ORIGINAL CONTRIBUTION

Brain Structure and Cerebrovascular Risk in Cognitively Impaired Patients

Shanghai Community Brain Health Initiative–Pilot Phase

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Objective: To investigate the associations among brain morphologic changes as seen on magnetic resonance imaging (MRI), cerebrovascular risk (CVR), and clinical diagnosis and cognition in elderly patients with mild cognitive impairment and dementia living in urban Shanghai.

Design: Cross-sectional study performed from May 1, 2007, to November 31, 2008.

Setting: Memory Disorders Clinic of the Huashan Hospital and the Shanghai community.

Participants: Ninety-six older people: 32 with normal cognition (NC), 30 with amnestic mild cognitive impairment (aMCI), and 34 with dementia.

Main Outcome Measures: For each patient, we administered a neurologic and physical examination, neuropsychological evaluation, and brain MRI and genotyped the apolipoprotein E-ε4 (*APOE-ε4*) gene. The volumes determined by MRI were assessed using a semiautomatic method.

Results: Brain volume was significantly smaller in the dementia patients compared with the NC ($P < .001$) and aMCI patients ($P = .04$). Hippocampal volume (HV) was lower and white matter hyperintensity (WMH) volume was higher in those with aMCI (HV: $P = .03$; WMH volume: $P = .04$) and dementia (HV: $P < .001$; WMH volume: $P = .002$) compared with NC participants. The presence of *APOE-ε4* was significantly associated with reduced HV ($P = .02$). Systolic blood pressure was positively associated with CVR score ($P = .04$); diastolic blood pressure ($P = .02$) and CVR score ($P = .04$) were positively associated with WMH volume. The WMH volume ($P = .03$) and CVR score ($P = .03$) were higher among dementia patients compared with NC participants.

Conclusions: Brain structure changes seen on MRI were significantly associated with clinical diagnosis. In addition, blood pressure was highly associated with CVR score and WMH volume. These results suggest that MRI is a valuable measure of brain injury in a Chinese cohort and can serve to assess the effects of various degenerative and cerebrovascular diseases.

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As the worldwide population of older adults increases, age-related illnesses such as cerebrovascular disease and Alzheimer disease (AD) are an increasing public health issue. Substantial numbers of longitudinal and cross-sectional studies[1-13] have been published on the etiology, epidemiology, and pathology of dementia, mild cognitive impairment (MCI), and aging across different racial and ethnic groups. Studies of different races are particularly important because recent US Census data show increasing racial and ethnic diversity in the elderly population of the United States.[3,14] However, to our knowledge, relatively few studies have been performed on persons of Chinese ethnicity.

Because the largest increase in dementia cases is expected to occur primarily in developing countries,[15-17] early diagnosis will be needed for effective treatment or prevention. Structural brain imaging is widely used to study the morphologic changes of the brain, particularly those associated with the AD and cerebrovascular disease processes.[13-21] Neuroimaging also can help in predicting the probability of developing future dementia and can measure progression of underlying neurodegenerative diseases.[22]

In this study, we compared quantitative magnetic resonance imaging (MRI) measures and cerebrovascular risk (CVR) factors among 3 cognitive groups in the Shanghai Community Brain Health Initiative–pilot phase (SCOBHI-P). The goals

of SCOBHI-P were to investigate the biological and cognitive changes among older people with normal cognition (NC), MCI, and dementia and evaluate associations between MRI markers and performances on neuropsychological tests.

METHODS

STUDY PARTICIPANTS

Study participants were recruited from the SCOBHI-P, a case-control study of individuals living in Shanghai, China. The target sample included approximately equal numbers of participants with NC, MCI, and mild to moderate dementia living in the community. Patients with dementia and MCI were identified from the Memory Disorders Clinic at Huashan Hospital, located in the Jingan District of Shanghai. We identified these patients from incident patients who had first been seen at the Memory Disorders Clinic from May 1, 2007, through November 31, 2008. One hundred nine patients and their informants were invited to participate; of these, 58 (53.2%) were recruited. Of the 51 not recruited, 42 refused, 8 were unreachable, and 1 had a stroke. Potential participants with NC were identified using a government-maintained "name list," which includes the name, sex, age, address, and telephone number of all residents. We obtained the name list for Jingan and focused on a resident group in a defined geographic area consisting of 5 buildings in the Jingan Temple Community. Potential participants were approached at the door to describe the study. Of 71 potential participants from the name list, 10 refused (14.1%). An additional 3 names on the name list were unreachable. The recruitment rate in the community was 81.6%. When the 58 residents in the community were clinically evaluated, 2 (3.4%) met the study criteria for dementia and 12 (20.7%) met the Petersen criteria for MCI.[23,24] These 14 individuals were added to the patient pool. Of the 116 patients and control participants, we also removed 4 patients with nonamnestic MCI and matched a set of 32 participants with NC, 34 with amnestic MCI (aMCI), and 34 with dementia by age and sex for our analyses.

CLINICAL EVALUATION

All participants received detailed medical history, physical, and neurologic examinations and were evaluated with the Clinical Dementia Rating[25] scale in the Huashan Hospital Memory Disorders Clinic. A neuropsychological battery was administered by the study psychometrist, which included the modern Chinese Cognitive Abilities Screening Instrument,[26] Wechsler Adult Intelligence Scale–Revised (WAIS-R) Digit Span,[27] Bells Cancellation Test,[28] Wechsler Memory Scale Logical Memory Test (WMS-M)[29] (immediate and delayed recall), Rey-Osterrieth Complex Figure (ROCF) test[30] (copying and recall), Stroop test,[31] Auditory Verbal Learning Test (AVLT),[32] Category Verbal Fluency Test (VFT), WAIS-R Similarities Test,[29] Trail Making Test B,[33] Clock-Drawing Test,[34] Boston Naming Test,[35] and Chinese version of the Mattis Dementia Rating Scale (DRS).[36] All participants were genotyped for apolipoprotein E (APOE)[37] and received 2 blood pressure (BP) measurements in a seated position. We interviewed controls about themselves and control informants about the control in a separate room. Data for cases were collected from proxy informants only.

Dementia was diagnosed using *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition)[38] criteria for dementia. Alzheimer disease was diagnosed using National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association[39] criteria. Vascular dementia was diagnosed using the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences[40] criteria. Mild cognitive impairment was diagnosed using the Petersen MCI criteria.[23,24] Normal cognition was diagnosed if there was no clinically significant cognitive impairment.

MRI ACQUISITION

Brain images were obtained at the Huashan Hospital. For MRI acquisition, we used a series of image acquisition protocols developed at the University of California at Davis Imaging of Dementia and Aging Laboratory, and the imaging parameters were as previously described.[3]

Qualitative assessment of all available image sequences was used to assist with clinical diagnosis, but the clinical diagnostic team was masked to the results of quantitative analyses. The images were sent to the Imaging of Dementia and Aging Laboratory, and image quantification was performed by a rater who was masked to age, sex, educational achievement, and diagnostic status.

IMAGE ANALYSIS

Brain and WMH Volumes

Analysis of brain volume (BV) and white matter hyperintensity (WMH) volume was based on the fluid-attenuated inversion recovery sequence, which was designed to enhance WMH segmentation.[41] Brain and WMH segmentation was performed in a 2-step process according to previously reported methods.[42]

Hippocampal Volumes

Boundaries for the hippocampus were manually traced according to previously reported methods,[3] which emphasize analysis of the anterior two-thirds of the hippocampus.

MRI Infarctions

Cerebral infarction on MRI was determined according to previously published protocols.[43,44] The MRI infarction was determined from the size, location, and imaging characteristics of the lesion based on review of the double echo, fluid-attenuated inversion recovery, and 3-dimensional T1 high-resolution image. Lesions 3 mm or larger qualified for consideration as cerebral infarcts.

CVR Factors

The presence or absence of 5 CVR factors (ie, stroke, transient ischemic attack, hypertension, diabetes mellitus, and coronary artery disease) was systematically assessed from the informant interview and the study participant's medical record. The BP was measured twice and averaged. Hypertension was defined as a measured BP that exceeded 140/90 mm Hg or was controlled by medication (informed from medical history).

STATISTICAL ANALYSES

Because MRI measures of BV, WMH volume, and hippocampal volume (HV) are known to vary by sex and age,[3,20,21] all MRI variables were divided by total cranial volume.[3,43] The distri-

Table 1. Characteristics of the Shanghai Community Brain Health Initiative–Pilot Phase Participants[a]

Characteristic	NC Participants (n=32)	aMCI Patients (n=30)	Dementia Patients (n=34)	*P* Value
Sex, No.				
Male	16	15	16	.35
Female	16	15	18	
Age, y	73.41 (5.51)	74.8 (3.95)	74.41 (5.56)	.54
Educational level[b]	2.67 (1.38)	2.93 (1.41)	2.23 (1.72)	.19
BV[c]	0.80 (0.03)[f]	0.77 (0.04)[f]	0.75 (0.05)[e]	<.001
HV[c]	0.39 (0.05)[f]	0.35 (0.05)[e]	0.33 (0.08)[e]	<.001
WMH volume[d]	–5.55 (0.99)[f]	–5.27 (1.24)[e]	–4.63 (0.80)[e]	.002
CVR score[e]	0.21 (0.13)[f]	0.27 (0.18)[e,f]	0.33 (0.17)[e]	.04
MRI infarct, %	18.8	24.1	34.4	.96

Abbreviations: aMCI, amnestic mild cognitive impairment; BV, brain volume; CVR, cerebrovascular risk; HV, hippocampal volume; MRI, magnetic resonance imaging; NC, normal cognition; WMH, white matter hyperintensity.

[a] Data are presented as mean (SD) unless otherwise indicated. Group differences were determined by simple analysis of variance or χ^2 analysis.

[b] 1 indicates 1 to 6 years of education; 2, 7 to 9 years; 3, 10 to 12 years; 4, 13 to 16 years; 5, 17 or more years.

[c] Reported as the percentage of intracranial volume. HV was reported as 100 times the percentage of intracranial volume.

[d] Reported as the percentage of intracranial volume, then log-transformed to normalize variance.

[e] Reported as the percentage of 5 risk factors.

[f] Means with different superscript letters indicate significant group differences after Tukey-Kramer adjustments for multiple comparisons ($P < .05$).

bution of normalized WMH was skewed. Therefore, WMH volumes were first divided by total cranial volume and then log transformed to better approximate a normal distribution for analysis as previously described.[3]

Data were then analyzed with the use of JMP8 statistical software (SAS Institute Inc, Cary, North Carolina). Analyses of variance models with diagnostic groups as the factor were used to detect group differences in demographic variables, MRI measures, and CVR scores. The χ^2 analysis was used to test group differences in sex and the prevalence of MRI infarcts. Analyses of covariance (ANCOVA) were used to further assess the associations among CVR score, presence of MRI infarct, *APOE-ε4* genotype, and diagnostic groups for each of the 3 MRI measures while controlling for educational level and sex. An ANCOVA approach was also used to evaluate the association of the 3 MRI measures with neuropsychological tests. The Tukey-Kramer method was used for all post hoc analyses. Logistic regressions were used to investigate the association between risk factors and diagnostic groups or the presence of MRI infarct. $P < .05$ was considered statistically significant.

RESULTS

CHARACTERISTICS OF THE STUDY PARTICIPANTS

The characteristics of the study participants are given in **Table 1**. No significant differences were found across diagnostic groups by age, sex, or educational level. In addition, we compared the age and sex of the 96 participants with the 64 individuals who refused to participate or were unreachable. The mean (SD) age was 74.2 (5.1) years among the participants and 75.7 (5.2) among nonparticipants ($t = -1.86$, $P = .06$). In addition, no significant differences were found in sex distributions ($\chi^2 = 0.02$, $P = .90$). Risk factor data were not collected for nonparticipants.

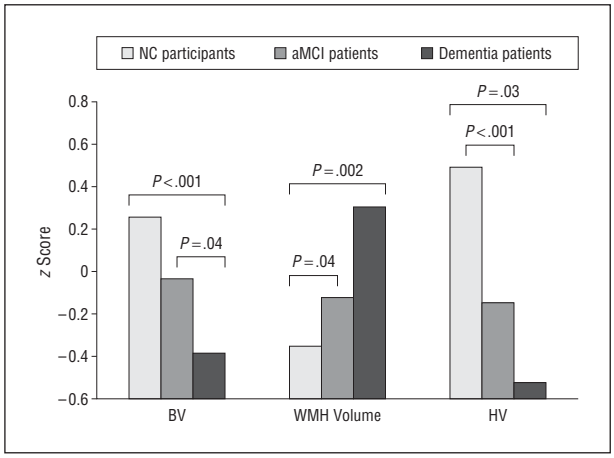

Figure. Normalized brain volume (BV) measures in participants with normal cognition (NC) and in patients with amnestic mild cognitive impairment (aMCI) and dementia. HV indicates hippocampal volume; WMH, white matter hyperintensity.

QUANTITATIVE MRI

For each MRI measure, analysis of variance models were performed with diagnostic groups as the factor. Patients with dementia had significantly smaller BV than those with NC ($P < .001$) and aMCI ($P = .04$). The HV was significantly smaller and the WMH volume was significantly higher for those with aMCI (HV: $P = .03$; WMH volume: $P = .04$) and dementia (HV: $P < .001$; WMH volume: $P = .002$) compared with those with NC (**Figure**). The χ^2 testing indicated that the percentage of patients with MRI infarct did not significantly differ across diagnostic groups.

Secondary analyses used ANCOVA models to examine the association among diagnostic groups, age, *APOE-ε4*, CVR score, MRI infarcts, and MRI measures, after controlling for educational level and sex (**Table 2**). Older age was significantly associated with decreased BV ($P < .001$), decreased HV ($P = .01$), and increased WMH volume ($P = .001$). The presence of *APOE-ε4* was associated with decreased HV ($P = .02$). A history of MRI infarct was significantly associated with increased WMH volume ($P = .002$). Post hoc Tukey-Kramer analysis showed that, after adjusting for covariates, individuals with dementia had significantly smaller BV than those with NC ($P < .001$) and aMCI ($P = .01$) but had significantly higher WMH volume than those with NC ($P = .01$). The HV was also significantly smaller among those with dementia compared with those with NC but did not differ between those with dementia and aMCI.

VASCULAR RISK FACTORS

Given the findings that increased WMH volume was associated with cognitive impairment, we further explored the association among CVR score, diagnostic group, and MRI measures. The CVR scores (mean [SD],

Table 2. Associations Among Risk Factors, Diagnosis, and MRI Measures[a]

	BV (SE)	WMH Volume (SE)	HV (SE)
Dementia patients/NC participants	**–0.04 (0.01) ($P < .001$)**	**–0.71 (0.24) ($P = .01$)**	**–0.06 (0.02) ($P < .001$)**
Demented/aMCI patients	**–0.03 (0.01) ($P = .01$)**	–0.54 (0.24) ($P = .06$)	–0.03 (0.02) ($P = .11$)
aMCI patients/NC participants	–0.01 (0.01) ($P = .33$)	–0.16 (0.24) ($P = .78$)	–0.03 (0.02) ($P = .14$)
Age	**–0.003 (0.001) ($P < .001$)**	**0.07 (0.02) ($P = .001$)**	**–0.003 (0.001) ($P = .01$)**
APOE-ε4 status	–0.01 (0.01) ($P = .14$)	–0.26 (0.24) ($P = .27$)	**–0.04 (0.02) ($P = .02$)**
CVR score	–0.02 (0.02) ($P = .47$)	0.71 (0.61) ($P = .25$)	–0.002 (0.039) ($P = .96$)
MRI infarcts	–0.005 (0.009) ($P = .60$)	**0.69 (0.22) ($P = .002$)**	0.03 (0.01) ($P = .07$)

Abbreviations: aMCI, amnestic mild cognitive impairment; APOE, apolipoprotein E; BV, brain volume; CVR, cerebrovascular risk; HV, hippocampal volume; MRI, magnetic resonance imaging; NC, normal cognition; WMH, white matter hyperintensity.

[a] Educational level and sex adjusted in the models. Sex and educational level were not significant in any of the models. Significant values ($P < .05$) are indicated in bold.

Table 3. Associations Among CVR Scores, WMH Volumes, and MRI Infarcts[a]

Model	Variable	WMH Volume (SE)	MRI Infarcts (SE)
Model 1	CVR score	**1.54 (0.64) ($P = .02$)**	–2.75 (1.53) ($P = .07$)
Model 2	CVR score	. . .[b]	–1.75 (1.65) ($P = .29$)
	WMH volume	. . .[b]	**–1.02 (0.33) ($P = .002$)**

Abbreviations: CVR, cerebrovascular risk; MRI, magnetic resonance imaging; WMH, white matter hyperintensity.

[a] Age and sex adjusted in the models. Significant values ($P < .05$) are indicated in bold.

[b] Ellipses indicate variable was not included in the model.

Table 4. Odds Ratios (95% Confidence Intervals) for Risk Factors in Logistic Regression Models[a]

	Dementia Patients vs NC Participants[b]	aMCI Patients vs NC Participants[b]	Dementia vs aMCI Patients[b]
BV	**0.61 (0.42-0.80)**	0.88 (0.71-1.07)	**0.80 (0.66-0.94)**
HV	**0.84 (0.70-0.96)**	**0.88 (0.76-1.00)**	**0.89 (0.78-0.99)**
WMH volume	**3.34 (1.33-10.28)**	1.16 (0.56-2.47)	**2.43 (1.09-6.11)**
CVR score	**3.78 (1.26-16.03)**	1.35 (0.66-2.93)	0.96 (0.49-1.86)
APOE-ε4	0.66 (0.05-6.34)	2.30 (0.39-16.15)	0.71 (0.16-3.10)
MRI infarcts	1.26 (0.13-12.40)	1.73 (0.41-7.42)	1.01 (0.21-5.93)

Abbreviations: aMCI, amnestic mild cognitive impairment; APOE, apolipoprotein E; BV, brain volume (divided by total cranial volume and then multiplied by 100); CVR, cerebrovascular risk (number of cerebrovascular risk factors); HV, hippocampal volume (divided by total cranial volume and multiplied by 10 000); MRI, magnetic resonance imaging; NC, normal cognition; WMH, white matter hyperintensity (divided by total cranial volume and then multiplied by 100).

[a] Age, sex, and educational level adjusted in the models. Significant values ($P < .05$) are indicated in bold.

[b] Reported as the odds ratio for a 1-unit increase in continuous predictor variables.

0.27 [0.17]) ranged from 0% to 60%, and 82 participants (85.4%) had at least 1 CVR factor; of 82 study participants with a CVR score greater than zero, 80 (97.6%) had hypertension. In addition, 81 participants (84.4%) in this sample were hypertensive (mean [SD] BP, 152.16 [21.62]/77.57 [10.39] mm Hg), despite the fact that most received treatment. The prevalence of MRI infarcts in this sample was 25.8%. Analysis of variance results revealed that the CVR score in patients with dementia was significantly higher than in those with NC ($P = .03$; Table 1). After adjusting for age and sex, ANCOVA estimates showed that increased CVR scores were associated with increased WMH volume ($P = .02$) but not the number of MRI infarcts. Using WMH volume and CVR score together as independent variables in a logistic regression model predicting MRI infarct, we found that increased WMH volume but not the CVR score was significantly associated with the increased risk of MRI infarct ($P = .002$; **Table 3**).

ASSOCIATIONS WITH CLINICAL SYNDROME

Logistic regression analyses were used to examine the effects of all risk factors (demographics, MRI measures, CVR score, and *APOE-ε4*) that optimally distinguished the diagnostic groups. Three separate models were fit to allow comparisons between dementia patients vs NC participants, aMCI patients vs NC participants, and dementia vs aMCI patients (**Table 4**). When comparing dementia patients with NC individuals, we found reduced BV ($P = .002$) and HV ($P = .02$) and increased WMH volume ($P = .03$) and CVR score ($P = .03$) to be independently and significantly associated with an increased risk of dementia. With each increase of 1% of BV, the odds of dementia were reduced nearly 40% (odds ratio [OR], 0.61; 95% confidence interval [CI], 0.42-0.80). With each 0.01% increase in HV, the odds of dementia were 16% lower (OR, 0.84; 95% CI, 0.70-0.96). Conversely, a 1% increase in WMH volume was associated with a 3-fold increase in the odds of dementia (OR, 3.34; 95% CI, 1.33-10.28). Similarly, the presence of each CVR factor was associated with a nearly 4 times increased odds of dementia (OR, 3.78; 95% CI, 1.26-16.03).

Similarly, when comparing aMCI with dementia, every 1% increase in BV was associated with a 20% lower odds of dementia (OR, 0.80; 95% CI, 0.66-0.94), and every 0.01% increase in HV was associated with an 11% decrease in the odds of dementia (OR, 0.89; 95% CI, 0.78-0.99). Conversely, each 1% increase in WMH volume was

Table 5. Associations Between Brain Structure and Scores on Neuropsychological Tests[a]

Neuropsychological Test	BV (SE)	WMH Volume (SE)	HV (SE)
WMS Logical Memory Test (delayed recall)	16.42 (9.50) ($P = .09$)	−0.69 (0.36) ($P = .06$)	**12.73 (5.74) ($P = .03$)**
WMS Logical Memory Test (immediate recall)	14.41 (9.84) ($P = .15$)	−0.66 (0.37) ($P = .08$)	6.33 (5.94) ($P = .29$)
Bells Cancellation Test	**19.70 (6.33) ($P = .003$)**	−0.34 (0.24) ($P = .16$)	0.60 (3.82) ($P = .87$)
ROCF copy test	**94.71 (22.96) ($P < .001$)**	**−1.89 (0.90) ($P = .04$)**	−2.79 (14.47) ($P = .85$)
ROCF delayed recall test	22.24 (18.37) ($P = .23$)	**−1.47 (0.69) ($P = .04$)**	**31.23 (11.09) ($P = .006$)**
Stroop test (color-word)	**109.57 (32.74) ($P = .001$)**	**−2.02 (1.23) ($P = .10$)**	0.63 (19.77) ($P = .97$)
WAIS-R Similarities Test	**45.79 (13.56) ($P = .001$)**	**−1.85 (0.51) ($P < .001$)**	−12.42 (8.19) ($P = .13$)
AVLT (short delayed recall)	6.73 (5.41) ($P = .22$)	−0.24 (0.20) ($P = .24$)	**8.64 (3.27) ($P = .01$)**
AVLT (long delayed recall)	7.49 (5.43) ($P = .17$)	−0.20 (0.20) ($P = .34$)	**9.20 (3.28) ($P = .006$)**
Trail Making Test B	**−845.76 (290.56) ($P = .005$)**	**42.74 (9.25) ($P < .001$)**	−24.18 (166.46) ($P = .88$)
Mattis Dementia Rating Scale	**225.76 (36.81) ($P < .001$)**	**−3.90 (1.34) ($P = .005$)**	−12.20 (21.63) ($P = .57$)
WAIS-R Digit Span, total	**10.98 (4.17) ($P = .01$)**	−0.13 (0.16) ($P = .40$)	−3.29 (2.52) ($P = .20$)
WAIS-R Digit Span, forward	**5.22 (2.00) ($P = .01$)**	0.05 (0.07) ($P = .49$)	−1.64 (1.21) ($P = .18$)
WAIS-R Digit Span, backward	**5.76 (2.86) ($P = .047$)**	−0.19 (0.11) ($P = .09$)	−1.65 (1.73) ($P = .34$)
Category Verbal Fluency Test[b]	**119.76 (23.94) ($P < .001$)**	**−2.28 (0.90) ($P = .01$)**	18.16 (14.46) ($P = .21$)
Boston Naming Test	9.95 (0.57) ($P = .52$)	−0.67 (0.57) ($P = .24$)	5.06 (9.19) ($P = .58$)
Clock-Drawing Test	8.34 (7.44) ($P = .27$)	0.14 (0.28) ($P = .63$)	3.53 (4.51) ($P = .44$)

Abbreviations: AVLT, Auditory Verbal Learning Test; BV, brain volume; HV, hippocampal volume; ROCF, Rey-Osterrieth Complex Figure; WAIS-R, Wechsler Adult Intelligence Scale–Revised; WMH, white matter hyperintensity; WMS, Wechsler Memory Scale.

[a] Age, sex, and educational level adjusted in the models. Significant values ($P < .05$) are indicated in bold.

[b] Total score for animals, fruits, and vegetables.

associated with 2.43 times greater odds of dementia (OR, 2.43; 95% CI, 1.09-6.11).

When comparing aMCI patients with NC individuals, an increase of 0.01% in HV was associated with a 12% reduction in the odds of aMCI (OR, 0.88; 95% CI, 0.76-1.00) (Table 4).

NEUROPSYCHOLOGICAL TEST SCORES AND MRI MEASURES

Finally, separate ANCOVA models controlling for age, educational level, and sex were used to assess the associations between MRI measures (BV, WMH volume, and HV) and performance on individual neuropsychological tests listed in **Table 5**. We found that increased BV was significantly associated with higher scores on the Bells Cancellation Test ($P = .003$), ROCF copying test ($P < .001$), Stroop color-word test ($P = .001$), WAIS-R Similarities Test ($P = .001$), Mattis DRS ($P < .001$), WAIS-R Digit Span total score ($P = .01$), and VFT ($P < .001$) and better scores on the Trail Making Test B ($P = .005$). Increased WMH volume was associated with worse performance on the ROCF copying ($P = .04$) and delayed recall ($P = .04$) tests, WAIS-R Similarities Test ($P < .001$), Mattis DRS ($P = .005$), and VFT ($P = .01$) and worse scores on the Trail Making Test B ($P < .001$). Increased HV was significantly associated with higher scores on the WMS-M delayed recall test ($P = .03$), ROCF delayed recall test ($P = .006$), and AVLT short ($P = .01$) and long delayed recall ($P = .006$).

COMMENT

Imaging-based volumetric measurements are widely used to characterize and assist in the diagnoses of dementia and MCI, particularly of the hippocampus, which is recognized as a brain region where AD pathological changes are likely to first appear.[19,45-47] Global brain atrophy and WMH volume are also recognized as structural brain measures associated with aging and dementia.[3,48-51] Our study in this Chinese sample found similar volumetric differences in brain, hippocampus, and WMH among the diagnostic groups, in which increasing atrophy and WMH were significantly associated with increasing clinically recognized cognitive impairment. Furthermore, these MRI measures were also associated with previously described risk factors, such as age and CVR factors, as well as *APOE-ε4* for the hippocampus. These findings are similar to those of previously reported MRI studies[47,52] of predominantly white populations. Because hippocampal atrophy shows the earliest and most consistent morphologic change in AD, our findings support the hypothesis that *APOE-ε4* also is a risk factor for aMCI and dementia in the Chinese population.

Cerebrovascular risk factors such as hypertension were strikingly common in this Chinese sample. The mean (SD) CVR score (0.27 [0.17]) was somewhat higher than for whites in a previous study at the University of California at Davis, Alzheimer Disease Center (0.22 [0.20]).[3] Although the prevalence of hypertension in SCOBHI-P (men, 85.1%; women, 83.7%) was similar to that in the Framingham Heart Study[43] (men, 87%; women, 82%) and 96.4% of patients were receiving treatment, their BP was less well controlled (men: 154.8 [21.5]/80.9 [10.2] mm Hg; women: 158.5 [19.1]/76.4 [10.8] mm Hg) compared with the Framingham study participants (men: 139 [18.8]/68.2 [11.9] mm Hg; women: 141 [20.8]/67.5 [10.8] mm Hg). We believe that this finding might explain the higher prevalence of MRI infarcts in this Chinese study compared with the Framingham study. Our data also show that undertreated hypertension may be a significant factor in dementia prevalence among the Chinese as evidenced by the increased CVR score and WMH volume associated with dementia (Table 4).

We found that patients with dementia differed significantly from the 2 other groups on measures of BV, WMH volume, and HV; aMCI patients differed significantly from NC participants on HV only; and the CVR score differed significantly between the patients with dementia and those with NC. Mild cognitive impairment is recognized to be the transitional state between normal cognition and dementia,[24] and individuals with aMCI are thought to display early manifestations of AD symptoms, with 13% per year on average converting to AD.[53,54] Our analysis confirmed that hippocampal atrophy is the earliest brain structure change in aMCI patients, whereas brain atrophy, WMH burden, and CVR factors were more strongly associated with dementia. Again, these findings are remarkably consistent with previous reports that studied white populations.

Our results also showed that brain atrophy was significantly associated with performance on the Bells Cancellation Test, ROCF copying test, Stroop color-word test, WAIS-R Similarities Test, WAIS-R Digit Span, Trail Making Test B, Mattis DRS, and VFT; WMH volume was significantly associated with ROCF delayed recall and copy tests, WAIS-R Similarities Test, Trail Making Test B, Mattis DRS, and VFT, although the significance of the relationship between WMH volume and the ROCF test is likely marginal given the number of individual analyses performed. The HV was significantly associated with the WMS-M delayed recall test, ROCF delayed recall test, and AVLT short and long delayed recall. These findings suggest that despite age, educational level, and cultural differences across studies, structural brain changes are consistently associated with cognitive measures. The presence of a strong association between HV and memory performance, especially in delayed recall tests, supports the theory that the hippocampus has a relatively specific role in retaining information after a delay[55,56] and supports the notion that delayed memory impairments and hippocampal atrophy are cardinal features of AD even in a Chinese population in whom vascular disease is relatively common. In contrast, hypertension was common in this sample and less well treated when compared with a reference white cohort. Given that BP was positively associated with WMH volume and that increasing WMH volume correlated with impaired cognitive syndrome, it is possible that poorly controlled BP may be partially responsible for cognitive impairment in our sample. Control of BP might be expected to decrease the prevalence of dementia in this population.

Our study, however, has several limitations. First, this is a cross-sectional study; consequently, we can only show association and not causality. The study participants were recruited not only from the community but also from the clinic; therefore, they may not reflect the general population. In addition, our dementia patients were not restricted to AD dementia. If the study population was strictly limited to AD dementia, we may have found brain differences more characteristic of AD. This limitation, however, is likely to be minimal because we found a significant reduction in HV, similar to previous findings in AD cohorts. More likely, these data reflect a much higher prevalence of comorbid cerebrovascular disease, even though a high percentage of dementia patients were diagnosed as having AD.

China is a country with a large older population that has received relatively little study. Despite obvious cultural differences from previously reported, predominantly white studies, we identified similar genetic factors and structural brain differences associated with dementia in this population. The greatest difference between this sample and other white samples appears to relate to the high frequency of vascular brain injury (eg, presence of MRI infarcts) and vascular risk factors, especially hypertension. Because cerebrovascular disease is a treatable disorder, further study and possible treatment are warranted.

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