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Profiles by Sex of Brain MRI and Cognitive Function in The Framingham Offspring Study

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Abstract

Objective—To examine whether there are sex-specific associations between brain MRI measures and neuropsychological test performance.

Background—Differences in cardiovascular risk factors (CVRF) have been linked to decreased total cerebral brain volume (TCBV) and white matter hyperintensities (WMH). Although brain morphology has been related to cognitive performance, few studies have addressed sex-specific effects in this relationship.

Methods—Framingham Offspring who were stroke and dementia-free underwent a brain MRI scan and neuropsychological (NP) testing (n=2,085; 978 men). Factor analysis identified four domain-specific neuropsychological factors. MRI participants were divided into four MRI subgroups based on measures of TCBV and combinations of the presence of WMH and silent cerebral infarcts (≥3mm; SCI).

Results—Overall, the relationship between MRI and NP measures was similar between the sexes. The exception was that only men showed a positive relationship between executive function (EF) and cerebrovascular disease defined as large white matter hyperintensity volume plus SCI. This finding was attributed only among men with FSRP scores > 90th percentile range (p=0.0019).

Conclusions—Measures of brain atrophy and subclinical markers of vascular disease showed that sex does not significantly alter the relationship between MRI and NP, except among men and women who are at high risk for stroke; these men show poorer performance on EF, whereas the women do not.

Keywords

Sex; Brain MRI; Cognition; Neuropsychological tests

INTRODUCTION

Smaller brain volume and large white matter hyperintensity (WMH) volumes have been linked with deficits in cognitive function,1–7 particularly in tests of executive function. Further,

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prevalent silent cerebral infarct (SCI) in conjunction with large WMH, resulted in deficits greater than those associated with presence of WMH only.8

These structural and cognitive changes have been associated with vascular risk factors. The Framingham Stroke Risk Profile (FSRP) score, a composite risk score of cardiovascular risk factors that measures 10-year probability of stroke9, has been negatively associated with total cerebral brain volume (TCBV)1 and positively related to prevalent white matter hyperintensities (WMH).10 Further, higher FSRP scores are also correlated with poor cognitive performance.11

Notable sex differences have been documented in the prevalence of cardiovascular risk factors and cardiovascular disease. [12–17] The incidence and progression rate of cardiovascular disease and hypertension is significantly higher in men than in women.[12] Given those sex differences, one might expect that sex differences might also appear in the interaction between vascular risk factors and brain structural imaging changes. We therefore sought to examine the interaction of sex and vascular risk factors in a large community-based cohort who underwent structural imaging and cognitive testing.

METHODS

Subjects

The community-based Offspring Cohort of the Framingham Study, recruited in 1971, served as the study sample. They have undergone seven periodic physical and medical examinations over a 30 year period to identify risk factors for cardiovascular and cerebrovascular diseases. [18] The Offspring cohort consists of the biological children of the Original cohort and their spouses (n=5,124); 88% of those alive in the Offspring cohort (3,539 of 4,031) participated in Exam 7.

After participating in Exam 7, 2,494 Offspring participants, who were free of clinical stroke, diagnosis of possible dementia, multiple sclerosis, or other neurological illnesses, agreed to neuropsychological testing from 1999 to 2005; 2,156 of these participants also had a brain MRI. The neuropsychological tests and brain MRI scan were administered on the same day to 96.9% of participants; 2,145 (99.5%) of participants had the MRI scan and neuropsychological tests within 6 months and were included in the analysis presented here.

From these 2,145 participants, we further eliminated 59 participants who had missing data, and one participant under the age of 35. After all exclusions, our total study size was 2,085.

Test Battery

The neuropsychological battery consisted of tests of verbal and visual memory, verbal learning, attention/concentration, tracking and mental flexibility. To reduce the number of NP variables, we conducted a factor analysis to identify four domain-specific factors: Verbal Memory (VM), Visuospatial Memory (VsM), Verbal Learning (VL), and Executive Function (EF). Within gender, each of the NP measures (log transformed as necessary) was regressed onto age and education (group) and the residuals were standardized to have mean zero and standard deviation one. These represent performance for a given age, education and gender. For each factor, the variable loadings were similar and we decided to sum the variables to create the factors. For example, Factor 1 is a linear combination of Wechsler Memory Scale (WMS) tests of Logical Memory Immediate Recall (LM-I) and Logical Memory Delayed Recall (LM-D), with coefficients nearly the same, and we define Factor 1 as the sum of the two. [11] Factor 2 is comprised of WMS Visual Reproductions Immediate Recall and Delayed Recall tests. Factor 3 combines WMS Paired Associates Immediate and Delayed Recall conditions, and Factor 4 is represented by timed performance on Halstad-Reitan Trails A and B tests.

MRI

Acquisition Parameters—Imaging was done on a Siemens Magnetom 1.0 Tesla field strength magnetic resonance machine using a double spin-echo coronal imaging sequence of 4 millimeter contiguous slices from nasion to occiput with a repetition time [TR] of 2,420 msec, echo time [TE] of TE1 20/ TE2 90 msec; echo train length 8 msec; field of view [FOV] 22 centimeters and an acquisition matrix of 182 × 256 interpolated to a 256 × 256 with one excitation. About 10% of scans were performed out-of-state and were conducted on a 1.5T machine using the same scan protocol. Test scans were performed on all off-site scanners and verified as done correctly (by C.D.).

Image Analysis—After acquisition of the MR scans, the digital information was transferred to a central laboratory directed by one of the authors (C.D.) for processing and analysis. All analyses were performed blind to any subject's personal identifying information. Image evaluation was based on a semiautomatic segmentation analysis that involves operator-guided removal of non-brain elements by operator-guided tracing of the dura matter within the cranial vault, including the middle cranial fossa, but above the posterior fossa and cerebellum. The resulting measure of the cranial vault was defined as the total cranial volume and served as an estimate of head size to correct for recognized gender differences.

Quantification of brain volumes and WMH required a multi-step process that began with image segmentation to define brain matter from cerebral spinal fluid (CSF). A difference image was created by the subtraction of the second echo image from the first echo image. After image segmentation into brain matter and CSF, the operator returned to the image for measurement of lobar brain volumes. Segmented brain-CSF images were rotated separately from the original image to preserve measurement precision.

After the image was transformed into anatomic standard space, the operator returned to the image and identified brain lobar and regional CSF measures. For segmentation of WMH from brain matter, the first and second echo images were summed after removal of CSF and correction of image intensity non-uniformities. A repeat gaussian distribution was fitted to the summed image data and a segmentation threshold for WMH was a priori determined as 3.5 S.D. in pixel intensity above the mean of the fitted distribution of brain parenchyma. Morphometric erosion of two exterior image pixels was applied to the image before modeling to remove the effects of partial volume CSF pixels on WMH determination. The presence of MRI infarction was determined from the size, location and imaging characteristics of the lesion. The image analysis system allowed for superimposition of the subtraction image, the proton density image and the T2 weighted image at three times magnified view to assist in interpretation of lesion characteristics. Only lesions 3 mm or larger qualified for consideration as cerebral infarcts. Other necessary imaging characteristics included (1) CSF density on the subtraction image and (2) if the infarct was in the basal ganglia area, distinct separation from the circle of Willis vessels. Three raters determined the presence of cerebral infarction on MRI. Kappa values for agreement amongst the three raters were generally good and ranged from 0.73 to 0.90.

All volumes were calculated as the sum of the pixels within the identified region of interest multiplied by the pixel volume in milliliters. Repeat analysis of intra- and inter-rater reliabilities for the purpose of this study were consistently above 0.90.[19]

TCBV Measure—TCBV was corrected for head size by computing the ratio of total brain volume over total cranial volume (TCV), multiplied by 100.[20]

WMH Quantification—WMH volume was corrected for head size by dividing by total cranial volume multiplied by 100 and logged due to the high skewness of the WMH/TCV ratio.

[21] Participants with large WMH volume (WMH-L; >1 SD above the mean for participant age group) were identified and those with little or no WMH were excluded.[7,21] In previous Framingham papers, we found that when WMH was considered as a continuous variable, no significant difference was seen.[7,10] However, when WMH is dichotomized, as was done here, an impact can be seen. This would suggest that there is a threshold value above which the effect of WMH can be seen clinically. A recent Framingham paper further suggests that the issue of WMH is complicated by concomitant SCI.[8] Therefore, four study groups were identified based on MRI results: 1) those with SCI only (SCI-O); 2) those with large WMH volume only (WMH-L); 3) those with both SCI and WMH-L (SCI-WMH-L); 4) those with neither SCI nor WMH-L (No SCI-No WMH-L).[8]

Procedure

Subjects were administered the neuropsychological test battery using standard test administration protocols for each test. In general, higher scores reflect better performance, except for the timed measures of Trail Making Tests A & B, where lower scores indicate better performance. However, the Executive Function factor was created from standardized Trail Making A and B, so a higher value indicates better performance.

Statistical Analysis

The significance of the sex-by-TCBV interaction (i.e., the significance of sex effect on the TCBV-cognition relationship) was assessed separately for each neuropsychological parameter using multiple linear regression (Trail Making Test A and B scores were log-transformed for analysis due to their skewness). The analysis on each factor was considered primary; the analysis on the individual test items within significant factors was considered secondary. We focused primarily on neuropsychological factors, rather than evaluating each individual test, in order to minimize the issue of multiple comparisons. The neuropsychological parameter was the regression outcome. TCBV, sex and TCBV-by-sex interaction were the primary independent variables, and the covariates were age, education, height, and the Framingham Stroke Risk Profile score. The significance of the sex-by-WMH-SCI group on cognitive function was assessed in a similar manner using analysis of covariance (ANCOVA). Sex-specific covariate-adjusted assessments of the linear relationship between the neuropsychological parameters and TCBV and of the linear trend in neuropsychological parameters across WMH-SCI categories (where categories are ordered as No SCI–No WMH-L, SCI-O, WMH-L, and SCI-WMH-L) were carried out using multiple linear regression and ANCOVA, respectively. Sex-specific covariate-adjusted assessment of the significance of the difference between SCI-WMH-L participants and participants in the remaining three categories pooled was carried out using ANCOVA.

RESULTS

Table 1 provides the demographics by SCI-WMH group. For each sex, there was a significant difference across all SCI-WMH groups in mean age and mean FSRP ($p<0.05$). Education levels were not significantly different among the 4 groups ($p>0.05$).

In Table 2, the average change in neuropsychological testing outcome per one SD increase in TCBV is listed for each NP factor for both sexes combined and for each sex separately. There were significant linear associations between co-variate adjusted TCBV and several NP outcomes for both men and women separately and combined, but no significant TCBVxSex interactions for any NP factor (see Table 2).

The trends in adjusted mean Executive Function factor score across SCI-WMH groups was similar for men and women, with the SCI-WMH-L group having the lowest adjusted mean

executive function for both sexes. However, when we compared the SCI-WMH-L group to the other 3 SCI-WMH groups combined, the SCI-WMH-L group for men performed significantly worse on average for EF factor (p=0.002), but not for women (p=0.226). Men in the SCI-WMH-L group did worse on both the TMT A (p=0.023) and TMT B (p<.001) tests, which comprise the EF factor, vs. the other three groups combined, while women in the SCI-WMH-L group did not (TMT A, p=0.502 and TMT B, p=0.272).

FSRP scores were significantly higher for men than in women (p<0.0001 for the difference in average FSRP between sexes which may contribute to the differences between sexes with respect to the effect of SCI-WMH group on executive function. To determine whether higher FSRP scores in men could account for the difference among those with SCI-WHM-L on EF, we dichotomized participants with FSRP ≤0.18 and >0,18 (where 0.18 is the overall 90th percentile for FSRP). Across the 4 SCI-WMH comparison groups, performance on EF was no different for men or women with FSRP ≤0.18 (p=0.642 and p=0.437, respectively). Across the 4 SCI-WMH comparison groups for women with FSRP >0.18, there was again no significant difference in EF performance (p=0.619). Among the men, however, those with FSRP>0.18, there was a significant trend of poor performance on EF across all 4 SCI-WMH-L groups (p=0.0019)

DISCUSSION

The literature suggests that there are higher levels of cardiac risk in men than women.12¯17 It has also been shown that higher CV risk is linked to smaller brain volume, and that this smaller brain volume was linked to poorer performance on executive function tests[1]. The primary results in this study, however, determined that sex did not modify the relationship between MRI measures of total cerebral brain volume and cognitive performance. There was also a lack of a significant interaction by sex for the association between measures of subclinical vascular disease (e.g., SCI) and cognitive function. In a prior Framingham study, we found that greater vascular burden (e.g., SCI-WMH-L) has a larger impact on cognition than either vascular measures in isolation. In this study, men with the greatest amount of subclinical vascular burden appear susceptible to deficits on neuropsychological tests associated with frontal/executive function. In contrast, there was no significant difference when evaluating the SCI-WMH-L comparisons in women. It is difficult to assess if the trend across SCI-WMH groups for women with large FSRP is due to a marginalizing effect of large FSRP in women, or simply a sample size issue (of the 52 women with high FSRP, 33 are in the No SCI-No-WMH-L group). Nevertheless, it appears the sex difference in Executive Function across SCI-WMH groups is in part due to men having higher FSRP scores (e.g., greater stroke risk) than women.

Limitations of this study include the primarily Caucasian cohort, which cautions against generalizing these results to other ethnic groups. In addition, this is a cross-sectional study and cannot assess change in the MRI-NP relation over time. These results also underrepresent persons with cardiovascular disease due to the exclusion of subjects with pacemakers, and persons too ill to lie flat for brain MRI scans.

In conclusion, this relatively young and stroke and dementia-free community based cohort did not demonstrate substantial sex differences in the impact of brain volume and subclinical markers of vascular disease on cognition. The stronger relationship of subclinical markers of vascular disease in men compared to women, suggest that decreasing cardiovascular risk may have a potentially greater impact in preserving cognitive function in men.

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Table 1

Subject Group Demographics

Men						
	No SCI-No WMH-L	**SCI-O**	**WMH-L**	**SCI-WMH-L**	**P-Value (Any Difference Across 4 Groups) ***	**P-Value (SCI-WMH-L vs 3 Remaining Groups Combined) ***
n	799	80	72	27	-	-
Mean Age (SD)	60.9 (9.2)	63.2 (9.4)	62.5 (9.5)	63.9 (11.0)	0.038	0.354
Mean FSRP (SD)	0.10 (0.10)	0.14 (0.14)	0.13 (0.11)	0.16 (0.12)	<0.001	0.049

Women						
	No SCI-No WMH-L	**SCI-O**	**WMH-L**	**SCI-WMH-L**	**P-Value (Any Difference Across 4 Groups) ***	**P-Value (SCI-WMH-L vs 3 Remaining Groups Combined) ***
n	890	88	103	26	-	-
Mean Age (SD)	60.5 (9.2)	63.7 (9.0)	62.5 (10.0)	63.9 (8.3)	0.002	0.384
Mean FSRP (SD)	0.05(0.06)	0.08 (0.08)	0.07 (0.09)	0.08 (0.07)	<0.001	0.376

*P-value generated from analysis of variance for age and FSRP.

Table 2

Change in Outcome per SD Increase of TCBV for each NP Test for Males and Females[†i]

	Both Sexes Combined		Men	Women
NP Measure	**Mean Change (95% CI) per 1 SD Increase in TCBV**	**TCBV-by-Sex Interaction p-Value**	**Mean Change (95% CI) per 1 SD Increase in TCBV**	**Mean Change (95% CI) per 1 SD Increase in TCBV**
VM	−0.040(−0.142–0.062)	0.3347	0.008(−0.150–0.167)	−0.081(−0.211–0.049)
VsM	0.110(0.009–0.211)*	0.7881	0.161(0.003–0.320)*	0.083(−0.046–0.212)
VL	0.120(0.021–0.219)*	0.4358	0.186(0.031–0.341)*	0.066(−0.061–0.193)
Exec. Function	0.264(0.174–0.355)***	0.2423	0.384(0.240–0.529)***	0.169(0.056–0.281)**

† The change in outcome is based on standardized z-scores to allow for comparison of change across NP tests.

i Lower and upper bound 95% confidence interval (CI) are listed for each NP test for males and females.

* p<0.05;

** p<0.01;

*** p<0.001 (from a multiple linear regression assessing relationship between TCBV and NP outcome adjusting for age, sex [for both sexes combined model], education, height, and the Framingham Stroke Risk Profile score). Interaction p-value is from linear regression with effects for sex, TCBV, TCBV-by-sex interaction, and the covariates age, education, height, and the Framingham Stroke Risk Profile score.