicates the frequency and extent of transitions in activity levels; 24-h model fit, from an extended cosine model (see line) pseudo-F statistic, indicates how well the data fits to a 24-h model; amplitude, derived from an extended cosine model, indicates rhythm height. More details on these common metrics are provided in the reviewed articles and elsewhere, e.g., see the study by Smagula (2).

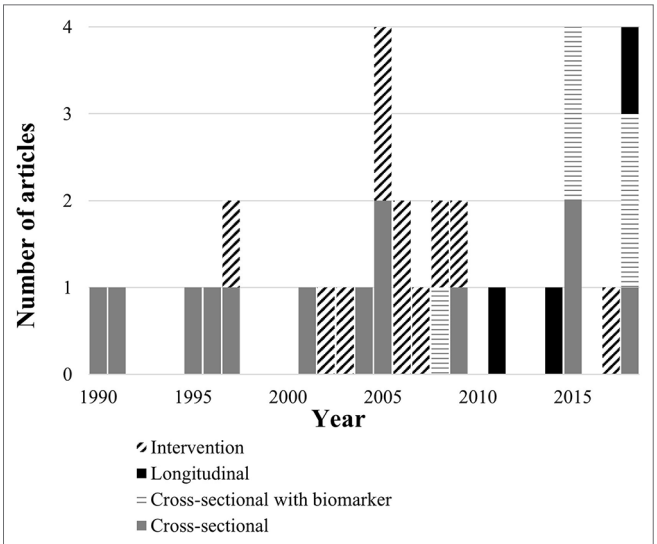

FIGURE 2 | Number of articles identified by year and study design.

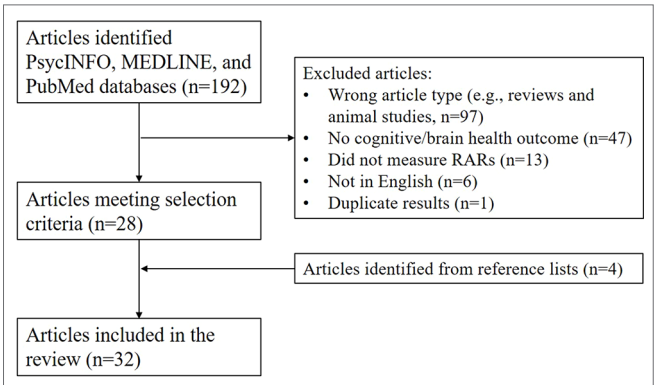

FIGURE 3 | Search process and article selection.

(as needed) of the 192 returned articles to determine if they met article inclusion criteria. Rating discrepancies were minimal and resolved *via* consensus discussion referencing the article's text. Returned articles were excluded because 97 were not the correct article type, 47 did not have a cognitive or relevant biomarker outcome, 13 did not examine objectively quantified RARs, 6 were not in English, and 1 reported the same results in two studies. Next, to minimize bias and errors, two raters (SFS and SG) reviewed each article and recorded selected summary information (see **Supplemental Tables**). Finally, the frequency and consistency of statistical results were then summarized across design, exposures, and outcome factors.

RESULTS

The search process outlined above returned 28 articles, meeting our inclusion criteria. Four additional articles were identified from their reference lists. Most studies used cross-sectional observational designs (n = 18) and five of these included biomarkers. Intervention studies were also common (n = 11). Few studies used longitudinal observational designs (n = 3).

*Cross-sectional studies (***Table 1***):* Consistent evidence demonstrated that people with dementia had less stable rhythms (5/6 studies 3–8). For example, the recent work by Saito et al. (5) demonstrated that, among nursing home residents, those with dementia had lower IS values (reflecting less stability across days). The one study (8) that failed to detect an overall statistically significant overall association between dementia and RAR stability did find stability was lower among people with dementia who were living in institutional settings (compared with community dwelling people with dementia and healthy controls); the sample of people with Alzheimer's disease living independently in this study was small (n = 8).

In addition, 4/6 studies (positive studies (3, 4, 7, 9 and nonsignificant studies 5, 8) found that cognitive impairment was related to higher RAR fragmentation. For example, the early work by Wittin et al. (3) demonstrated that Alzheimer disease patients had higher intra-daily variability, reflecting more fragmented (less consistent) rhythms. All of the studies examining goodness-of-fit and amplitude measures found that cognitive impairment was associated with less robust rhythm fits and lower amplitude rhythms (3/3 4, 6, 12 and 5/5 4, 6, 7, 14, 15, respectively).

Findings regarding associations of RARs and cognitive performance have been more nuanced. Both Luik et al. (9) and Oosterman et al. (10) showed that RAR fragmentation related to processing speed and executive function measures; furthermore, Luik et al. (9) found that the association of fragmentation and executive function was stronger among older compared with younger participants. Luik et al. (9) also found stability related to these cognitive measures, but Oosterman et al. (10) did not. Gehrman et al. (13) did not find an association between rhythm model fit and global dementia severity.

*Biomarker studies (***Table 2***):* Only five studies investigated RARs and dementia biomarkers. Three studies assessed markers of neurodegenerative processes (21–23: 1) Musiek et al. (22) found fragmentation related to markers of amyloid deposition; 2) Van Someren (21) reported that greater fragmentation correlated with lower medial temporal lobe volume better than any other risk factor studied; and 3) Sherman et al. (23) noted a relationship between 24-h rhythm fit and memory performance that was statistically mediated by anterior hippocampal hyperactivation during an associative memory task.

Two studies linked RAR measures with cerebrovascular disease markers. Oosterman et al. (20) found that white matter lesions were related to RAR stability, but Zuurbier et al. (19) did not; however, note that, while Oosterman et al. found associations in occipital periventricular and frontal regions, but not elsewhere, Zuurbier et al. examined only whole brain white matter lesion volume and not regional levels. Zuurbier et al. (19) found an association of RAR fragmentation with overall white matter lesion burden, and while Oosterman et al. did not (20), correlations of RAR fragmentation with white matter lesion volumes were similar in both studies (r = 0.10–0.12 in the study by Oosterman et al. (20) and 0.10 in the study by Zuurbier et al. (19); sample sizes differed substantially: 135 (20) and 970 (19).

TABLE 1 | Summary of evidence relating RAR and cognitive measures.

		Studies comparing RARs by cognitive status	Study examining associations of RARs with cognitive test performance
Cross-sectional studies	Stability (IS)	5/6 studies reported associations (3–7). The one nonsignificant study (8) was mixed: people with dementia had lower IS (compared with controls) if living in a nursing home but not community settings	1/2 studies: Luik et al. (9) found lower IS related to worse performance on measures of processing speed and executive function, whereas Oosterman (10) did not.
	Fragmentation (IV)	4/6 studies reported associations (3, 4, 7, 11). Note that Harper et al. (4) found frontal-temporal dementia, but not AD, was associated with higher IV. Van Someren et al. (8) and Saito et al. (5) failed to find associations between IV and cognitive status.	2/2 studies: Luik et al. (9) and Oosterman et al. (10) found associations of higher IV with slower processing speed and worse executive function.
	Goodness of fit measures (R^2, pseudo-F, or 24-h autocorrelation coefficient)	3/3 studies reported associations (4, 6, 12) but results differed by disease. Aharon-Peretz et al. (12) found patients with multi-infarct dementia had worse fit than AD and controls. Harper et al. (4) found frontal-temporal dementia had worse fit than AD and control.	Gehrman et al. (13) did not find an association between overall rhythm robustness with global dementia severity. However, among participants with less robust RARs, less severe dementia was associated with higher F statistic, steeper, and wider RARs. Among those with more robust RARs, less severe dementia was associated with earlier acrophase and narrower active periods.
	Amplitude (cosine-based model or nonparametric)	5/5 studies reported associations (4, 6, 7, 14, 15)	
Longitudinal studies	Goodness of fit measures (pseudo-F)	2/2 (16, 17) studies found having lower rhythm robustness and lower amplitude was associated with future cognitive status. Tranah et al. (16) found women with lower robustness and amplitude were more likely to have dementia or MCI approximately 5 years later. Rogers-Soeder et al. (17) found men with lower robustness and amplitude were more likely to have clinically significant cognitive decline approximately 3 years later.	Walsh et al. (18) reported that lower robustness was associated executive function task performance approximately 5 years later; these associations were attenuated after adjustment for other health factors.
	Amplitude (cosine-based model)		Walsh et al. (18) reported that lower amplitude was associated with executive function task performance approximately 5 years later (independent of adjustments for other health factors).

TABLE 2 | Summary of evidence relating RAR and neurobiological measures.

Stability (IS)	Lower IS was associated with: • Cerebral microbleeds (p = 0.06) (19) • Occiputal periventricular and frontal white matter lesions in Oosterman et al. (20); not global white matter lesions in Zuurbier et al. (19) • Lower medial temporal lobe volume, but this association was attenuated when adjusting for age (21).
Fragmentation (IV)	Higher IV was associated with: • Greater levels of amyloid deposition markers in the brain and cerebrospinal fluid (22). • Lower medial temporal lobe volume (21) • White matter lesion volumes in Zuurbier et al. (19) but not Oosterman et al. (20)
Goodness of fit measures (pseudo-F)	Better fit was associated with better memory performance, and this association was statistically mediated by hyperactivation in the hippocampus (23)
Amplitude (cosine-based model or nonparametric)	Lower amplitude was associated with lower medial temporal lobe volume, but this association was attenuated when adjusting for age (21).

*Longitudinal studies (***Table 1***):* In both studies reporting (16, 17), lower rhythm robustness (24-h model goodness-of-fit measure) and amplitude were associated with future cognitive decline. In terms of changes in cognitive test performance, Walsh et al. (18) found that lower robustness and amplitude were associated with executive function test performance 5 years later; in this study, the association of amplitude, but not robustness, was independent of other health characteristics (e.g., BMI, medical morbidities, medication use, and physical activity levels). Note that these prospective studies all included over 1,000 participants.

*Intervention studies (***Table 3***):* An early report noted that unattended daytime bright light has beneficial effects on RAR stability and fragmentation among patients with intact vision (31). However, additional studies of bright light interventions have shown modest or no effects on rhythms in people with dementia. Regarding the strength of intervention evidence, note (**Supplemental Table 4**) that published studies almost always focused on pre-post effects (rather than whether pre-post effects differed by randomized group) and always had follow-up periods of less than 3 months; therefore, these interventions were all considered studies with "level II" evidence strength according to previously published criteria (30). Two studies (27, 28) did report controlled results. That said, the intervention studies have shown:

TABLE 3 | Summary of light interventions targeting RARs.

Intervention	Effects on:			
	Stability (IS)	**Fragmentation (IV)**	**Goodness of fit**	**Amplitude**
Morning bright light	No intervention effects in the study by Dowling et al. (24), although stability increased in patients who had aberrant rhythms (defined as their least active 5 h beginning after 3 AM).	Dowling et al. (24) found no intervention effects.	0/4 studies observed intervention effects (24–27). Ancoli-Israel (26) observed a trend for improvement in the pseudo-F statistic in the morning light group (p = 0.06).	0/3 studies (24–26) although Dowling et al. (24) found that relative amplitude increased in people with aberrant rhythms at baseline.
Morning bright light + Melatonin	No effects (28)		Positive effects light+melatonin (27) on cosine-based amplitude	
Afternoon			No effect (26)	No effect (26)
Evening bright light			2/2 studies showed significant pre-post improvements (28, 29)	0/2 studies showed effects (28, 29)
Daytime (unattended) bright light	Improvements but only in patients with intact vision (30)			

An early report noted that unattended daytime bright light had beneficial.

- Morning bright light did not have statistically significant effects on RAR stability (25), fragmentation (25), 24-h model fit (24–27)| and amplitude (24–26). Among people classified as having aberrant rhythms at baseline, however, Dowling et al. (25) observed that morning light was associated with increases in stability and a trend towards increased amplitude. One controlled study (28) found that morning bright light plus melatonin has positive effects on 24-h model fit and amplitude.
- Afternoon light had no effects on 24-h model fit and amplitude in one study reporting controlled results (27).
- Evening light did have significant pre-to-post intervention effects on 24-h model fit in the two studies reporting (24, 26), no effects on amplitude were observed.

A few reports examined effects of other intervention approaches. Two studies (29, 32) using peripheral electrical stimulation did not have effects on stability or fragmentation. Moving to a small-scale care facility (33) and a hand movement intervention (34) also did not have statistically significant effects on RARs. Finally, one study found that 2 weeks of institutional care lead to a dampening (relative amplitude reduction) of RARs that recovered after returning home (35).

DISCUSSION

In summary, this systematic review of available evidence found consistent evidence that RAR disruption is more common in people with dementia. New evidence from large studies shows that RAR disruption predicts future cognitive decline. Evidence for these associations is strong, given the consistency of results across studies and the wide range of sample sizes and populations examined. Recently, biomarker studies have shown RAR disruption relates to the neurobiological hallmarks of dementia; however, as discussed below, these studies have been in relatively small cross-sectional samples and therefore cannot infer temporality in these relationships. Finally, note that several studies investigated whether light interventions modify RAR disruption or the disease course in people who already have dementia. These studies did not consistently show light interventions modify RARs; the most promising findings were from two studies using evening light (24, 26), one study using a combination of morning light and melatonin (28), and when analyses restricted to patient subgroups (those with intact vision (23 and RAR disruption at baseline 25).

The largest and most consistent evidence indicates that RAR disruption is more common in people who have dementia. Every study identified found that people with dementia have lower activity levels (reflected in RAR amplitude measures) (4, 6, 7, 14, 15), and most studies found that people with dementia have more fragmented (3, 4, 7, 11) less stable (3–8) rhythms, that fit a 24-h pattern relatively poorly (4, 6, 12). While these past studies were limited by their cross-sectional design, evidence from recent large prospective cohort studies have shown that RARs disruption also predicts future cognitive function (in people free of dementia at study baseline) (16, 17). However, it is not yet clear whether RAR disruption relates to dementia and dementia risk as a pathogenic contributor or as a downstream marker of existing pathology.

When reaching the severity that typically mandates institutional care (the setting where most RAR research began), people with dementia have already experienced significant neurodegeneration and likely have cerebrovascular disease (36). This macrostructural damage can affect the neural circuits that control circadian rhythms including the suprachiasmatic nucleus (37). Thus, it is not surprising that people with dementia frequently exhibit RAR disruption. Advanced-stage pathology could also explain why, in cases of overt dementia, increasing exogenous signals to the circadian system *via* light produces mixed or no effects (e.g., light may be inputting on already-damaged circadian circuits that have little remaining control effects).

Furthermore, recent studies have shown that RAR characteristics are associated with the neurobiological biological hallmarks of dementia early in the disease process (i.e., in community and pre-clinical samples) including amyloid deposition (22), medial temporal lobe atrophy (21), and cerebrovascular disease (although associations may be region specific) (19, 20). In addition, the study by Sherman et al. showed that RAR disruption related to hippocampal hyperactivation (23), which is considered a component of pre-clinical dementia pathophysiology related to early memory decline (e.g., see the study by Smagula et al. (38). In this context, findings from longitudinal epidemiological studies (showing RAR disruption

predicts future cognitive decline) might be due to RARs already reflecting early-stage neuropathology (which was not controlled for in existing longitudinal studies). Thus, available evidence does not resolve whether RAR disruption hastens the progression of, or simply reflects, early-stage pathology to dementia.

However, there are other sources of evidence that suggest rhythm disruption can contribute to dementia etiology; for example, an animal model of circadian misalignment affects neuronal structure (39), and chronic jet-lag (disrupting natural rhythms) is associated with reduced temporal lobe volume (40). Future prospective observational studies can be designed to determine whether RARs reflect or affect the pathogenesis of dementia. If RAR fragmentation in everyday human life uniquely contributes to the progression of amyloid pathology and neurodegeneration, then interventions aimed at modifying RAR fragmentation would be warranted. Alternatively, if RARs do not contribute to the progression of dementia above and beyond pre-existing neurobiological pathology, then interventions modifying RARs are less likely to succeed (although measuring RARs might still be useful for risk stratification).

Thus, longitudinal and intervention studies are needed to place associations of RARs and brain health in greater context. Apparent discrepancies in available literature may be because the role of RAR differs by age, life stage, or pre-existing pathology (which vary across study samples). It is not clear why associations between RAR fragmentation and cognition are stronger in older subsets of the sample in the study of Luik et al. (9) The meaning or role of RAR stability might differ depending on life stage (e.g., pre- or post-retirement) or other factors like the presence of cardiovascular risk factors, sedentary behavior, or poor sleep. Differences in these factors across samples could explain why Luik et al. (community sample; sample average age = 59) (9) found stability related to cognitive test performance, but Oosterman et al. (clinic-based sample; average age = 69) (10) did not. Future longitudinal studies are needed to identify the modifiable factors that lead to RAR disruption.

Psychosocial and physical activity have been associated with stronger RARs in people with dementia (41). This suggests that boosting or maintaining activity participation would be a logical approach to modify RARs. But, there remains a need to clarify which, of several inter-related risk factors (RARs, physical activity, social activities, and sleep), have the most potent and unique affects on brain health, and at what point in life. Our review of existing evidence suggests that interventions to curtail effects of RARs on brain health may require targeting specific subgroups (25, 31) and/or using multiple approaches (28).

CONCLUSION

Decades of research has produced solid evidence that people with dementia are more likely to exhibit RAR disruption. Recent studies have demonstrated that, even in pre-clinical samples, RARs relate to early markers of dementia neurobiology and may increase dementia risk. Several questions remain to be answered. Different measures of RAR robustness appear related to dementia neurobiology and risk, but future research is needed to identify the specific aspects of RARs that best signal these processes. Furthermore, it remains unclear how relationships between RARs and brain health play out time, what leads to RAR disruption, and whether modifying RARs at different stages in disease pathogenesis could prevent dementia. Available evidence supports the idea of promoting healthy RARs to prevent dementia, but doing so may require intervening early in disease pathogenesis and using multiple approaches (e.g., scheduling activity, bright light, and sleep interventions).

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/ **Supplementary Material**.

AUTHOR CONTRIBUTIONS

SS and RK conceptualized the project and literature search. SS, CC, and SG performed the search and tabulated the results. SS drafted the manuscript, and all authors critically revised the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2019.00778/full#supplementary-material

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REVIEW
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A Brief Review of Paradigm Shifts in Prevention of Alzheimer's Disease: From Cognitive Reserve to Precision Medicine

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Alzheimer's disease (AD) and related dementias can be an enormous economic burden for taxpayers, patients, their families, medical systems, and society as a whole. Since disease-modifying treatments have failed, several studies have instead focused on a paradigm shift for preventing and treating AD. A higher cognitive reserve (e.g., greater education, occupational attainment, or more leisure activities) is associated with protection against disease-related cognitive decline. Precision medicine aims to optimize the effectiveness of disease prevention and treatment by considering specific biological components of individuals. We suggest that research into cognitive reserve and precision medicine could be a key to overcoming the limitations of traditional approaches to the prevention and treatment of AD.

Keywords: Alzheimer's disease, cognitive reserve, precision medicine, prevention, aging, biomarkers

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INTRODUCTION

Dementia is a broad spectrum of neurodegenerative diseases that are characterized by cognitive decline and have a negative impact on daily functions without an acute change of consciousness. In particular, Alzheimer's disease (AD) refers to a type of slowly progressive dementia that is associated with significant memory dysfunction during the early stages of the pathology. AD and related dementias can be an enormous economic burden for taxpayers, patients, their families, medical systems, and society as a whole (1). According to recent estimates, the total direct medical expenditures associated with AD and related dementias in the United States will increase from $236 billion in 2016 to more than $1 trillion in 2050 due to projected increases in the elderly population (1, 2).

Since a German psychiatrist and neuropathologist, Dr. Alois Alzheimer, introduced the case of memory loss, disorientation, and hallucinations in the patient Auguste D., many follow-up studies have been performed to investigate the pathophysiology of AD. Despite continuing debate, the Aβ hypothesis and tau pathology have become the dominant models of AD pathogenesis in the fields of psychiatry, neurology, and neuroscience. Glenner and colleagues suggested that Aβ, a special amyloid protein accumulated in the brain, could be causative of AD (3). In several studies for more than three decades, researchers have consistently accumulated data and have become increasingly supportive of this theory (4–9). Most researchers have naturally paid attention to Aβ pathology as a promising treatment target for AD. However, this expectation has encountered numerous

failures of phase-III clinical trials that aimed to modify AD such as by slowing down or stopping its progression. Consequently, researchers are currently more interested in tau pathology as an alternative therapy target, but more study is needed to determine whether tau pathology could be a major target for disease-modifying treatment.

Although the Aβ hypothesis and tau pathology are important to AD pathology, it could be realistically and pragmatically necessary to discuss the various paradigm shifts to overcome the failures in developing disease-modifying treatments for AD. The literature reviewed below is focused on the value of inquiries on cognitive reserve (CR) and precision medicine (PM) for AD as preventive measures. The attention paid to CR is due to the observation of interindividual variability in cognitive decline without parallel changes to neuropathological processes. In this context, researchers have considered that other factors may affect the path of cognitive function in not yet demented individuals. The concept of PM, also called "personalized medicine" or "individualized medicine," is rapidly advancing in medical, clinical, and research settings (10). A new paradigm of PM aims to optimize the effectiveness of disease prevention and treatment by taking account of the specific biological compositions of individuals (10, 11).

COGNITIVE RESERVE

Sister Bernadette (not her real name), a Catholic nun living in the School Sisters of Notre Dame convent, showed no decline in cognitive function and activities of daily life. After her death due to a massive heart attack, an autopsy showed a great spread of AD pathology in her brain. The discordance between the degree of brain pathology and the clinical manifestation in her lifetime suggested that her neocortex was resistant and resilient to Alzheimer's-related neurodegeneration (12). Katzman and colleagues reported cases of elderly people who had normal cognitive function but were found to have advanced AD pathology in their brains at the time of death (13). Therefore, researchers needed a concept that could explain individual variabilities in cognitive function, activities of daily life, or clinical decline in a manner relative to aging and neurodegenerative disease.

Definition of CR, Brain Reserve, and Brain Maintenance

Cognitive Reserve

Although several studies have defined CRs and related concepts, the terms have been used in conjunction with a common denominator, but in different ways in published studies. A recent whitepaper published by the Reserve, Resilience and Protective Factors PIA Empirical Definitions and Conceptual Frameworks Workgroup defined CR as the adaptability of cognitive processes related to differential susceptibility of cognitive abilities or day-to-day function to brain aging, pathology, or insult (14). This concept concludes that the diversity of an individual's CR is the result of the interaction between life exposures and genetic factors. Therefore, individuals exhibit differences in adaptation to brain diseases and aging according to their own CR.

Brain Reserve

The whitepaper (14) demarcated the concept of a brain reserve, which is distinct from CR. Brain reserve refers to individual variation in the structural characteristics of the brain at any point in time, rather than a macroscopic construct that is not related to verifiable neurobiology or the mechanisms of finer particles. In this context, macroscopic structural characteristics such as total brain volume, volume of a specific neural substrate, or white matter integrity could influence the threshold of the emergence of cognitive impairment.

Brain Maintenance

Brain maintenance is conceptually and temporally subdivided from CR, although it is highly relevant to brain reserve. Brain maintenance refers to a decline in the development of age-related changes in the brain and protection against the effects of neuropathology (14). Therefore, brain maintenance influences an individual's cognitive function for their lifespan through an interaction between lifetime experiences and genetic factors. While brain reserve includes the neurobiological resources of a specific point in time, brain maintenance has the potential to maintain or enhance brain function over time (14).

Evidence for CR

Most researchers seem to agree that CR is an appropriate concept for describing the interaction between genetic factors and lifetime experiences and consequent phenotypes. Although the definitions of CR are becoming clearer as several studies progress, a number of studies still tend to use the CR definition within various boundaries. The authors will follow the definition of the whitepaper (14) but use a broader definition of concepts when describing evidence for CR.

Education, Occupation, Leisure Activities

Individuals with less education were associated with a higher risk of developing dementia compared to those with more education (15, 16). Indeed, education has been widely accepted as one of the proxies of CR. Several studies have presented biological evidence that could support the epidemiologic evidence for CR. Higher education was associated with reduced white matter integrity in the medial temporal lobe areas and association fiber tracts when controlled for age, gender, and dementia severity (17). Higher education is a protective factor against AD and is associated with lower plasma tau levels in patients (18). Through analysis with brain magnetic resonance imaging, the magnitude of the contribution of education is seen as greater than the negative impact of either a neuropathological burden such as white matter hyperintensities or hippocampal atrophy (19).

Occupational attainment acts as a proxy for CR and is associated with a lower risk of AD and a delayed onset of symptoms (20, 21). Moreover, occupational complexity may grant resilience against the negative effects of neuropathology on cognition in people at risk for AD (22). In a fluorodeoxyglucose (^{18}F) positron emission tomography (FDG-PET) brain imaging study, Garibotto and colleagues showed an inverse correlation between a reserve index, accounting for educational/

occupational level, and metabolism in the posterior cingulate cortex and precuneus in both APOE ε4 carriers and noncarriers. Their results suggested that education and occupation act as proxies for a reserve in epsilon4 carriers, compensating for an unfavorable genetic background (23). However, not all studies have found these relationships; Myung and colleagues found that the protective effect of high occupational attainment against cognitive decline disappeared in the MCI stage (24).

Participation in leisure activities, known to have a protective effect against developing AD, is one of the proxies for CR (25–27). Among leisure activities such as walking for pleasure, visiting friends, reading, playing games, religious activity, physical conditioning, and so on, social, cognitive, and physical leisure activities appear to have protective effects against the risk of dementia (20, 28, 29). Physical activity, particularly aerobic exercise, is protective against age-related gray and white matter loss. Cognitive training of executive functions is associated with an improvement in prefrontal network efficiency (30).

The potential mechanisms of CR are not yet elucidated. However, Engeroff and colleagues showed that regular physical activity might be beneficial for preserving brain plasticity age and was positively associated with brain-derived neurotrophic factor (BDNF) levels in healthy elderly people (31). Ward and colleagues showed that BDNF played an important role in the capacity for building or accessing CR. A significant positive relationship between CR and executive function was identified in BDNF Val homozygotes but was not evident in BDNF Met carriers (32).

Other Proxies for CR

Premorbid intellectual function could account for discrepancies in clinical status between MCI and AD patients that have similar levels of neuropathology and comorbid medical diseases (33). Minicolumn thinning of neurons in the cerebral cortex, which is related to cognitive ability, occurs in old age. AD patients with a higher IQ were older and had less pathology at the time of death, which provides the neural evidence for the CR hypotheses (34).

While the results of the prospective cohort study showed that there was no association between bilingualism and the delayed onset of AD, retrospective studies have claimed the opposite (35). However, Perani and colleagues studied brain metabolism, a direct index of synaptic function and density, and neural connectivity to shed light on the effects of bilingualism in AD (36). They observed that bilingual individuals were 5 years older than their monolingual peers on average. Through the metabolic connectivity analyses, they supported the neuroprotective effect of bilingualism by showing an increased connectivity in the executive control and default mode networks in bilingual, compared with monolingual, AD patients. Furthermore, the degree of lifelong bilingualism was significantly correlated to functional modulations in crucial neural networks, suggesting both neural reserve and compensatory mechanisms. They suggested that lifelong bilingualism acts as a powerful CR proxy in dementia and exerts neuroprotective effects against neurodegeneration. However, further studies appear to be needed to assess if bilingualism can be used as a proxy for CR.

Other studies have suggested that learning a foreign language could enhance an individual's CR. Bubbico and colleagues showed that learning a foreign language significantly improved global cognition, along with increased functional connectivity in the right inferior frontal gyrus, right superior frontal gyrus, and left superior parietal lobule in healthy elderly subjects (37). They suggested that language learning practice could be another important way to enhance and reorganize brain networks.

In the last few years, several large studies investigated lifestyle-related risk factors in people at risk for dementia. The FINGER (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) study (38) showed that multidomain intervention had beneficial effects on cognitive functions, especially in executive functioning and processing speed. The control group only received regular health advice, whereas the intervention group received dietary counselling, physical exercise and cognitive training, and vascular risk factor monitoring. These results are in line with the concept of CR described in this paper. Other large studies have shown variable results. The PreDIVA (Prevention of Dementia by Intensive Vascular Care) (39) contradicted the FINGER study by suggesting that multidomain cardiovascular intervention had no positive effect on dementia. In addition, the MAPT (Multidomain Alzheimer Preventive Trial) (40) study included a multidomain intervention group (including integrated cognitive training, physical activity, dietary advice, preventive consultations, and intake of omega-3 polyunsaturated fatty acids (PUFAs)) versus an only multidomain intervention group versus an only omega-3 PUFAs group versus a placebo capsule group. The results presented no significant difference between any of the three intervention groups compared with the placebo control group. Nevertheless, the MAPT study also presented meaningful results in that the multidomain intervention group showed less cognitive decline than groups without multidomain intervention.

PRECISION MEDICINE

PM is a medical approach that recommends preventing and treating diseases based on the unique genetic makeup and lifestyle of an individual. Conceptually and clinically, PM for AD is closely related to CR. The concept of CR includes a heterogeneous phenotype and takes into account that the same pathological findings might not result in the same clinical symptoms. The concept of PM also allows that individuals could be diagnosed with the same disease even if they have different biological makeups, such as genetic, epigenetic, biomarker, phenotypic, lifestyle, and psychosocial characteristics. While the traditional approach to neurodegenerative diseases focuses on brain proteinopathies as homogenous clinicopathological or clinicobiological entities, the new paradigm of PM aims to optimize the effectiveness of disease prevention and treatment by taking into account biological components that could influence the heterogeneity of a disease by considering specific biological factors (11). Up until now, clinicians have usually used a universal treatment strategy by applying the same intervention to a particular disease. While this treatment strategy, the so-called "one-size-fits-all" method, could be very successful for some

patients, it may not be effective for others. PM is an innovative approach that embraces individual differences in the genetics, environments, and lifestyles of each individual.

Genetics in PM

The extensive complexity of the genetics of AD is one of the main causes of clinical and pathological diversity. Since the heritability of AD is estimated to be from 58% to 79% (41, 42), a requisite for prevention and early intervention is to qualitatively and quantitatively obtain a large amount of information about the extensively complex genetic variants in AD. Many studies, including large-scale genome-wide association studies (GWAS), the first round of whole exome sequencing (WES), and whole genome sequencing (WGS), investigated susceptibility loci that were associated with molecular pathways in AD, including the amyloid pathway, immune system, lipid metabolism, and hippocampal synaptic function (10).

Mutations in the amyloid precursor protein (APP, located at chromosome region 21q21.2) (43), presenilin 1, (PSEN1, located at 14q24.3) (44), and presenilin 2 (PSEN2, located at 1q42.13) (45) are well known to cause early onset AD. These genetic mutations have a strong penetration effect on AD pathology.

APOE is the most notable lipoprotein in AD research and is divided into three forms, apoE2, apoE3, and apoE4. The risk of AD is two to three times higher in people with an APOE ε4 allele and about 12 times higher in people with two APOE ε4 alleles (46, 47). The APOE ε4 allele is associated with higher deposits of Aβ in the brain (48). In addition, the APOE genotype may influence the topography of regional atrophy and cortical thinning in AD. Cortical thickness in AD patients was significantly lower in the medial temporal and left parietal regions of the APOE ε4 allele group, and in the medial temporal lobe of the group with two APOE ε4 alleles, compared with controls (49).

Despite significant progress in identifying the underlying genetics, studies have only illuminated the genetic factors underlying the pathophysiology of neurodegenerative diseases. Further genetic studies in the future are expected to clarify the pathogenic mechanisms of AD that could be used for preventing AD and treating AD patients. Since a genetic variant in an individual might contribute a small effect to neuropathology in AD, and a qualitative and quantitative aggregate of susceptibility genes could determine the progress of neurodegeneration, it may be useful to calculate the genetic burden of individuals with a polygenic scoring system. Furthermore, many follow-up studies and expert consensus will be necessary to determine the qualitative and quantitative weights of various genetic information.

Neuroimaging Data for PM

In their structural MRI research, Tondelli and colleagues reported that the reduced brain volume of the medial temporal lobe such as the hippocampus, amygdala, and entorhinal cortex in cognitively intact individuals is a predictive factor of later cognitive decline (50).

FDG-PET is a nuclear medicine functional imaging technique that is used to observe the cerebral metabolic rate of glucose (CMRglu). Several FDG-PET studies have shown that CMRglu reduction can occur decades before the onset of AD (51). Therefore, individuals with normal cognition have the potential to develop AD if CMRglu reduction is consistently observed in a particular area such as the parieto-temporal areas, posterior cingulate cortex, and medial temporal lobe (51, 52).

In an amyloid PET study, Petersen and colleagues showed that amyloid load *in vivo* was independently associated with a future decline in cognition (53). Elevated amyloid levels were associated with worse cognition, imaging biomarkers, greater clinical decline, and neurodegeneration (54). With ^{18}F-flortaucipir and ^{18}F-florbetaben positron emission tomography scans, Cho and colleague presented a mutually influential relationship between tau and Aβ deposition. Therefore, investigations of tau and Aβ deposition with PET scans still need to consider the mutual influence between tau and amyloid pathologies.

Blood Biomarkers

Cerebrospinal fluid biomarker signatures are recognized as useful tools for diagnosing presymptomatic, prodromal, typical, and atypical forms of AD (55). Olsson and colleagues showed that t-tau, P-tau, Aβ42, and NFL levels in the CSF should be used in clinical practice and clinical research for diagnostic purposes (56). However, more research is needed on blood biomarkers that are minimally invasive and relatively inexpensive, unlike the process of obtaining CSF.

Studies of blood biomarkers, however, do not show consistent results for the diagnosis of presymptomatic, MCI, and AD patients. The present limitations to the development of blood biomarkers is that brain-specific proteins must cross the blood-brain barrier and that they are observed at lower concentrations in the blood than in CSF. Nonetheless, high plasma tau was associated with cognitive impairment, brain atrophy, and brain hypometabolism in an Alzheimer's Disease Neuroimaging Initiative (ADNI) (57). Higher plasma tau was related to lower scores in global cognition, memory, and attention tests and to reduce cortical thickness in AD neural substrates, after adjustments for age, sex, education, and APOE genotype; however, tau levels in MCI were not statistically significantly higher than in controls (58).

Several studies have investigated plasma neurofilament light (NFL) as a blood biomarker of neurodegenerative disease. Higher plasma NFL was observed in patients with MCI and AD in comparison with controls. In addition, higher plasma NFL was associated with Aβ pathology in MCI and AD patients. Thus, higher plasma NFL is correlated with poor cognition and atrophy in AD signature regions and with brain hypometabolism (59).

DISCUSSION

CR for the Prevention of AD

CR is a widely used term among psychiatrists, neurologist, and neuroscientists who study neurodegenerative diseases. In the psychiatric field, especially regarding posttraumatic stress disorder, adjustment disorder, and depression, resilience is

defined as an individual's ability to adapt to adverse events in life and recover to prestress adaptation levels. In a similar vein, brain resilience is defined as the ability to cope with AD pathology and is measured by a better-than-expected cognitive performance, brain structure, or brain function, despite some level of AD pathology (28). Just as the neurobiology of resilience is under investigation, the neurobiology of CR has also greatly advanced. Indeed, the investigation of genetics, neuroimaging, and epidemiology for CR could be compared to the development of shields that defend against the pathology of neurodegenerative diseases. Stern and colleagues summarized all of the studies that calculated the protective effects of higher CR and found that it reduced the risk of developing dementia by 46% (20). The studies mentioned above suggest a significant mechanism of higher CR for the preservation of cognitive function, which is associated with protection against disease-related cognitive decline. This paper refers to several proxies for CR, such as education, occupational attainment, leisure activities, premorbid intellectual function, and bilingualism. Among the proxies, some are capable of increasing CR by promoting educational and occupational opportunities through individual effort and policy-based approaches. Public authorities must promote many education and occupational attainment opportunities for young people. These policies have to encompass lifelong education (home schooling, adult education, job training, learning a foreign language, etc.) and social, physical, and cognitive leisure activities for the elderly.

There are also interesting studies in a different context. Once symptoms of dementia appear, individuals with a higher reserve (e.g., greater education, occupational attainment, or more leisure activities) are hypothesized to be associated with a more rapid cognitive decline and died sooner than those with lower reserves (60–63). Since individuals with higher CR could be resistant and resilient to more neuropathology, higher levels of CR are also hypothesized to be associated with a faster rate of cognitive decline after the neuropathology passes over a certain threshold and emerges as cognitive decline (60). Although individuals with higher levels of CR are resistant and resilient enough to withstand advanced neuropathology, after crossing the critical threshold, they have little brain reserves left to endure neurodegeneration. Nevertheless, it cannot be worthless to elevate CR levels. Some estimates indicate that delaying the onset of dementia by only 5 years would result in a 50% reduction in dementia prevalence (64).

PM for the Prevention of AD

Conceptually, PM is a model that supports integrated research and clinical approaches. Hampel and colleagues presented the framework of the Alzheimer Precision Medicine Initiative (APMI) (65). The contents of this model are as follows: (1) collection of big and deep data consisting of biomolecular, imaging, literature, and clinical data through research and clinical practice, (2) processing heterogeneous multidimensional big and deep data through standardization, management, integration, and analysis, and (3) developing an "actionable" model that predicts the trajectory of individualized, patient-centric detection, or treatment within a P4 (predictive, preventive, personalized, and participatory) implementation strategy. An integrated approach such as this model could be a valuable paradigm shift for researchers and clinicians trying to overcome the "one-size-fits-all" treatment that has now revealed its limitations. In the field of oncology, PM seems to have made significant progress in the standard of care by incorporating genetic information and biomarkers. However, PM for AD might need to be investigated from a different and more complex point of view than the field of oncology. This paper has discussed CR as a protective factor against the pathology of neurodegenerative diseases. The authors suggest that researchers and clinicians should consider the CR of an individual at risk of AD whenever they use PM to establish a prevention and treatment plan. In other words, although risk assessment with PM may be the same between individuals, the patient with a lower CR may need more aggressive prevention and treatment plans.

The authors suggest that a system of integrating and interpreting results from research with enormous biological implications must be established in order to bring about a successful paradigm shift from traditional medicine to PM. In this context, data science, which is a field of study dedicated to the principled extraction of knowledge from complex data (66), will be widely applied to the field of PM. Data science already plays a significant role in many human activities and in the world of science. This field is supported by the remarkable and super high-speed development of artificial intelligence and machine learning, despite positive and negative opinions about its development. The development of traditional research areas such as genetics, neuroimaging and biomarkers, and the innovation of data science, which encompasses and incorporates research from these areas, will certainly make a significant contribution to the personalization of prevention and treatment strategies using PM.

CONCLUSIONS

We suggest that research into CR and PM could be a key to overcoming the limitations of traditional approaches in the prevention and treatment of AD.

AUTHOR CONTRIBUTIONS

CH was responsible for conception and design as well as initial drafting of the manuscript. All authors (CH and CL) were responsible for revising the manuscript critically for important intellectual content of the version of the manuscript to be published. All authors read and approved the final manuscript.

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Neuroprotective Effect of Resveratrol via Activation of Sirt1 Signaling in a Rat Model of Combined Diabetes and Alzheimer's Disease

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Background: Alzheimer's disease (AD) and diabetes mellitus (DM) often coexist in patients because having one of these conditions increases risk for the other. These two diseases share several pathophysiological mechanisms, such as specific inflammatory signaling pathways, oxidative stress, and cell apoptosis. It is still unclear exactly which mechanisms associated with DM are responsible for increased AD risk. Studies have found that even transient elevation of brain Aβ levels can allow T2DM to slightly disrupt the neural milieu in a way that encourages pathologies associated with the onset of memory deficits and AD. A recent study argues that a potential common pathogenetic mechanism underlying both DM and AD is evidenced by the cooccurrence of amyloid brain legions and deposits containing both tau and Aβ in pancreatic β cells. Given these links, an investigation detailing disease mechanisms as well as treatment options for patients with cooccurring DM and AD is urgently needed. The biological effects of resveratrol relevant to DM and AD treatment include its abilities to modulate oxidative stress and reduce inflammation. A rat model of DM and concomitant AD was created for this study using intraperitoneal injection of streptozotocin and hippocampal injection of Aβ1–40 to characterize resveratrol's potential protective action.

Results: Resveratrol significantly increased the Sirt1 expression, inhibited the memory impairment, the increased acetylcholinesterase, malondialdehyde, interleukin-1β and interleukin 6 levels, and the decreased levels of choline acetyltransferase (ChAT), superoxide dismutase (SOD), and glutathione in this rat model of diabetes and concomitant AD. The Sirt 1 inhibitor EX527 partially reversed the effects of resveratrol.

Conclusion: This study suggests that resveratrol may have a neuroprotective action through activation of Sirt1 signaling in diabetes and AD with concurrent onset.

Keywords: resveratrol, Alzheimer's disease, diabetes mellitus, oxidative stress, Aβ1-40, neuroprotective, Sirt1, resteratrol

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Abbreviations: Aβ, amyloid β-protein; AchE, acetylcholinesterase; AD, Alzheimer's disease; BCA, bicinchoninic acid; ChAT, choline acetyltransferase; DM, diabetes mellitus; DMSO, dimethyl sulfoxide; DTNB, 5,5-dithiobis(2-nitrobenzoic acid); ELISA, enzyme-linked immunosorbent assay; GSH, glutathione; MDA, malondialdehyde; MWM, Morris water maze; NBT, nitroblue tetrazolium; NF-κB, nuclear factor kappa B; PVDF, polyvinylidene difluoride; SOD, superoxide dismutase; STZ, Streptozotocin; T2DM, type 2 diabetes mellitus.

INTRODUCTION

Alzheimer's disease (AD) is a disorder involving selective central nervous system degeneration, including neuron loss and gradual development of amyloid plaques and neurofibrillary tangles (Iwatsubo, 2000). At present, the cause of AD remains unclear, although aberrant Aβ production or clearance from the brain is currently considered the most probable cause (Pereira et al., 2004). The deleterious effect of Aβ involves oxidative stress (Butterfield et al., 2013), inflammatory responses, neuronal apoptosis, etc. (Agostinho et al., 2010). Owing to the recent rapid growth of older populations, the incidence of AD has naturally increased, imposing a substantial cost on the economy and impacting the well-being of families and society at large. The 2019 Alzheimer's Association Report states that Americans currently living with AD number about 5.8 million, and by 2050, the prevalence of AD will reach more than 13.8 million cases in the United States alone. In 2019, an estimated $290 billion will be spent providing health services, long-term care including assistance with daily living, and hospice care to dementia patients aged 65 or older (Alzheimer's Association, 2019).

Diabetes mellitus (DM) is a disease of disturbed metabolism wherein aberrant insulin secretion and/or action leads to hyperglycemia (Marklova, 2001). Modern improvements in living coupled with decreased activity levels have increased the prevalence of both obesity and DM. A retrospective cohort study reported an increase in the rate of type 2 diabetes mellitus (T2DM) from 2.39% in 2000 to 5.32% in 2013 (Sharma et al., 2016). Approximately 415 million people worldwide had DM in 2015 with 90% of the cases being T2DM (Shi and Hu, 2014). In 2017, approximately 451 million people worldwide between the ages of 18 and 99 years suffered from diabetes, and by 2045, prevalence will climb to approximately 693 million cases. In 2017 alone, approximately USD 850 billion was spent worldwide on diabetes care (Cho et al., 2018).

Both AD and DM are associated with aging, and because onset of either disease increases risk for the other, concurrent onset is common. A longitudinal population-based study has revealed high risk for AD in DM patients (Biessels et al., 2005). Dementia is two to three times more common in patients with DM than in patients without DM (Sridhar et al., 2015). However, it is still unclear exactly which mechanisms associated with DM are responsible for increased AD risk. Su et al. (2019) found that even transient elevation of brain Aβ levels can allow T2DM to slightly disrupt the neural milieu in a way that encourages pathologies associated with the onset of memory deficits and AD. Martinez-Valbuena et al. (2019) argue that a potential common pathogenetic mechanism underlying both DM and AD is evidenced by the co-occurrence of amyloid brain lesions and deposits containing both tau and Aβ in pancreatic β cells. Therefore, an investigation detailing disease mechanisms as well as treatment options for patients with co-occurring DM and AD is urgently needed.

The natural phenol resveratrol occurs in several common foods, most notably in grapes. Research has cataloged its antioxidant, anti-inflammatory (Wood et al., 2010), and anti-carcinogenic effects (Athar et al., 2009). Sirt1, a homolog of Sirt2, is a highly conserved NAD+-dependent deacetylase. Sirt1 operates via histone/non-histone deacetylase activity and helps to regulate many cell processes, such as DNA damage, apoptosis, transcription, and metabolism through a reversible acetylation–deacetylation reaction (Paraiso et al., 2013). In addition, Sirt1 is also involved in caloric restriction and aging (Tissenbaum and Guarente, 2001). Studies have suggested that resveratrol is a Sirt1 activator (Pallas et al., 2009; Wu et al., 2011). However, studies evaluating the effect of resveratrol on the pathophysiology of co-occurring DM and AD are still lacking. In this study, we used intraperitoneal injections of streptozotocin with hippocampal injections of Aβ1–40 to model diabetes with co-occurring AD in rats to examine resveratrol's potential to alter the pathophysiology of DM and AD.

MATERIALS AND METHODS

Reagents

Aβ1–40 (Sigma-Aldrich, St Louis, MO, United States) was dissolved (10 μg/μl) in sterile saline solution at 37°C for at least 7 days. After dissolution of the Sirt1 inhibitor EX527 (Tocris Bioscience, Bristol, United Kingdom) in dimethyl sulfoxide (DMSO), the resultant mixture was diluted with saline to reach the appropriate concentration (final DMSO concentration <2%). Streptozotocin (STZ) (Sigma-Aldrich, St. Louis, MO, United States) was dissolved in 0.1 M citrate buffer (pH 4.5). Resveratrol (Sigma-Aldrich, St. Louis, MO, United States) was dissolved in sterile saline. Nanjing Jiancheng Bioengineering Institute (Nanjing, China) supplied the kits for measuring AchE and ChAT activity. Thermo Fisher Scientific (Shanghai, China) supplied the MDA and SOD measurement kits. Cayman Chemical (Ann Arbor, MI, United States) supplied the GSH assay kit. Nanjing KeyGEN Biotech. Co., Ltd. (Nanjing, China), supplied the interleukin (IL)-1β and IL-6 enzyme-linked immunosorbent assay (ELISA) kits. Sigma-Aldrich (Beijing, China) supplied the mouse monoclonal anti-Sirt1 antibody and the mouse monoclonal antibeta-actin antibody. Pierce Biotechnology (Rockford, IL, United States) supplied the bicinchoninic acid (BCA) assay. Amersham (United Kingdom) supplied the ECL advance Western blotting detection kit. All kits were purchased.

Animals

Wistar rats (Henan Laboratory Animal Research Center, Zhengzhou, China) of approximately 8–10 months of age (250–300 g) were used in this study and were held in conventional cages with *ad libitum* feeding, a constant ambient temperature of 22 ± 2°C, humidity of 55 ± 5%, and a light–dark cycle of 12 h (7:00–19:00). All aspects of this research have complied with the Guideline on the Humane Treatment of Laboratory Animals instituted by the Ministry of Science and Technology of the People's Republic of China. The Committee on Ethics in Life Sciences of Zhengzhou University approved this study.

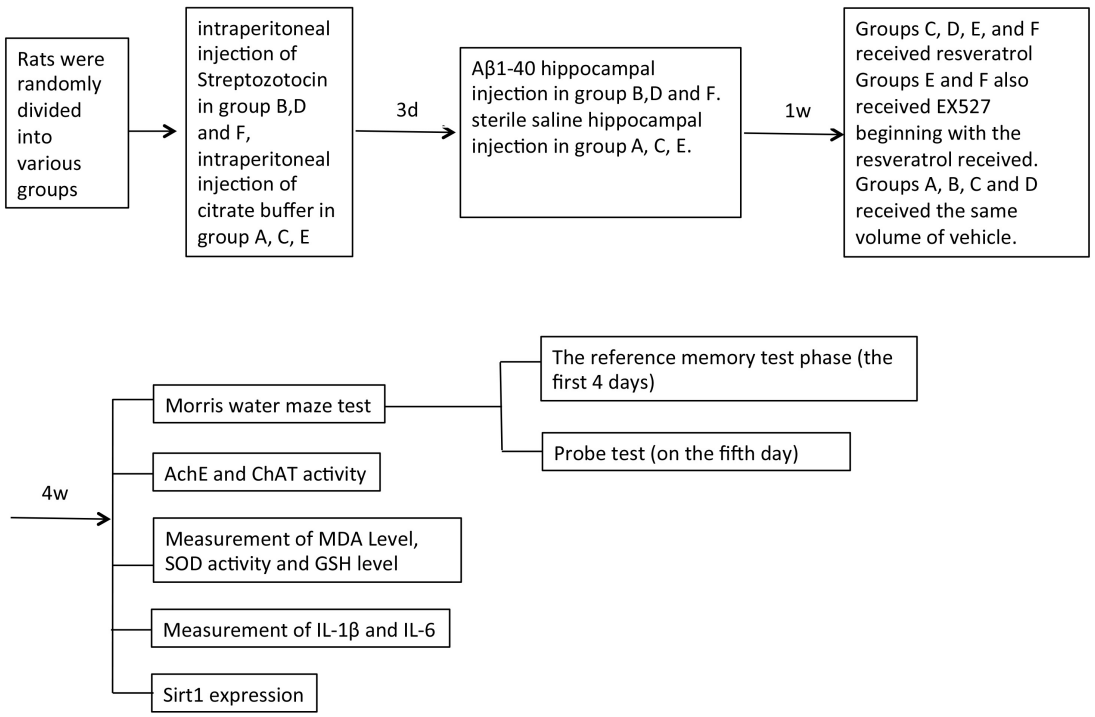

FIGURE 1 | Experiment flow chart.

Experimental Design

Groups (n = 21) were formed by random assignment of rats as follows: normal control group to receive sham operation (group A), group treated to establish a concurrent diabetes and AD disease model (group B), resveratrol control group to receive sham operation with resveratrol (group C), model rats receiving treatment with resveratrol (group D), resveratrol and EX527 (Sirt1 inhibitor) control group to receive sham operation with resveratrol and EX527 (group E), and model rats receiving treatment with both resveratrol and EX527 (group F). The concurrent diabetes and AD disease model was established by intraperitoneal injection of streptozotocin and subsequent hippocampal injection of Aβ1–40 in groups B, D, and F only. Only citrate buffer and sterile saline with neither streptozotocin nor Aβ1–40 were injected in groups A, C, and E. Resveratrol (25 mg/kg) was orally administered to groups C–F daily from 1 to 5 weeks postoperation. One 5 mg/kg dose of EX527 was also administered to groups E and F through intraperitoneal injection every 2 days (beginning concurrently with the first resveratrol dose) for a total of four doses. An equivalent volume of vehicle was administered to groups A–D (**Figure 1**).

Diabetes and Alzheimer's Disease Rat Model

A single 55 mg/kg dose of dissolved streptozotocin (in 0.1 M citrate buffer, pH 4.5) administered via intraperitoneal injection was used to induce experimental DM in rats. Three days postinjection, blood samples were collected from fasting rats (12 h overnight) by tail vein sampling, and a glucose meter with test strips (Ascensia Entrust, Bayer Polychem Ltd., Thane, India) was used to determine blood glucose level. A fasting blood glucose level over 16.7 mmol/dl was taken to indicate diabetes, and only rats exceeding the cutoff were retained for subsequent experiments. Ten percent chloral hydrate (0.4 ml/100 g; Sigma-Aldrich, St. Louis, MO, United States) administered via intraperitoneal injection was used to anesthetize diabetic rats. Atropine sulfate (0.1 mg/kg, i.m., Polfa Warszawa, Poland) was also given to avoid intraoperative respiratory depression and distress in rats. Stereotaxic surgical technique including a frame (Stoelting Co., United States) was used to localize the hippocampus of anesthetized rats. After scalp incision, a mini-drill was used to drill through the cranium to a depth of 2.8 mm. The CA1 region of the hippocampus was localized 2.0 mm lateral and −3.0 mm anterior to the posterior fontanel, in accordance with the Paxinos and Watson rat atlas. One microliter of Aβ1–40 was gradually injected over a 10-min period bilaterally into each hippocampus using a 26-gauge needle connected to a microsyringe. Following injection, the needle was slowly removed. Identical surgical procedure was followed for control rats, with the exception of injection of 1 μl of sterile saline instead of Aβ1–40.

Morris Water Maze

The MWM (Chinese Academy of Medical Sciences) was used to assess spatial learning and memory function at 5 weeks

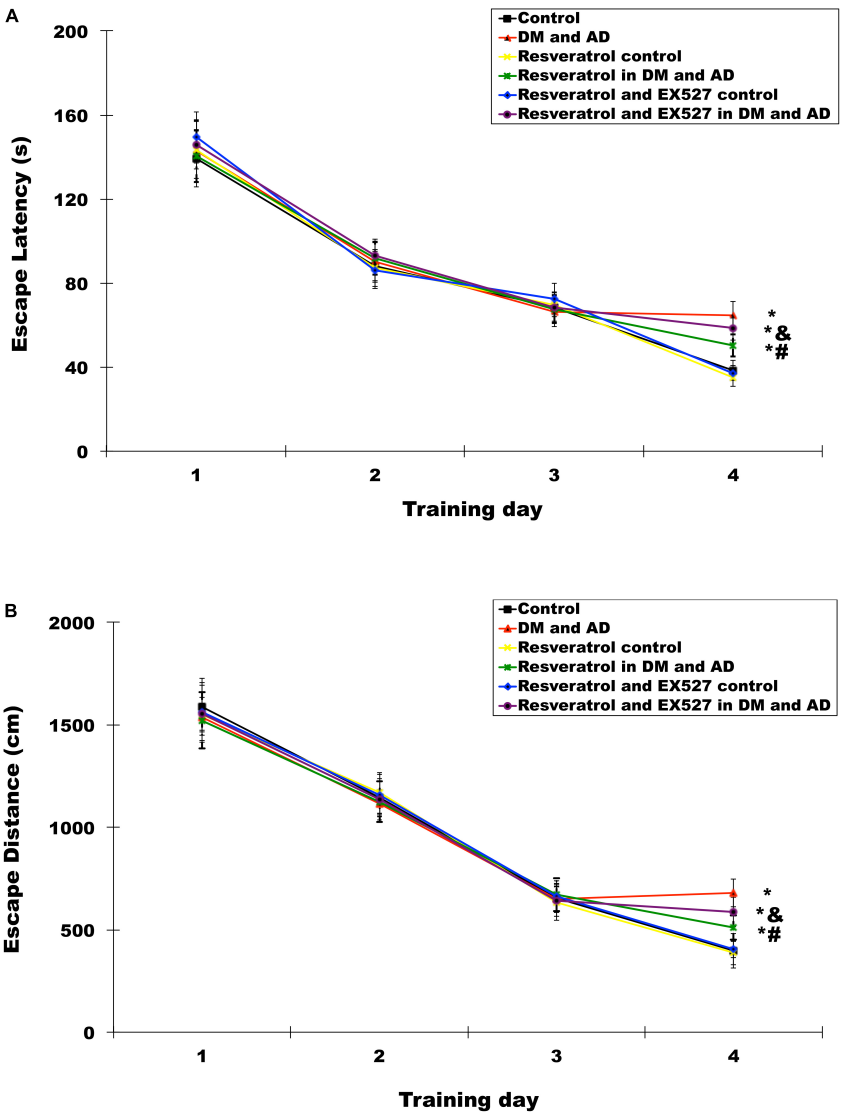

FIGURE 2 | Effects of resveratrol on memory impairment in Diabetes mellitus (DM) and Alzheimer's disease (AD) rats. The Morris water maze (MWM) was used to test rats' memories by measuring escape latency **(A)** and escape distances **(B)**. Three independent experiments were performed. Data are expressed as mean ±SD; $^{*}P < 0.05$ vs. control group, $^{\#}P < 0.05$ vs. DM and AD group, $^{\&}P < 0.05$ vs. resveratrol in DM and AD group.

postoperation as has been described in previous studies (Ma et al., 2013; Sun et al., 2014). The design of the maze included a painted circular pool (120 cm diameter; 30 cm depth) with a hidden platform (9 cm diameter) resting obscured 1.5 cm below the surface. For the test, rats were first trained to seek the submerged platform and exit the pool. Titanium dioxide was used to opacify the water in the pool, and during all training and testing procedures, water temperature was kept at 22°C. The pool was partitioned into four sections: north (target), south (opposite), east (adjacent 1), and west (adjacent 2). A tracking system connected to a computer and equipped with a camera was used to record experiments.

The MWM test was continually performed for 5 days. During the first test phase, rats were trained to develop a reference memory. The first phase required 4 days, during which rats completed four trials per day with a 30- to 40-min interval between trials for a total of 16 trials in the entire phase. Each trial began with the rat being placed in one randomly selected section of the maze facing the wall. Each rat was given 180 s to find and climb atop the hidden platform. The rat was removed 30 s after successfully mounting the platform and placed in a warmed holding cage. If a rat was unsuccessful in finding and climbing the submerged platform within 180 s, then it was shown the path to the platform by the operator's gentle guidance and was left on the platform for a period of 30 s before removal and transfer to the warmed holding cage. The rats' movements were tracked by a camera mounted above the pool. The time necessary for rats to locate and climb the platform (escape latency) as

well as the distance swum (escape distance) were determined using MWM software (Shanghai Jiliang Software Technology Co., Ltd., China) calculations based upon video review. The second phase of testing beginning on the fifth day included a probe test to examine memory maintenance or deficit after platform removal. Rats were initially positioned in one of the sections beside the platform (adjacent 1 or adjacent 2 quadrant) and animals were tracked during a free swimming period of 120 s. Recordings were taken to note time and distance spent in the target quadrant, expressed as a percentage of total time and distance swum. To ensure proper blinding procedure, the probe test was conducted by an administrator with no knowledge of the experimental design.

Sample Preparation and Biochemical Evaluations

Samples were prepared as has been described in prior studies (Ma et al., 2013). Administration of a pentobarbital overdose was used to euthanize rats. After immediate removal of the brains, some (n = 6) were stored at −80°C for future Western blot testing and others (n = 15) were immediately processed by isolating the cerebral cortex and hippocampus on ice. The isolated cortical and hippocampal tissue was homogenized in 0.1 M phosphate-buffered saline (pH 7.4) and spun down at 10,000 × g at 4°C for 15 min in a centrifuge to separate the supernatant and debris. Supernatant protein concentration was quantified via the BCA Protein assay kit (Pierce Biotechnology, Rockford, IL, United States) with BSA used as a standard.

AchE and ChAT Activity

AchE activity was assessed via Ellman's reagent colorimetric assay as has been described in prior papers (Ellman et al., 1961). In brief, 0.75 mM acetylthiocholine and 0.5 mM 5,5-dithiobis(2-nitrobenzoic acid) (DTNB) in 5 mM HEPES buffer (pH 7.5) was used to measure AchE activity at 412 nm. ChAT activity was assessed via the radiochemical method as has been described in previous studies (Sterri and Fonnum, 1980). Following incubation of samples with ^{14}C-labeled acetyl coenzyme A, the reaction was interrupted to measure the resultant quantity of ^{14}C-labeled acetylcholine at 324 nm.

Measurement of Levels of MDA and GSH and SOD Activity

Malondialdehyde level was determined using thiobarbituric acid spectrophotometric colorimetry as has been previously reported (Ma et al., 2013). In brief, MDA, the degraded product of peroxidized lipids, was condensed with thiobarbituric acid resulting in the formation of a red product that displayed a maximum absorption peak at 532 nm, which was measured using the SP-75 ultraviolet spectrophotometer (Shanghai Spectrum, Shanghai, China). Activity of SOD was determined via an assay based upon SOD's ability to inhibit the photoreduction of nitroblue tetrazolium (NBT) by the superoxide anion radical resulting from the reaction of xanthine and xanthine oxidase. SOD was measured using nitrite spectrophotometry as has been previously reported (Ma et al., 2013). The enzymatic recycling method based on DTNB and glutathione reductase was utilized to quantify glutathione (GSH) level spectrophotometrically, as has been previously reported (Ma et al., 2013).

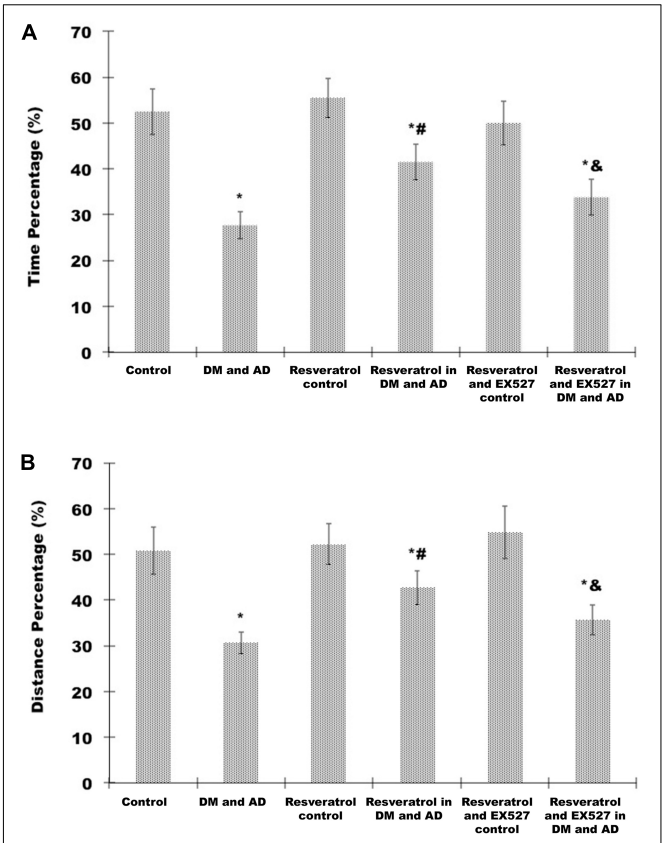

FIGURE 3 | Effects of resveratrol on memory impairment in DM and AD rats. A probe test was used to analyze maintenance of memory in the MWM by measuring the percentage of time spent **(A)** and distance swum **(B)** in the target quadrant. Three independent experiments were performed. Data are expressed as mean ±SD. $^{*}P < 0.05$ vs. control group, $^{\#}P < 0.05$ vs. DM and AD group, $^{\&}P < 0.05$ vs. resveratrol in DM and AD group.

Quantification of IL-1β and IL-6

IL-1β and IL-6 levels were detected using ELISA kits following the manufacture's protocol. A SpectraMax M2 spectrometer (Molecular Devices, Sunnyvale, CA, United States) was used to analyze resultant data.

Western Blot

Previously stored brain tissue was homogenized for 30 min using lysis buffer [10 mM Tris, pH 7.4, 100 mM NaCl, 1 mM EDTA, 1 mM EGTA, 1 mM NaF, 20 mM $Na_4P_2O_7$, 2 mM Na_3VO_4, 0.1% sodium dodecyl sulfate, 0.5% sodium deoxycholate, 1% Triton-X 100, 10% glycerol, 1 mM phenylmethylsulfonyl fluoride (made from a 0.3 M stock in DMSO), 60 μg/ml aprotinin, 10 μg/ml leupeptin, 1 μg/ml pepstatin]. The sample was then centrifuged for 20 min at 2,500 × g at a temperature of 4°C to retrieve the supernatant. The BCA assay (Pierce

Biotechnology, Rockford, IL, United States) was used to determine the total concentration of protein in the sample. Western blot testing was performed according to previously described procedure (Sun et al., 2008; Lee et al., 2013). Protein samples (20 μg each) were boiled (100°C) in buffer (Fermentas) for 10 min. Sodium dodecyl sulfate polyacrylamide gel (8–10%) was used to separate the proteins, which were then moved to polyvinylidene difluoride (PVDF) membranes (Bio-Rad, Hercules, CA, United States) via electrotransfer. A solution of 5% non-fat milk in TBST buffer (10 mM Tris–HCl, pH 8.0, 150 mM NaCl, and 0.2% Tween-20) was used to block the membranes by soaking for 1 h at room temperature. Next, membranes were incubated overnight at 4°C with one of two primary antibodies: either a 1:1,000 dilution of Sirt1 antibody (Sigma-Aldrich, Beijing, China) or a 1:5,000 dilution of beta-actin antibody (Sigma-Aldrich, Beijing, China). Following primary incubation, membranes were thoroughly washed two times with TBST and then incubated for 1 h at room temperature with horse horseradish peroxidase secondary antibodies (1:5000 dilution of anti-mouse/rabbit horse horseradish peroxidase). Amersham ECL Advance Western Blotting Detection kit (Amersham, United Kingdom) was used for signal development. Finally, an Axiocam digital microscope camera (ZEISS, Germany) and KS400 image analysis system software (Version 3.0) were used to quantify band intensities via densitometry.

Statistical Analysis

Each test and assay was run in duplicate in three to five separate experimental trials. One-way ANOVA and a two-tailed *t*-test were run using SPSS Statistics 16.0 software (SPSS, Chicago, IL, United States), with $P < 0.05$ being statistically significant. Data are expressed as mean ±standard deviation.

RESULTS

Effects of Resveratrol on Memory Deficits in Rat Model of Diabetes and Alzheimer's Disease

The time needed for rats to find and mount a water maze platform (escape latency) and total swimming distance before escape (escape distance) were measured using the MWM test. For the first 3 days, there was no significant difference in escape latency (**Figure 2A**) ($P > 0.05$) or distance (**Figure 2B**) ($P > 0.05$) for each group. However, by the fourth day, the model group exhibited significantly longer escape latency and escape distance compared to controls ($P < 0.05$). Furthermore, escape latency and distance were significantly shorter in the rats receiving treatment with resveratrol versus model rats ($P < 0.05$) (**Figure 2**). However, escape latency and escape distance in rats treated with both resveratrol and EX527 were significantly longer compared to rats treated with resveratrol alone ($P < 0.05$) (**Figure 2**), indicating that the Sirt1 inhibitor EX527 can partially reverse the effects of resveratrol.

Probe testing showed that swim time (**Figure 3A**) and distance swum (**Figure 3B**) in the target quadrant (expressed as a percentage of total time and distance swum) were significantly shorter in the model group than in the control group ($P < 0.05$). Compared with model rats, percentage of time (**Figure 3A**) and percentage of distance swum (**Figure 3B**) were significantly greater in rats treated with resveratrol ($P < 0.05$) (**Figure 3**). However, the percentage of time (**Figure 3A**) and percentage of distance swum (**Figure 3B**) in rats receiving both resveratrol and EX527 were both significantly less compared to rats receiving only resveratrol ($P<0.05$) (**Figure 3**), indicating the ability of the Sirt1 inhibitor EX527 to partially reverse the effects of resveratrol.

Cortical and Hippocampal Activity of Acetylcholinesterase and Choline Acetyltransferase

As shown in **Table 1**, cortical and hippocampal AchE activity was significantly increased, while ChAT activity was significantly decreased in the brains of rats from the disease model group versus healthy controls ($P < 0.05$). In contrast, a significant decrease in AchE activity and simultaneous significant increase in ChAT activity were observed in the cortex and hippocampus of rats receiving resveratrol treatment versus model rats ($P < 0.05$) (**Table 1**). However, cortical ad hippocampal AchE activity was significantly increased, and ChAT activity was significantly decreased ($P < 0.05$) in the brains of resveratrol- and EX527-treated rats versus the resveratrol-only group ($P < 0.05$) (**Table 1**), indicating the ability of the Sirt1 inhibitor EX527 to partially reverse the effects of resveratrol.

Cortical and Hippocampal Levels of Malondialdehyde and Glutathione and Superoxide Dismutase Activity

As reported in **Table 2**, a significant increase in cortical and hippocampal levels of MDA and concurrent significant decrease in SOD activity and GSH levels were observed in rats from the disease model group relative to healthy controls ($P < 0.05$). A significant decrease in cortical and hippocampal MDA levels and concurrent significant increase in SOD activity and GSH levels were observed ($P < 0.05$) in resveratrol-treated rats relative to model rats ($P < 0.05$, **Table 2**). Finally, a significant increase ($P < 0.05$) (**Table 2**) in cortical and hippocampal levels of MDA and concurrent significant decrease in SOD activity and GSH levels were observed ($P < 0.05$) (**Table 2**) in the resveratrol- and EX527-treated rats versus rats receiving resveratrol alone ($P < 0.05$) (**Table 2**), indicating the ability of the Sirt1 inhibitor EX527 to partially reverse the effects of resveratrol.

Cortical and Hippocampal Levels of IL-1β and IL-6

As shown in **Table 3**, a significant increase in cortical and hippocampal levels of IL-1β and IL-6 was observed in rats from the disease model group versus healthy controls ($P < 0.05$). Conversely, cortical and hippocampal levels of IL-1β and

TABLE 1 | The AchE and ChAT activity in the cortex and hippocampus.

	AchE (U/mg protein)		ChAT (U/mg protein)	
	Cortex	Hippocampus	Cortex	Hippocampus
Control	1.83 ± 0.15	2.76 ± 0.21	365.46 ± 33.46	413.26 ± 37.28
DM and AD	3.96 ± 0.25*	4.77 ± 0.35*	238.13 ± 19.37*	273.35 ± 23.27*
Resveratrol control	1.79 ± 0.28	2.69 ± 0.30	374.67 ± 24.58	421.47 ± 27.69
Resveratrol in DM and AD	2.64 ± 0.22#	3.23 ± 0.31#	312.36 ± 25.29#	347.17 ± 28.71#
Resveratrol and EX527 control	1.85 ± 0.19	2.80 ± 0.24	379.37 ± 27.41	418.35 ± 31.79
Resveratrol and EX527 in DM and AD	3.54 ± 0.31&	3.89 ± 0.32&	273.55 ± 29.85&	315.36 ± 27.97&

*AchE activity was determined by Ellman's colorimetric method and ChAT activity was determined by the radiochemical method. Data are expressed as mean ±SD. *$P < 0.05$ vs. normal control group. #$P < 0.05$ vs. model group. &$P < 0.05$ vs. resveratrol treatment group.*

TABLE 2 | MDA levels, SOD activity, and GSH levels in the cortex and hippocampus.

	MDA levels (nmol/mg protein)		SOD activity (U/mg protein)		GSH levels (nmol/mg protein)	
	Cortex	Hippocampus	Cortex	Hippocampus	Cortex	Hippocampus
Control	14.23 ± 1.3	10.24 ± 0.91	3.56 ± 0.32	4.57 ± 0.39	55.25 ± 5.20	102.97 ± 9.72
DM and AD	22.92 ± 0.25*	18.47 ± 1.13*	1.26 ± 0.11*	2.25 ± 0.24*	34.16 ± 3.31*	74.86 ± 8.61*
Resveratrol control	14.78 ± 1.16	9.98 ± 1.02	3.46 ± 0.31	4.72 ± 0.35	53.27 ± 5.25	104.62 ± 9.63
Resveratrol in DM and AD	17.04 ± 1.43#	13.16 ± 1.23#	2.28 ± 0.23#	3.78 ± 0.31#	46.27 ± 4.21#	91.92 ± 8.74#
Resveratrol and EX527 control	14.49 ± 1.21	10.39 ± 1.16	3.43 ± 0.37	4.65 ± 0.39	54.42 ± 4.93	105.37 ± 10.07
Resveratrol and EX527 in DM and AD	20.37 ± 1.86&	16.58 ± 1.45&	1.74 ± 0.15&	2.78 ± 0.26&	36.75 ± 4.12&	80.73 ± 9.27&

*Malondialdehyde levels were determined using thiobarbituric acid spectrophotometric colorimetry, SOD activity was determined using nitrite spectrophotometry, and GSH was determined spectrophotometrically using the DTNB-GSH reductase recycling method. Data are represented as mean ±SD. *$P < 0.05$ vs. normal control group. #$P < 0.05$ vs. model group. &$P < 0.05$ vs. resveratrol treatment group.*

TABLE 3 | IL-1β and IL-6 levels in the cortex and hippocampus.

	IL-1β (U/mg protein)		IL-6 (U/mg protein)	
	Cortex	Hippocampus	Cortex	Hippocampus
Control	1.54 ± 0.146	1.683 ± 0.125	1.297 ± 0.136	1.426 ± 0.151
DM and AD	2.756 ± 0.157*	2.946 ± 0.235*	2.694 ± 0.217*	2.975 ± 0.225*
Resveratrol control	1.60 ± 0.147	1.749 ± 0.208	1.327 ± 0.178	1.512 ± 0.172
Resveratrol in DM and AD	2.13 ± 0.192#	2.34 ± 0.185#	1.963 ± 0.231#	2.13 ± 0.201#
Resveratrol and EX527 control	1.615 ± 0.135	1.712 ± 0.176	1.317 ± 0.91	1.482 ± 0.123
Resveratrol and EX527 in DM and AD	2.364 ± 0.181&	2.687 ± 0.197&	2.305 ± 0.123&	2.583 ± 0.215&

*IL-1β and IL-6 levels were determined by ELISA. Data are expressed as mean ±SD. *$P < 0.05$ vs. normal control group. #$P < 0.05$ vs. model group. &$P < 0.05$ vs. resveratrol treatment group.*

IL-16 were significantly decreased in resveratrol-treated rats compared to model rats ($P < 0.05$) (**Table 3**). However, a significant increase in cortical and hippocampal levels of IL-1β and IL-6 in rats treated with both resveratrol and EX527 was observed ($P < 0.05$) relative to rats receiving resveratrol alone ($P < 0.05$) (**Table 3**), indicating the ability of the Sirt1 inhibitor EX527 to partially reverse the effects of resveratrol.

Sirt1 Expression in the Brain

Sirt1 expression in the brain was measured by Western blot analysis. As shown in **Figure 4**, a significant increase in expression of Sirt1 was observed in rats from the resveratrol control group and resveratrol treatment group versus healthy controls ($P > 0.05$) (**Figure 4**) and model rats ($P > 0.05$) (**Figure 4**), respectively. However, in the resveratrol and EX527 control rats as well as the resveratrol- and EX527-treated rats, all of the changes induced by resveratrol were reversed ($P < 0.05$) (**Figure 4**).

DISCUSSION

Traditionally, AD and DM have been considered two independent diseases. However, recent studies have shown that they share several pathophysiological mechanisms, including specific inflammatory signaling pathways (Bozluolcay et al., 2015), oxidative stress, and cell apoptosis. For example, in

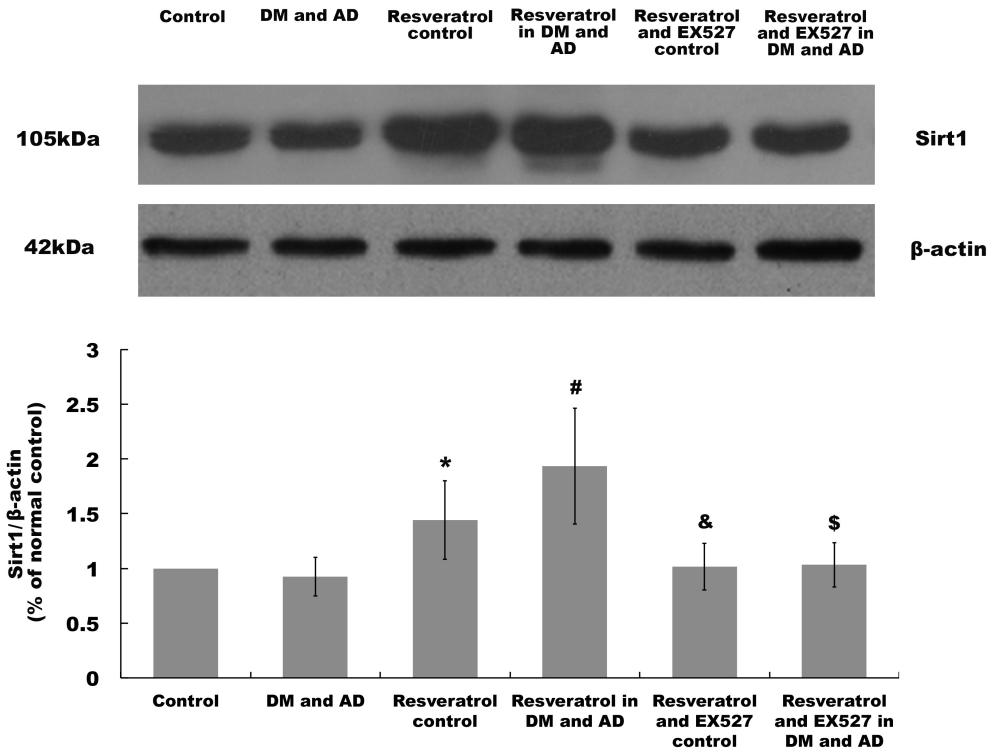

FIGURE 4 | Sirt1 expression in the brain. Sirt1 expression in the brain was determined by Western blot. Three independent experiments were performed. Data are expressed as mean ±SD ($^{*}P < 0.05$, vs. control group; $^{\#}P < 0.05$, vs. DM and AD group; $^{\&}P < 0.05$, vs. resveratrol control group; $^{\$}P < 0.05$, vs. resveratrol in DM and AD group).

T2DM, impaired insulin signaling can result in the formation of Aβ plaques, mitochondrial dysfunction, inflammatory responses, and oxidative stress in peripheral tissues. The central nervous system exhibits all these pathological changes in AD, as well (I. Kim et al., 2010; Mittal and Katare, 2016). However, no therapeutic interventions are available that simultaneously address AD and DM.

Clinically, resveratrol exhibits numerous broad benefits that may help control many conditions, like DM (Shen et al., 2013; Szkudelski and Szkudelska, 2015) and AD (Vingtdeux et al., 2008; Li et al., 2012). For example, resveratrol can affect both glucose and lipid metabolism, and it was found to protect pancreatic β cells in a spontaneous T2DM model due to its as yet unexplained ability to induce activation of AMP-activated protein kinase and its downstream targets (Do et al., 2012). There is evidence that oxidative damage and subsequent deficits in cognition can be prevented via routine dosing of resveratrol as shown in another animal model of AD (Kim et al., 2007; Kumar et al., 2007). Resveratrol has also been found to inhibit Aβ secretion in various cell lines (Marambaud et al., 2005), prevent the formation and elongation of Aβ fibrils, and destabilize plaques (Mishra et al., 2009). A model of diabetes with AD in rats was developed for our study based on streptozotocin injection via the intraperitoneal route followed by hippocampal injection of Aβ1–40 to examine the effect of resveratrol. Our study suggests that resveratrol can protect the function of spatial sense and memory in the combined DM and AD rat model. In addition, examination of the cortex and hippocampus showed that resveratrol partially reversed the increase in AchE activity and the decrease in ChAT activity in the DM and AD rat model. These findings suggest that AchE and ChAT changes in the cortex and hippocampus may correlate with spatial sense and memory dysfunction in the rat model, and resveratrol may protect memory function in rats with concurrent diabetes and AD.

Among the final products of lipid peroxidation is MDA, which can be measured as an indicator of oxidative stress (Greilberger et al., 2008). SOD catalyzes the dismutation of the superoxide anion radical to either H_2O_2 or O_2, regulating antioxidant defenses. GSH is noted for mitigating oxidative stress within cells by maintaining the redox state (Takahashi, 2012). Our results indicate that resveratrol treatment can partially reverse increased MDA levels and decreased SOD activity and GSH levels in the cortical and hippocampal brain regions of model rats. Thus, resveratrol exhibits significant antioxidant effects in the animal model of concurrent diabetes and AD.

One of the defining pathological changes responsible for sustaining the inflammatory response is cytokine production, and numerous studies have reported that cytokines are increased in the brains of both AD patients and diabetic patients (De Luigi et al., 2001; Devaraj et al., 2006). For example, IL-1β expression is increased sixfold in AD patients versus healthy controls of the same age (Griffin et al., 1989). IL-6 is also reportedly elevated in

amyloid plaques found in the cortical and hippocampal tissue of AD patients. Devaraj et al. (2006) have reported that IL-6 and IL-1β levels were elevated in blood samples of type 1 diabetic patients versus samples from controls. Our results showed increases in IL-1β and IL-6 levels in model rats relative to normal rats, with resveratrol treatment partially reversing these changes. These findings suggest the existence of an inflammatory process in rats with concurrent diabetes and AD and indicate that resveratrol can interrupt the inflammatory cascade in the animal model of combined diabetes and AD.

Recently, many studies have suggested that Sirt1 has neuroprotective effects that slow the degeneration common to many neurological diseases, such as AD, Huntington's disease, and Parkinson's disease (Jiang et al., 2012; Lalla and Donmez, 2013; Herskovits and Guarente, 2014), and it is important for the regulation of many functions, including metabolism, stress tolerance, cell survival and aging, the inflammatory immune response, endothelial function, and circadian rhythm (Chung et al., 2010). Sirt1 modulates inflammatory reactions through deacetylating histones and critical transcription factors, such as activator protein 1 and nuclear factor kappa B (NF-κB), which block transcription of specific genes promoting inflammation (Xie et al., 2013). Olmos et al. (2013) found that Sirt1 supports vascular endothelial cells by regulating antioxidant genes via a FoxO3a/PGC-1α complex. Kobayashi et al. (2005) also found that Sirt1 impacts cellular aging and tolerance to stress by mediating NAD-dependent deacetylation of FOXO in a process triggered by oxidative signals. Studies have suggested that resveratrol is a Sirt1 activator (Pallas et al., 2009; Wu et al., 2011) and that Sirt1 is integral to the main neuroprotective mechanism of resveratrol. Moreover, the AMPK (Chiang et al., 2018; Guo and Zhang, 2018; Pineda-Ramirez et al., 2019), PI3K-AKT (Yin et al., 2017; Hui et al., 2018), and cAMP (Zhang et al., 2013) signaling pathways are also involved in resveratrol's protective action in some disease models. In this study, we found that Sirt1 expression was significantly increased in the brains of rats from the resveratrol control group and resveratrol treatment group versus healthy controls and model rats, respectively, and that these changes were reversed by the Sirt1 inhibitor EX527. Our study demonstrates the partial reversal of resveratrol's beneficial effects in a model of concurrent diabetes and AD in rats by coadministration of resveratrol with a Sirt1 inhibitor. Our findings suggest that resveratrol provides a protective effect in the animal model of combined diabetes and AD via activation of Sirt1 and its downstream targets. In addition, there may be additional signaling pathways, such as the AMPK, PI3K-AKT, and cAMP pathways, involved in resveratrol's neuroprotection in the model of DM and AD, and further research is needed to confirm this.

CONCLUSION

Resveratrol prevents neurodegeneration in a rat model of diabetes with concurrent AD by activating Sirt1 and its downstream targets to regulate the cholinergic system and control oxidative stress and the inflammatory response.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

The animal study protocol was preapproved by the Life Science Research Ethics Committee of Zhengzhou University, and all procedures were conducted in accordance with the Guidance for the Care and Use of Laboratory Animals, formulated by the Ministry of Science and Technology of China.

AUTHOR CONTRIBUTIONS

XM, ZS, XH, and SL designed and/or performed the experiments. XM, ZS, XJ, and SC analyzed the data. ZS and XM wrote the manuscript. SC and JZ critically revised the manuscript. HL and JZ finally approved the manuscript.

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Decision-Making Under Ambiguity or Risk in Individuals With Alzheimer's Disease and Mild Cognitive Impairment

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Background: Making advantageous decisions is essential in everyday life. Our objective was to assess how patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD) make decisions under conditions of ambiguity or risk. In addition, the study also aimed to examine the relationship between decision-making competence and memory and executive function.

Methods: Patients with MCI (n = 36) and AD (n = 29) and healthy elderly controls (HC, n = 34) were recruited from the memory clinic. All subjects were administered a comprehensive neuropsychological battery test. We used the Iowa Gambling Task (IGT) to measure decision-making under ambiguity and the Game of Dice Task (GDT) to measure decision-making under risk. Pearson's correlation was used to examine the relationship between the performance of IGT and GDT with delayed recall and the Stroop test.

Results: In the GDT, MCI and AD patients presented similar performance but showed different patterns when compared with the HC group. The proportion of those making advantageous choices was lower in the AD group than in the HC group ($p = 0.01$), while the MCI and HC groups did not differ ($p = 0.14$). Meanwhile, concerning the ratio of accepting negative feedback, the AD ($p < 0.01$) group was significantly different from the HC patients, but the MCI ($p = 0.06$) and HC groups did not differ. In the IGT, MCI and AD patients selected randomly from advantageous and disadvantageous decks ($p = 0.94$ and $p = 0.54$), showing no significant change in performance over time. In contrast, the HC group made increasingly frequent advantageous selections over time ($p = 0.04$). Furthermore, the proportion of advantageous decision-makers for the GDT had a linear relationship with delayed recall of the Hopkins Verbal Learning Test and Stroop color words ($p < 0.01$ and $p < 0.01$, respectively).

Conclusion: Our findings suggest that decision-making ability under ambiguity is compromised in MCI and AD, and the decision-making under risk is only impaired in AD. Reduced decision-making performance under risk is closely correlated with lower executive functions and memory.

Keywords: decision-making, Alzheimer's disease, mild cognitive impairment, executive function, memory

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INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia symptoms and involves a progressive decline in many cognitive domains, such as memory, attention, and executive functions (1). Mild cognitive impairment (MCI) is described as a transitional period between normal aging and the diagnosis of clinically probable very early AD, and it involves memory impairment and slight cognitive deficits beyond those expected for age (2, 3).

The impairment of these functions may affect the abilities of patients with AD and MCI, such as decision-making. Several studies have shown that impaired memory, attention, and executive functions most likely compromise decision-making (4–6). Making decisions is essential for these two types of clinical patients in terms of domains of daily life including medical care (choosing between different treatment options), financial issues, and anticipating or planning possible nursing home placement. A study showed that older adults who make fewer advantageous decisions in laboratory decision-making tasks are more vulnerable to being deceived by misleading advertisements than older adults who are good at decision-making (7). In real life and laboratory investigations, there are two general types of decision-making situations: decisions under uncertainty and decisions under risk. Several studies have found that some healthy older adults present difficulties in making advantageous decisions, especially when information about the options is ambiguous, missing, or misleading (8–10). When a situation is complex, people need to learn from experience which options are best for them in the long term (5). The poor ability to learn from experience over time, resulting from compromised executive function (11, 12) and other neuropsychological abilities (5), may account for decision-making difficulties in normal elderly (9). AD and MCI patients, who have more cognitive impairment compared with healthy controls, may have severe difficulties in decision-making under different situations.

Recent research has shown that patients with MCI perform worse than healthy peers in decision-making tasks under risk (13, 14). In this situation, explicit information about the possible results of various options and their associated probabilities is provided, and participants can depend on their own strategy patterns by calculating or estimating (6). Difficulties also emerge in decision-making in situations of ambiguity (14–17). AD patients are also found to show poorer performance than healthy controls in decision-making under risk (8) and ambiguity (15–18), but they do not differ from MCI patients under risk (19) and ambiguity (15–17). However, one study reported a relatively intact decision-making ability of mild AD patients under risk (20). Previous studies have inconsistent results about decision-making in MCI and AD patients. Meanwhile, these studies either studied decision-making just in one group of MCI and AD patients compared with healthy controls or two groups just under one decision-making condition. A recent study provided compelling evidence that low decision-making ability is an early harbinger of adverse cognitive outcomes and a manifestation of accumulating AD pathology in the brain (21). Furthermore, the ability of decision-making in different conditions among individuals with MCI and AD needs further investigation.

Previous studies found the decision-making under risk might be related with executive function (22–24) rather than working memory (22). However, the role of executive function and working memory in decision-making under ambiguity remains unclear (25, 26). There have been controversies on how memory and explicit recall might impact decision-making (27–29). Concerning MCI and AD, previous studies found a positive relationships between executive function and decision making under risk (17, 19). However, Bayard et al. did not observe significant relationship between working memory, executive functions and decision-making under ambiguity (15), while studies by Zamarian and colleagues did in MCI and mild AD (30, 31). Therefore, decision making under risk or ambiguity might have diverse relationship with cognitive functions in MCI and AD. All in all, further studies are needed to understand how neurocognitive functions interact with making advantageous decisions in different situations in AD and MCI patients. It is anticipated the findings would trigger specific strategies that help people with cognitive disorders make a favorable decision in daily life.

To the best of our knowledge, this study is the first to compare the decision-making performance of older adults with MCI and AD in both risky and ambiguous conditions. Because of slighter cognitive deficits in MCI patients than in AD patients, patients with MCI may not show difficulties in decision-making under risk but may perform worse in decision-making under ambiguity. It may be hypothesized that decision-making performance for individuals with MCI under risk is better than that of individuals with AD, but in conditions under ambiguity, the performance of patients with MCI is similar to that of patients with AD. Based on previous decision-making studies, decision-making under risky conditions is measured by the Game of Dice Task [GDT, (22)], and under ambiguous conditions, decision-making is commonly evaluated using the Iowa Gambling Task [IGT, (32)]. In this study, we aimed to investigate the aforementioned hypothesis by comparing the performance of MCI and AD patients with that of healthy controls in two gambling games. Meanwhile, we intended to explore the potential relationship between the decision-making competence and memory and executive function in AD and MCI patients.

METHODS

Participants

From May to November 2018, 36 patients with MCI and 29 patients with AD were recruited from the case registry of the Dementia Care & Research Center of Peking University Institute of Mental Health. The case registry has been described in a previous study (33). Briefly, the participants completed a standardized neuropsychological assessment, underwent clinical interviews and brain imaging examinations, and received a clinical diagnosis by a memory specialist.

All participants with MCI met Petersen's MCI criteria as follows: (a) memory problems confirmed by an informant, (b) preserved general cognitive function (minimental state examination (MMSE) score of > 24), (c) intact activities of daily living (an ADL score of ≤ 26), and (d) failure to meet the diagnosis of dementia (34). Other inclusion criteria were as follows: (a) age ≥ 55 years, (b) schooling education (≥5 years), (c) a Clinical Dementia Rating (CDR) score = 0.5 and (d) a Hamilton Depression Scale (HAMD) score of < 12. The exclusion criteria of MCI were as follows: Axis I psychiatric disorders listed in the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV); history of stroke, subdural hematoma, tumor, other intracranial space-occupying diseases or cerebrovascular disorders, and presence of significant risk factors for cerebrovascular disorders (i.e., a score higher than 4 on the modified Hachinski Ischemia Scale); current or previous neuropsychiatric diseases such as Parkinson's disease, epilepsy; and presence of a physical illness that could affect cognition.

A clinical diagnosis of AD was made according to the criteria for dementia cited in the International Classification of Diseases, 10th Revision (34). Other inclusion criteria were as follows: more than 6 months' duration of the disease and an MMSE score of 15–24 [for more details, see (35)].

Thirty-four participants met the inclusion criteria of healthy controls. They underwent the neuropsychological assessments and CDR to exclude cognitive impairment. Healthy controls met criteria as follows: (a) age ≥ 55 years; (b) with more than 5 years of schooling education; (c) with preserved general cognitive function [MMSE score of > 24 and Montreal Cognitive Assessment (MoCA) score of >26]; (d) a CDR score = 0; and (e) a HAMD score of < 12.

The present study was approved by the Ethics Committee of Peking University Institute of Mental Health (Sixth Hospital), Beijing, China. All participants were fully informed regarding the study protocol and provided written informed consent.

Neuropsychological Tests

All participants underwent a neuropsychological assessment. For the purpose of this study, we included the score of the MMSE, the MoCA, the Hopkins Verbal Learning Test (HVLT) and the Stroop color word tasks.

Decision-Making Under Risk

The GDT is often used to measure decision-making under risk conditions (22). Participants are asked to sit in front of a computer screen and watch the computer throwing dice and to choose among different alternatives that are explicitly related to a specific amount of gain/loss and that have distinct winning probabilities. Before each throw, they can choose a single number or a combination of two, three, or four numbers. If one of the numbers of the combination that they choose is thrown with the die, the participants receive the associated amount of money. In contrast, the subjects lose the same amount of money when none of the chosen numbers is thrown. In this task, subjects are asked to maximize the starting fund (1,000 *yuan*) within 18 throws. One single number with a winning probability of 1/6 and a combination of two numbers with a winning probability of 2/6 are defined as disadvantageous or risky decisions, and a combination of three numbers and four numbers are defined as advantageous or nonrisky decisions. Selecting advantageous options leads to a positive outcome throughout the test, whereas selecting disadvantageous options leads to a negative outcome [for more details about the rules of GDT, see (36)].

We calculated the (a) final capital and (b) net score (the number of nonrisky options minus the number of risky options) and (c) utilization of negative feedback. If participants chose a disadvantageous option (one number or the combination of two numbers) and obtained a loss and then in the next trial immediately chose an advantageous choice, we identified this behavior as "using negative feedback." In contrast, if participants chose a disadvantageous option immediately after receiving a loss for a disadvantageous option, we defined this behavior as "not using negative feedback." The utilization of negative feedback is the frequency of choosing advantageous option after choosing a disadvantageous option divided by the frequency of using negative feedback; and (d) the frequency of choosing each of the four possible choices, making disadvantageous choices, and making advantageous choices.

Decision-Making Under Ambiguity

The IGT is used to measure decision-making under conditions of uncertainty (37). Participants must choose between four different decks (A, B, C, D). Card selections from decks A and B result in large monetary gains followed by large penalties at unpredictable times, leading to a negative balance. Therefore, we define decks A and B as disadvantageous choices. Decks C and D are advantageous choices because they lead to moderate gains but also to moderate or low losses, leading to a positive final balance. Participants attempt to solve the task successfully but are not told the rules for gains and losses [for more details about the rules of IGT, see (38)].

We calculated the following: (a) the net score, which was selected from decks C and D minus selections from decks A and B. One hundred choices were equally divided into five blocks. The calculation of the net score for each block was used to quantify the progressive change in the selection across the IGT; (b) the utilization of negative feedback: if participants chose a disadvantageous option (A and B) and obtained a loss and then, in the next trial, immediately chose an advantageous choice (C and D), we identified this behavior as "using negative feedback." If the opposite occurred, we defined the behavior as "not using negative feedback"; (c) the frequency of making four possible choices; (d) the frequency of advantageous and disadvantageous choices; (e) the advantageous profile: a positive net score [(C+D) − (A+B) > 0] indicates more frequent selection from advantageous decks, whereas a negative net score [(C+D) − (A+B) < 0] indicates more frequent selection from disadvantageous decks. We designed five blocks into two parts: the initial phase (trials 1–40; Blocks 1 and 2) and the second part of the IGT (trials 41–100; Blocks 3, 4, and 5). We defined the number of subjects whose net score on the second part was positive as an advantageous profile; and (f) the change ratio in frequency of choosing advantageous choices among Blocks 1–5; that is, the result is the frequency of making advantageous choices in

Block 1 subtracted from the frequency of making advantageous choices in each block, divided by the frequency of making advantageous choices in Block 1. For example, the result is the subtraction of the frequency of making advantageous choices in Block 1 from the frequency of making advantageous choices in Block 2, divided by the frequency of making advantageous choices in Block 1 ((B2-B1)/B1).

Statistical Analysis

All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) version 20.0 for Windows. The data were examined for normal distribution (tested with the Kolmogorov-Smirnov test) and homogeneity of variance (tested with the Levene test). The variables were normally distributed ($p > 0.05$).

Because the neuropsychological tests were associated with age and education, the neuropsychological testing data of the three groups were compared with these two demographic variables as covariates. An analysis of covariance (ANCOVA) with age and education as covariates and with the group as the between-subjects factor was performed to examine the measures of GDT and IGT. For the measures of IGT, we used an ANCOVA with age and education as covariates and with the group as the between-subjects factor for the variables (for all 100 trials) of IGT. For the score of the blocks, we conducted a repeated measures analysis of variance (ANOVA) with age and education as covariates and with block (1–5) as the within-subject factor and group (AD, MCI, controls) as the between-subjects factor for the frequency of advantageous choices and a repeated-measures ANOVA with age and education as covariates and for the advantageous choices of each group (AD, MCI, controls). Finally, relationships between the neuropsychological tests and performance on the gambling tasks were determined using Pearson product-moment correlations.

RESULTS

Demographic Characteristics

The AD and MCI participants were older (both $p < 0.01$) than the controls, but the AD and MCI participants did not differ in age. The AD group was less educated than the MCI group ($p < 0.01$) and the controls ($p < 0.01$), with no difference between the controls and the MCI participants. The groups were matched for sex (see **Table 1**).

Neuropsychological Tests

The AD participants performed worse than the MCI participants ($p < 0.001$) and controls ($p < 0.001$) on the MMSE. A significant difference was also observed between the MCI participants and controls ($p = 0.02$). The same situation was also found for MoCA in that the AD participants performed worse than the MCI participants ($p < 0.001$) and controls ($p < 0.001$), and the MCI participants and controls ($p < 0.001$) were found to be significantly different.

Poorer executive functions were found with the Stroop color word test (MCI vs. controls, $p < 0.001$; AD vs. controls, $p < 0.001$). Additionally, the AD group performed worse than the MCI group (all $p < 0.001$). With regard to the performance of memory function on the HVLT Delayed Recall (HVLT-DR), the AD ($p < 0.001$) and MCI ($p < 0.001$) groups were significantly different from the controls (see **Table 1**).

Decision-Making Under Risk

When controlling for age and education, between-group differences were observed for the final capital ($p < 0.001$). The AD and MCI groups were significantly lower than the controls ($p < 0.001$ and $p < 0.01$, respectively), with no difference between the AD and MCI groups ($p = 0.10$) in the final capital.

An ANCOVA with age and education as covariates and with group as the between-subjects factor was performed to examine the utilization of negative feedback ($F = 5.08$, $p = 0.008$, $\eta^2 = 0.10$). The AD patients showed a lower utilization of negative feedback than the controls ($p < 0.01$), but the MCI group did not differ from the controls ($p = 0.14$).

When controlling for age and education, between-group differences were observed for the frequency of advantageous choices ($p = 0.04$) and the frequency of single numbers (the most disadvantageous choice) ($p < 0.001$). The AD patients showed a lower preference for advantageous options than the controls ($p = 0.01$), but individuals with MCI showed no difference from the AD group or controls (**Figure 1**). In addition, individuals with AD ($p < 0.01$) and MCI ($p < 0.001$) selected more single number options than the controls (**Figure 2**). For the other three options, there was no difference among the three groups (see **Table 2**).

Decision-Making Under Ambiguity

Based on the adjusted ANCOVA analysis for the IGT total net score, the three groups did not differ. A repeated-measures ANOVA, with block as the within-subject factor and group

TABLE 1 | Demographic and cognitive performance in three groups.

	AD (N = 29)	MCI (N = 36)	Control (N = 34)	F/χ2	p
Age	75.1 (7.92)*	76.9 (7.27)*	65.1 (6.82)	25.86	<0.001
Sex (men/women)	11/19	11/25	15/19	1.38	0.502
Education	11.5 (3.57)*	13.8 (3.03)	13.6 (2.79)	5.26	0.007
MMSE	20.0 (4.76)*#	26.6 (2.41)*	29.3 (2.54)	41.97	<0.001
MoCA	13.8 (4.70)*#	22.3 (3.38)*	26.6 (2.02)	72.33	<0.001
StroopCW	18.8 (8.77)*#	29.3 (10.83)*	38.5 (9.81)	15.11	<0.001

MMSE, minimental state examination; MoCA, Montreal Cognitive Assessment, HVLT-DR, Hopkins Verbal Learning Test Delayed Recall; StroopCW, Stroop color word tasks.
**vs. controls p < 0.05, #MCI vs. AD p < 0.05.*

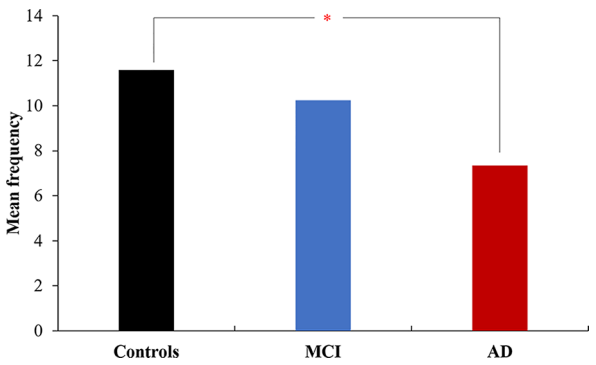

FIGURE 1 | The mean frequency of advantageous decisions in the three groups. The AD patients made fewer advantageous choices than the controls. The MCI patients did not differ from the controls. *$p < 0.05$.

(AD, MCI, controls) as the between-subjects factor was conducted on the frequency of four choices (A, B, C, D). The results showed that there was no significant effect of block and group on the frequency of three choices (A, C, D). The interactions between block and group on the frequency of choice A ($p = 0.01$) and choice D ($p = 0.02$) were significant. For choice B, the main effect of group ($p = 0.02$) as well as the interaction between block and group ($p = 0.01$) were significant. Overall, the AD patients showed significant differences compared to the healthy controls (*post hoc* contrasts $p < 0.001$), whereas the MCI patients and controls did not differ from each other in the frequency of choice B.

A repeated-measures ANOVA (adjusted with age and education) with block (Blocks 1–5) as the within-subject factor and group (AD, MCI, and controls) as the between-subjects factor was conducted on the change ratio of the frequency about advantageous choices. The results showed that there was a significant effect group on the change ratio in frequency of advantageous choices ($p = 0.03$), and AD patients showed significant differences from MCI patients (*post hoc* contrasts $p < 0.01$). The interaction between block and group on advantageous choices ($p < 0.01$) was significant.

A repeated-measures ANOVA for the change ratio among Blocks 1–5 of each group (AD, MCI, and controls), adjusted with age and education, found that the controls selected more advantageous choices over time (block effect $p = 0.04$), whereas

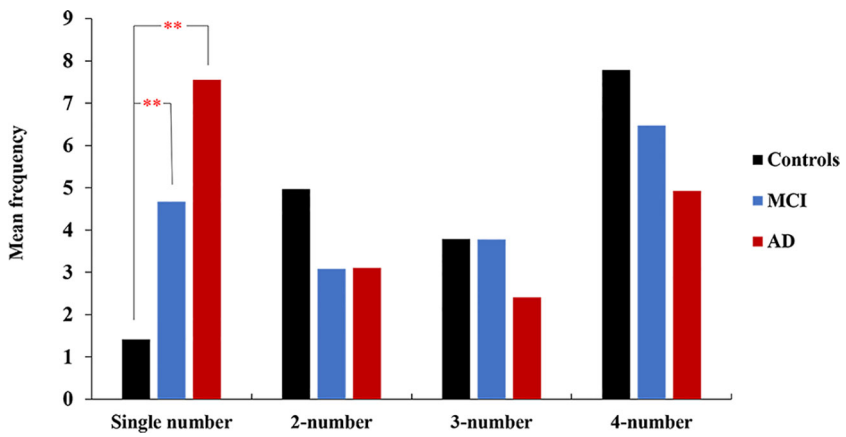

FIGURE 2 | The AD and MCI patients selected one number most frequently, and the controls were more likely to select four-number combinations. Single comparisons between groups revealed significant differences in the frequency of choosing one single number but not two numbers, three numbers and four numbers. **$p < 0.01$.

TABLE 2 | The comparison of the performance on the Game of Dice Test (GDT) in three groups [mean (SD)].

	AD (N = 29)	MCI (N = 36)	Control (N = 34)	F/χ2	*p*
Net score	−3.3 (9.11)*	2.5 (9.45)	5.2 (13.65)	3.43	<0.05
Final capital	−4,113.8 (3,342.45)**	2,094.4 (3,465.25)**	23.5 (2,726.64)	9.74	<0.001
Feedback (%)	0.4 (0.25)*	0.6 (0.28)	0.7 (0.38)	5.08	<0.01
Single number	7.6 (4.96)**	4.7 (4.22)**	1.4 (3.52)	10.53	<0.01
2-number	3.1 (2.41)	3.1 (2.22)	5 (5.91)	0.89	0.414
3-number	2.4 (1.8)	3.8 (2.72)	3.8 (4.56)	0.67	0.515
4-number	4.9 (4.1)	6.5 (5.20)	7.8 (7.2)	1.95	0.148
Advantageous choices, n (%)	10.7 (60)*	7.8 (40)	6.4 (40)	3.43	<0.05
Disadvantageous choices, n (%)	7.3 (40)*	10.3 (60)	11.6 (60)	3.43	<0.05
A/D ratio	1.4 (2.08)**	2.5 (3.40)*	4.7 (6.02)	5.38	<0.01

A/D, Frequency of making advantageous choices/Frequency of making disadvantageous choices.
**vs. controls p < 0.05, **vs. controls p < 0.05.*

the MCI (p = 0.94) did not differ and AD (p = 0.54) made advantageous choices more randomly over the task (**Figure 3**).

Based on an adjusted ANCOVA analysis for the frequency of advantageous choices and the ratio of advantageous choices to disadvantageous choices, there was no difference among the three groups. A statistically nonsignificant trend was observed for the advantageous profile.

Correlations Between Decision-Making Competence and Cognitive Performance

The GDT variables, including final capital, net score, utilization of negative feedback, frequency of a single-number choice and frequency of advantageous choices, correlated significantly with neuropsychological performance (Stroop color word test, HVLT-DR) (see **Table 3**). However, when education was adjusted, there was no significant correlation between the GDT variables and neuropsychological performance (all p > 0.05). We did not observe a significant correlation between the IGT variables and neuropsychological performance.

DISCUSSION

The present study investigated decision-making in patients with AD and MCI in two gambling tasks under risk or ambiguity. We assessed many measures of the GDT and IGT, as stated in the methods. In the GDT, the AD patients utilized less negative feedback and chose more disadvantageous options than the healthy controls. This finding indicates that AD patients learn very little from information over time and prefer to choose unfavorable options. However, the MCI patients did not differ from the healthy controls. In the IGT, with regard to performance changes over the task, the healthy controls had a stronger tendency toward safe and advantageous responses than the AD and MCI patients. While the healthy controls demonstrated learning as the task proceeded, the AD and MCI patients did not adapt their strategies. In this task, the profile of decision-making for the MCI patients resembled that of the AD patients.

In the GDT, the AD patients chose more risky options than the healthy controls. This result is inconsistent with the finding by Delazer et al. that patients with mild AD chose safe alternatives as frequently as healthy elderly persons (20). It might be partly due to the heterogeneity of the illness. An earlier study found that subjects with worse emotional control abilities chose more risky options (23). People with AD may present impairment in emotional control (23, 39) and executive function (5) in addition to memory decline. However, the results of this study that people with AD chose more risky options than healthy controls are in line with previous investigations (31, 40). Recent investigations have credited the important role of executive functions and numerical processing in decision-

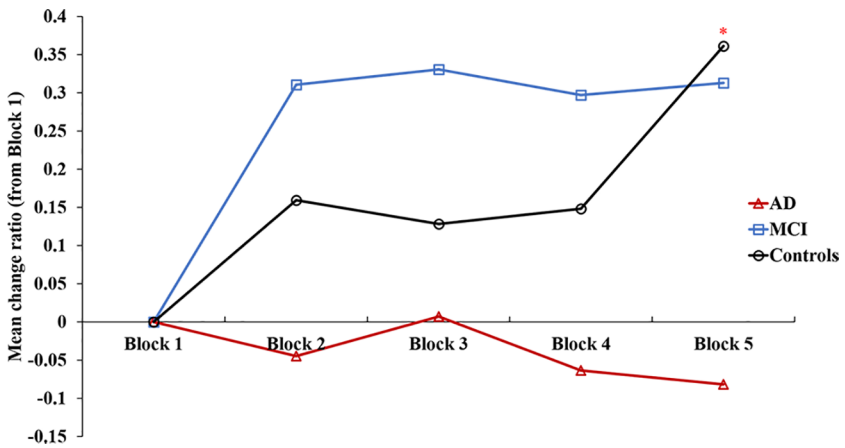

FIGURE 3 | The change ratio of making advantage choices in an Iowa gambling task for 1-5 blocks. Controls selected more advantageous choices over time, whereas the MCI did not differ, and AD chose advantageous choices more randomly over the task. *vs Block 2, Block 3, Block 4 p < 0.05.

TABLE 3 | Correlations of the performance of gambling dice test with the executive function and memory test.

	Final capital	Net score	Utilization of negative feedback	Single number	Advantageous choices	A/D ratio
Age	–0.152	–0.052	–0.041	0.253*	0.052	0.047
Education	0.321**	0.277**	0.247*	–0.312**	–0.277**	0.287**
StroopCW	0.418**	0.296**	0.346**	–0.477**	–0.296**	0.168
HVLT-DR	0.437**	0.358**	0.355**	–0.555**	–0.358**	0.252*

*A/D, Frequency of making advantageous choices/Frequency of making disadvantageous choices; StroopCW, Stroop color word tasks; HVLT-DR, Hopkins Verbal Learning Test Delayed Recall. *p <0.05, ** p <0.01*

making under risk (5, 6, 22, 36, 41), as the prefrontal cortex is involved in both processes (5, 42). Additionally, executive function and numerical training improved their performance in decision-making under risk (43). Therefore, the presence of executive function and numerical processing impairments in AD patients may be the main cause of poor performance in the GDT.

The MCI patients showed no significant difference from the controls and AD patients. This result is inconsistent with previous studies of decision-making under risk in patients with MCI. In two previous studies, MCI patients performed worse than healthy controls (14, 19). Compared with these two previous studies, although this study examined the decision-making ability of MCI patients under risk, this study used different gambling games. The GDT used in this study may not be as sensitive as the tasks in previous studies, or the MCI of patients in this study may have been more severe than in previous studies. These two reasons may be the main cause of this situation.

In the IGT, the AD and MCI patients showed significant differences from the healthy controls. The AD and MCI patients made random decisions and showed poor strategy stability. In contrast to the two groups of clinical patients, the healthy controls made increasingly frequent advantageous selections over time. This finding suggests that the healthy controls assessed the advantageous decks more favorably than the disadvantageous decks and learned to decide advantageously by utilizing feedback and modifying their strategy over time, but the patients with AD and MCI did not. The response patterns of the two groups of clinical patients may be attributed to deficits in memory and executive function, which prevents them from establishing new stimulus-reward relationships and eliminating previously learned responses due to the parietal and temporal atrophy they present (44). Another possible explanation of these results is a dysfunctional ventromedial prefrontal cortex (VMPC) in patients with AD (45–47) and MCI (48). The VMPC is supposed to mediate the use of feedback for current decisions (49). The somatic marker hypothesis was based on the defective decision-making about VMPC damage, which suggested that decision-making is often assisted by emotional processes and somatic "markers" (49, 50). However, little study about the relationship between decision-making damage and VMPC in AD and MCI patients was found. In the future, more confirmatory studies are needed to eliminate even the most resilient skepticism in this regard.

These results verify earlier reports that in MCI patients, the performance of decision-making under ambiguity mimicked that of AD patients and was impaired compared with that of healthy controls (14, 15, 17). The MCI patients manifest slight impairments in cognitive functions, which do not meet the criteria for a diagnosis of dementia (2, 3), and less VPMC atrophy than AD patients (51). In addition, a study found that lower executive functions are required to make advantageous decisions in situations of risk than in situations of ambiguity (19). Therefore, the lower cognitive impairments and relatively intact VMPC function of MCI patients in comparison with those of AD patients may be the reason for this study's finding that persons with MCI show no difficulties in making advantageous decisions under risk but have difficulties in situations of ambiguity. We can infer that MCI patients may still have intact competence when making decisions under conditions of risk but show impairment in decision-making under ambiguity.

The observation that individuals with MCI and AD did not differ in IGT is similar to previous studies (15, 17, 52). It may indicate that people with MCI and AD have similar disadvantageous decision-making profile in the IGT. However, in our study the MCI subjects exhibited more positive changes from baseline up to the Block 4 task in IGT test compared with control group. It may imply that MCI individuals preserve part neuroplasticity in learning. With repeated trials, individuals with MCI might learn from the feedback over time and make more advantageous choices. Further investigations are warranted to explore the potential mechanism.

In this study, we implemented a correlation analysis to explore the possible contribution of memory and executive functions to decision-making performance. The results indicated that the capacity to utilize feedback in the decision-making under risk was associated with good executive ability and good memory. Executive functions contribute to decision-making under risk by guiding the categorization of information and alternatives, the development and application of strategies and the integration of feedback (5, 19). People usually depend on declarative memory to form and update a long-term representation that integrates the variations in reward and punishments across decks and across experiences during the process of decision-making (29). Without such relational record, an individual has no choice but to rely on the immediately available information and thus, the decision sticking to a certain deck or switching to another deck relies on each single outcome (29). Therefore, intact episodic memory is important for making good decisions (14). The memory deficit in conditions, such as AD and MCI, could trigger the impairment on decision-making (28, 29).

We identify two possible limitations of our study. First, the experimental methods we used may not reflect the actual deficits in decision-making. A study showed that older adults who make fewer advantageous decisions in laboratory decision-making tasks are more vulnerable to being deceived by misleading advertisements (7). Therefore, it would be interesting to validate our findings with real-world decision-making tasks. Second, we observed the great variation in performance on IGT and GDT in three groups. It might be partly attributed to not only the sample size but also the potential neuropathological heterogeneity of the subjects.

In conclusion, to our knowledge, we present the first study that shows that individuals with MCI do not make exactly the same decisions as individuals with AD under conditions of ambiguity and risk. This study finds that AD patients have difficulty making advantageous decisions under ambiguity and risk; however, MCI patients have problems making advantageous decisions under ambiguity but not under risk. We also document the relationship between the decision-making measures under risk and cognitive performance. The capacity tested by GDT and IGT may be considered as the analogue of real-world decision-making, which is essential for care planning and financial arrangement in one's daily living (20, 53, 54). Therefore, our study highlights the significance of measuring the decision making under ambiguity for early detection of MCI. In the

future, more real-life decision-making needs to be performed in patients with MCI and AD, and more longitudinal studies should be conducted to verify that low decision-making ability is associated with increased risk for incident AD and MCI.

DATA AVAILABILITY STATEMENT

The datasets generated and analyzed during the current study are not publicly available because we are preparing an additional manuscript. However, they are available upon reasonable request to the corresponding authors, TX (xieteng@gmail.com) and HW (huali_wang@bjmu.edu.cn).

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Institutional Review Board of Peking University Sixth Hospital with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Institutional Review Board of Peking University Sixth Hospital.

AUTHOR CONTRIBUTIONS

TS, TX, JW, XY, and HW conceived the study and supervised the work. TS, JW, and HW designed the study and collected the data. TS, TX, LZ, YT, and KW analyzed the data. TS and TX wrote the manuscript. All authors contributed to the subsequent drafts and approved the final version.

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Cognitive Reserve Moderates Effects of White Matter Hyperintensity on Depressive Symptoms and Cognitive Function in Late-Life Depression

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Introduction: White matter hyperintensity (WMH) has been regarded as one of the major contributor of the vascular hypothesis of late-life depression (LLD) and cognitive decline in the elderly. On the other hand, cognitive reserve (CR) has long been hypothesized to provide resilience and adaptability against age- and disease-related insults. This study examined the role of CR, using proxy of education, in moderating the association between WMH and clinical LLD expression.

Methods: A total of 54 elderly diagnosed with major depressive disorder and 38 matched healthy controls participated in this study. They received MRI scanning and a battery of neuropsychological tests. WMH was quantified by an automated segmentation algorithm. Linear regression analyses were conducted separately in the LLD and control groups to examine the effects of WMH, education and their interaction in depression severity and various cognitive domains.

Results: WMH was significantly and negatively associated with executive function only in the healthy controls. In patients with LLD, we observed a significant interactive effect in education on the association between WMH and depression severity and language domain (category fluency task). Specifically, those with high education showed less depressive symptoms and cognitive decline as WMH increased.

Conclusion: WMH is associated with lower cognitive function. However, in patients with LLD, high education attenuates the deleterious effect of WMH on mood and cognition.

Therefore, CR appears to exert a protective effect on neurocognitive functioning in people with LLD.

Keywords: cognitive reserve, education, white matter hyperintensity, late-life depression, verbal fluency, cognitive function

INTRODUCTION

Late-life depression (LLD) is a common psychiatric disorder associated with disability, decreased mental well-being, and completed suicides in the elderly (1). On the contrary to mildlife depression, LLD is substantially attributed to aging process and cerebrovascular changes (2). Such characteristics have given rise to the formation of the "vascular depression" hypothesis, which states that cerebrovascular factors predispose, precipitate, or perpetuate the geriatric depressive syndromes (3). Since the advent of magnetic resonance imaging (MRI), neuroimaging-defined vascular changes, particularly the white matter hyperintensities (WMH), have provided ample evidence in support of the vascular hypothesis of LLD (2, 4).

Pathologically, WMH is caused by demyelination, gliosis, and axonal loss in the periventricular or deep white matter (5). Clinically, WMH occurs with normal aging, and is associated with increased risk of subsequent stroke, dementia, and death (6). Importantly, a fourth-fold increase in the prevalence of having WMH was found in late-onset compared with early-onset LLD (7). It is hypothesized that WMH strategically disrupts the communication between cortical and subcortical regions, causing the frontolimbic compromise, and gives rise to affective and cognitive symptoms in LLD (2). Frontolimbic dysfunction was evidenced by the heightened limbic affective reactivity in depressed elderly patients with high WMH loading (8). Moreover, WMH was associated with cognitive impairment in LLD (9). Although WMH could predict poor antidepressant response in LLD, its predictive power was out-performed by the baseline cognitive function (10). However, some studies have failed to find an association between high WMH and poor antidepressant response (11, 12). Therefore, other factors should be considered when assessing the impact of WMH on depression and cognitive function in LLD.

Cognitive reserve (CR) is the notion encompassing the active process of efficient utilization of brain networks in an effort to sustain normal functions despite brain insults (13, 14). Indicated by education, occupational attainment, or leisure activities, CR could reduce or delay the occurrence of dementia (15). Similarly, CR may reduce cognitive decline in LLD by ameliorating the detrimental effects incurred by cerebrovascular diseases and hippocampal atrophy (16). In a large population-based cohort, CR could moderate the negative association between depression and cognitive function (17). However, a previous study reported that high education did not buffer the deleterious effect of LLD on cognitive decline (18). Furthermore, in another community-based sample, those with high CR showed more pronounced cognitive decline as depressive symptoms escalated (19).

Previous studies in the literature suggest that both CR and WMH are indispensable factors and should be considered together in the evaluation of the depressive symptoms and cognitive function in the elderly. A few studies have been conducted in normal elderly individuals have shown that education may modify the negative association between WMH and processing speed (20) or other cognitive domains (21). Similarly, cognitive leisure activities may buffer the negative association between WMH and processing speed (22). However, parallel studies in LLD are scarce. Therefore, based on the framework of the vascular hypothesis in LLD, we specifically examined whether CR (using the proxy of education) could modify effects of WMH on depressive symptoms and different cognitive domains. Based on the prior findings, we hypothesized that WMH will be associated with more severe depressive symptoms and cognitive decline in elderly individuals with lower CR than in those with higher CR.

METHODS

Participants

Following the approval of the institutional review board from Chang Gung Memorial Hospital (IRB number: IRB104-0928C), we recruited elderly patients from the psychiatric department of Chang Gung Memorial Hospital. All of them had been informed about the purpose of the study with written consent. Patients were at least 60 years of age, with their first major depressive episode (MDE) occurring after 50 years of age (i.e., late onset). Diagnostic interviews were conducted by certified geriatric psychiatrists (C. Lin and S.W. Lee) based on the DSM-5 criteria were conducted to ascertained the MDE diagnosis. Patients with other major mental illnesses, including psychotic disorders, bipolar disorder, substance use disorders, and major neurocognitive disorders were excluded. However, patients with anxiety disorders were included owing to high comorbidity with depression. Elderly controls recruited *via* advertisement presented no life-time history of Axis I major mental disorders. All participants were right-handed and scored at least 24 on the Mini-Mental State Examination (MMSE). Other exclusion criteria for both groups included a history of significant head trauma (with loss of consciousness), major neurological disorder, stroke, thyroid dysfunction, or other systemic illnesses. Due to ethical considerations, a steady dose of psychotropics was maintained in LLD patients for at least 2 months before MRI.

Behavioral Measures

The following assessments were performed on the day of functional MRI (fMRI): 15-item Geriatric Depressive Scale (GDS) (23) and an array of neuropsychological tests including

digit symbol substitution test (DSST, where participants need to write down the symbols below an array of numbers as fast as they can based on the pairing rules in the instruction), digit span forward/backward (i.e. to test the longest sequence one can remember in a normal or reverse order after presented with the sequence), letter-number sequencing (LNS, where participants must respectively recite the letters and numbers in an alphabetic and ascending order after given a group of random letters and numbers) (24), facial memory (memory domain; where participants are presented with 24 faces, 1 at a time for 2 seconds, and then are asked to identify these faces among 48 faces, 24 seen and 24 unseen), and category verbal fluency (language domain; where participants need to name as many words as possible in 60 s in the category of colors, animals, fruits, and towns without repeating). We derived the other two cognitive domains—processing speed and working memory—by averaging the scores of the DSST plus digit span forward and digit span backward plus LNS. All scores of the neuropsychological tests were standardized by using the mean and standard deviation of scores of the normal controls. The z-score of the DSST was reversed such that higher values in each domain represented higher functioning. Education (in years) was selected a proxy for CR in this study.

MRI Acquisition and Image Preprocessing

MRI data were collected using an 8-channel head coil on a 3T MRI scanner (Discovery MR750, GE Healthcare, Milwaukee, WI). T1-weighted structural images were acquired as follows: TR = 8 ms, TE = 3 ms, flip angle = 12°, FOV = 250 × 250 mm^2, voxel size = 0.98 × 0.98 × 1 mm^3, slice number = 160. Moreover, T2-weighted FLAIR scans were acquired (TR/TE= 9,000 ms/140ms, inversion time = 2,250 ms, matrix = 320 × 224, slice thickness = 3.5 mm, slice number = 32) with a 0.5-mm gap. A semi-automated segmentation procedure was followed to derive total brain volume and WMH volume, as previously described (25). Briefly, WMH was quantified using the fuzzy connectedness segmentation algorithm on WM lesions from T2-FLAIR images. WMH was registered and localized onto the John Hopkins University White Matter Atlas. WMH was subsequently divided by total brain volume and log-transformed to generate the normalized WMH, serving as a marker for cerebral vascular burden for linear regression analysis.

Statistical Analysis

We first compared the group differences in demographic and behavioral data as well as WMH loading between patients of LLD and normal controls. We then performed serial linear regressions using GDS and the four cognitive domains as dependent variables; education, WMH, and the interaction between education and WMH were independent variables, with age and sex as covariates of no interest. Education and WMH were centered with their means before creating the interaction variable to avoid multi-collinearity. These five independent regressions were repeated in the LLD and control groups separately. All analyses above were performed using SPSS v21 (SPSS, Inc., Chicago, IL, USA), with significance level set at $p < 0.05$.

RESULTS

We enrolled 54 patients with LLD and 38 normal controls. The first MDE occurred at an average age of 61.0 ± 6.1 years with a mean of 1.5 ± 1.1 episodes. The average patient age in the LLD group was 66.8 ± 5.6 years, and that in the control group was 68.2 ± 5.3 years. The average duration of education was 7.3 ± 2.5 years in the LLD group, which was significantly lower than 11.2 ± 4.3 years in the control group. As expected, the LLD group scored higher on GDS than the control group (7.3 ± 2.5 versus 2.6 ± 2.0, respectively). Furthermore, LLD patients showed marginally lower MMSE scores and significantly lower neurocognitive function in terms of processing speed, working memory, and language domain. However, no significant group difference was found in WMH load and memory function (**Table 1**). In terms of medical comorbidities, 19 out of all 92 pariticipants were diagnosed of hypertension (20.7%), 9 (9.8%) of hyperlipidemia, 7 (7.6%) of diabetes mellitus, 9 (9.8%) of hyperlipidemia, 2 (2.2%) of coronary artery disease, and 1 (1.1%) of osteoarthritis.

Next, we tested whether education could moderate effects of WMH on depressive symptoms and cognitive function. In LLD patients, there was no main effect of education or WMH alone on GDS, but there was a significant interaction effect of these parameters on GDS (β = −0.96, 95% CI = −1.87, −0.04; p = 0.040). This effect remained significant after controlling for antidepressant loading (p = 0.045) or MMSE scores (β = −0.97). Furthermore, more depressive symptoms were associated with higher WMH only in individuals with low education (**Figure 1**). No main or interaction effect was found in controls.

TABLE 1 | Demographic and clinical features of patients with late-life depression and elderly controls.

	LLD (n = 54)	NC (n = 38)	Statistics
Age	66.8 ± 5.6	68.2 ± 5.3	t=-1.21, p=0.230
Gender (M/F)	20/35	14/24	χ^2 = 0.01, p=0.990
Education	7.3 ± 2.5***	11.2 ± 4.3	t=-5.01, p < .001
Geriatric Depression Scale	7.6 ± 3.5***	2.6 ± 2.0	t=8.62, p < .001
MMSE	27.4 ± 2.4	28.2 ± 1.5	t=-1.92, p=0.060
Log normalized WMH	-3.7 ± 0.5	-3.9 ± 0.6	t=1.21, p=0.260
Neurocognitive function			
Processing Speed	-0.755 ± 0.779***	0 ± 0.752	t=-4.65, p < 0.001
Working Memory	-0.455 ± 0.748*	-0.032 ± 0.96	t=-2.34, p=0.021
Memory	-0.028 ± 0.943	-0.021 ± 1.011	t=-0.03, p < 0.973
Language	-0.772 ± 0.783***	0.004 ± 1.02	t=-4.12, p < 0.001

**P < 0.05; ***P < 0.001; Mini-Mental State Examination, MMSE; Values in the neurocognitive function are z-scored.*

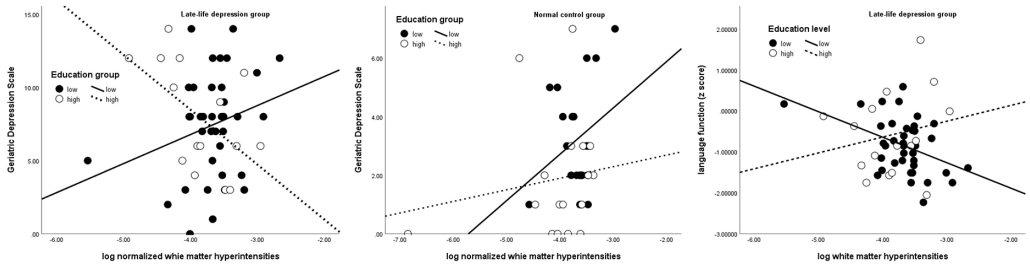

FIGURE 1 | Interactive effect of education on the association between white matter hyperintensity, depressive severity (left and middle), and language domain (right) Solid line and black dots represent low education group; dotted line and white dots represent high education group.

Education was positively associated with processing speed both in the LLD (β = 0.13, 95% CI = 0.05, 0.21; p = 0.002) and control groups (β = 0.08, 95% CI = 0.01, 0.14; p = 0.018) and with language only in the control group (β = 0.12, 95% CI = 0.04, 0.20; p = 0.003). WMH was negatively associated with working memory (β = −1.38, 95% CI = −2.36, −0.40; p = 0.007) in the control group. In the language domain, an interaction effect between education and WMH was noted only in LLD patients (β = 0.23, 95% CI = 0.02, 0.44; p = 0.030) (**Table 2**), wherein those with high education and high WMH loads showed less decline in language function than those with low education (**Figure 1**). This interaction effect remained significant even when GDS or antidepressant loading was entered into the regression (β = 0.23, p = 0.041).

Lastly, given the interactive effect of education and WMH on GDS and language function only in LLD group, we tested whether if there was a three-way interaction between group, education and WMH across all subjects. A three-way interaction was found in group x education x WMH in predicting GDS (β = −1.08, 95% CI = −1.92, −0.23; p = 0.013), but not in predicting language function (β = 0.20, 95% CI = 0.12, −0.03; p = 0.096) (**Table 3** and **Figure 1**).

TABLE 3 | Three-way interaction effect between group, education, and white matter hyperintensity (WMH) on the depressive symptoms and cognitive function in language domain across all the participants.

Variables	unstandardized β [95% CI]			
	GDS		Language	
intercept	2.85	[-24.93,30.62]	-1.74	[3.95,-9.48]
Age	0.05	[-0.06,0.17]	-0.03	[0.02,-0.06]
Gender	0.93	[-0.3,2.15]	-0.11	[0.17,-0.45]
Education	-0.26	[-1.99,1.46]	0.15	[0.25,-0.33]
Group	30.82	[-1.44,63.08]	-4.12	[4.58,-13.10]
WMH	0.38	[-6.44,7.21]	-0.65	[0.97,-2.56]
Group x Education	-3.90*	[-7.17,-0.63]	0.70	[0.46,-0.21]
Group x WMH	7.47	[-1.13,16.07]	-1.14	[1.22,-3.54]
Education x WMH	0.00	[-0.47,0.46]	0.01	[0.07,-0.12]
Group x Education x WMH	-1.08*	[-1.92,-0.23]	0.20	[0.12,-0.03]

WMH, White matter hyperintensities; GDS, geriatric depression scale; p < 0.05.*

DISCUSSION

Our findings demonstrate that the effects of WMH on depressive symptoms and cognitive function in LLD depend on education level. Higher education may mitigate the negative association of

TABLE 2 | Linear regression showing the association of white matter hyperintensity (WMH), education, and their interaction with depressive symptoms and different cognitive domains.

Group	Variables	unstandardized β [95% CI]									
		GDS		Processing speed		Working memory		Language		Memory	
LLD	Intercept	4.97	[-12.35, 22.28]	-0.78	[-4.34, 2.77]	1.46	[-2.26, 5.18]	0.62	[-2.72, 6.72]	2.00	[-2.72, 6.72]
	Age	0.02	[-0.16, 0.20]	-0.02	[-0.06, 0.01]	-0.03	[-0.07, 0.00]	-0.02	[-0.10, 0.00]	-0.05	[-0.10, 0.00]
	Gender	-2.00	[-4.02, 0.01]	0.15	[-0.26, 0.57]	-0.12	[-0.55, 0.31]	0.01	[-0.45, 0.65]	0.10	[-0.45, 0.65]
	Education	-0.10	[-0.52, 0.31]	0.13**	[0.05, 0.21]	0.06	[-0.03, 0.14]	0.05	[-0.07, 0.15]	0.04	[-0.07, 0.15]
	WMH	-1.32	[-3.8, 1.16]	-0.10	[-0.61, 0.41]	-0.05	[-0.58, 0.48]	0.11	[-0.90, 0.45]	-0.22	[-0.09, 0.45]
	WMH x Education	-0.96*	[-1.87, -0.04]	0.10	[-0.09, 0.29]	0.11	[-0.09, 0.30]	0.23*	[0.02, 0.44]	0.05	[-0.20, 0.30]
NC	Intercept	-3.93	[-17.82, 9.96]	1.83	[-3.45, 7.12]	-3.25	[-9.63, 3.12]	-0.52	[-7.20, 6.15]	2.28	[-5.36, 9.93]
	Age	0.13	[-0.01, 0.26]	-0.05	[-0.1, 0.01]	-0.03	[-0.10, 0.03]	-0.04	[-0.11, 0.02]	-0.03	[-0.10, 0.05]
	Gender	0.71	[-0.64, 2.05]	0.39	[-0.12, 0.91]	-0.13	[-0.74, 0.49]	0.24	[-0.40, 0.89]	0.42	[-0.32, 1.16]
	Education	-0.24	[-0.40, -0.07]	0.08*	[0.01, 0.14]	0.05	[-0.02, 0.13]	0.12**	[0.04, 0.20]	0.07	[-0.02, 0.16]
	WMH	0.17	[-1.97, 2.30]	0.07	[-0.74, 0.88]	-1.38*	[-2.36, -0.40]	-0.46	[-1.49, 0.56]	0.52	[-0.65, 1.70]
	WMH x Education	0.09	[-0.25, 0.43]	-0.05	[-0.18, 0.08]	0.14	[-0.02, 0.30]	0.00	[-0.17, 0.16]	-0.14	[-0.33, 0.05]

LLD, Late-life depression; NC, normal control; p < 0.05; p < 0.005***

WMH with depressive symptoms and language function. This implies that high CR, using the proxy of education level, could moderate deleterious effects of WMH in LLD.

Severe WMH is associated with higher prevalence of depressive symptoms (26). In late-onset LLD, higher WMH in the left superior longitudinal fasciculus and the right uncinate fasciculus was positively correlated with depression severity (27). As most of our patients were under antidepressant treatment for a period of time, higher depressive symptoms in current study may be indicative of greater refractoriness or treatment resistance. Similarly, recent evidence has demonstrated that non-remitters showed significantly WMH increase than remitters following a 12-week antidepressant course against LLD (28). Our results further extend these findings by showing such an association only in those with low education. A number of epidemiological studies have proposed lower education as a risk factor for LLD (29–31), with socioeconomic disparity as the probable cause for this association. However, uncovering the neuroscientific basis of this phenomenon requires application of the framework of CR to the existing vascular hypothesis of LLD.

Lower WM integrity on diffusion tensor imaging was found in elderly patients with high CR, measured in terms of education level (32) or life-long bilingualism (33); those with high CR were speculated to be better able to endure WM lesions. The specific WM tracts related to CR include the inferior longitudinal fasciculus/inferior fronto-occipital fasciculus, the fornix (33), and corpus callosum (32, 33). However, these do not coincide with the tracts (e.g., cingulum bundle, uncinated fasciculus, and superior longitudinal fasciculus) typically reported to harbor WMH in LLD (34, 35). Given this discrepancy, education may enhance network efficiency and re-organization of the network topology (36), circumventing the tracts with high WMH in order to maintain function. For example, the corpus callosum, which is involved in CR, is crucial for inter-hemispheric communication (37), supporting the claim that CR promotes brain plasticity in the face of brain pathology (38).

In this study, we found WMH to be associated with lower working memory in elderly controls. This is consistent with other studies showing that lower performance of WM was associated with high WMH in the periventricular region (39, 40). Furthermore, we found that education modified effects of WMH on language function in LLD patients. Here, we measured the language function by using categorical verbal fluency—a parameter that is amenable to effects of education (41). Although working memory is required as verbal fluency is a speeded task (42, 43), language function is the most critical component in this task (44). Multiple brain areas, such as the left inferior/middle frontal gyrus, anterior cingulate gyrus (ACC) (45), left superior parietal lobule and left hippocampal formation (46), are activated in the verbal fluency task. Conversely, hypoactivation in the left prefrontal cortex, left ACC and frontopolar region is associated with poor task performance in depression (47) or late-onset LLD (48). Since WMH disrupts long range connections in the brain, it affects executive function or working memory is affected (49) and jeopardizes verbal fluency function. As opposed to the age decline in fluid intelligence (Gf), crystallized intelligence (Gc) is relatively spared (50, 51). Benefits bestowed by education on Gc may offset detrimental effects of WMH on Gf, thereby sustaining the integrity of verbal fluency. However, how education attainment preserves language functioning is out of the scope of the current study. A possible explanation is that it promotes synaptogenesis, which in turn increases the redundancy and neuroplasticity of the brain (52).

It is intriguing that CR moderates the effects of WMH on mood and cognitive function in a much more significant way in LLD patients than in normal elderly individuals. For example, a three-way interaction between group, education and WMH was found in predicting the scores of GDS. A possible explanation lies in the threshold theory (53, 54), which posits that cognitive function is compromised only after the WMH load reaches a certain threshold. Therefore, low WMH load in the elderly controls may be insufficient to observe benefits of CR. Alternatively, a brain with LLD may be functionally and structurally more compromised, rendering those afflicted with depression more susceptible to other insults. Since overall WMH in our LLD patients did not surpass that in the elderly controls, we suspect that these lesions may be located in strategic areas that control cognitive and emotional function. Thus, CR could play a pivotal role in linking these symptoms to LLD (16). This may explain the failure of a previous study in demonstrating a significant moderating effect of CR on the association between depressive symptoms and WMH as it could be due to inclusion of participants not formally diagnosed with depression (19).

Limitations and Conclusions

Our study has a few limitations. First, due to ethical concerns, all the participants were receiving pharmacotherapy at the time of data collection. However, this does not influence our interaction results since the antidepressant dose did not differ between high or low education individuals within the LLD group. Second, we used education as a proxy for CR. Further studies incorporating occupational attainment and leisure activities may provide a more comprehensive evaluation of CR. Third, we did not specify periventricular or deep WMH, which may result in a lack of association in other cognitive domains. However, periventricular and deep WMH are highly correlated and may all reflect total WMH (55). Moreover, we specifically excluded patients with stroke or significant cardiovascular comorbidity, resulting in relatively low WMH loads in both groups. Therefore, we evaluated total WMH in order to gain more power in the analysis. Finally, our study enrolled a small sample size and only examined WMH. Studies with larger sample size evaluating other biomarkers for cognitive decline (e.g., amyloid deposition or tau pathology) are warranted to further elucidate the underlying mechanism.

In conclusion, we demonstrated that education is an important modifier of the association between WMH and clinical LLD presentation. Our finding implies that education level must be taken into consideration while analyzing consequences of WMH in LLD. Previous discrepancies in LLD research may be attributed to the failure to consider CR and WMH at the same time. Overall, our result reiterates the notion that education is related to increased CR

and supports the hypothesis that higher CR confers a higher threshold for symptom manifestation of LLD (16, 56).

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding authors.

ETHICS STATEMENT

The institutional review board of the Chang Gung Memorial Hospital approved this study (IRB number:IRB104-0928).

AUTHOR CONTRIBUTIONS

CL, C-MH, H-LL, S-HL, and TL designed the project. CL, H-LL, Y-LC, S-HL, and TL performed the experiment. CL, C-MH, Y-TF, and HA analyzed the data. CL wrote the manuscript. All authors have read and approved the final version of the manuscript.

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