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Association between Atrial Fibrillation and Volumetric MRI Brain Measures: Framingham Offspring Study

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Abstract

Background—The increased risk of stroke and cognitive impairment associated with atrial fibrillation (AF) is well documented. However, there is a paucity of research investigating the relations between AF and brain morphology.

Objective—Our study investigated the association between AF and brain volume measures on magnetic resonance imaging (MRI).

Methods—The study sample included stroke- and dementia-free participants who attended the Framingham Heart Study Offspring cohort 7th examination cycle (1999–2005) and underwent contemporaneous MRI. We examined the association between prevalent AF and brain volume measures (total cerebral volume, frontal lobe volume, temporal lobe volume, temporal horn volume, hippocampal volume, and white matter hyperintensity volume) with linear regression. We first adjusted models for age and sex, and then for vascular risk factors and APOE4.

Results—We studied 2144 (mean age=61.8±9.3 years; 54% women) individuals; 73 (3.4%) participants had prevalent AF at the time of MRI. In age- and sex-adjusted models, AF was inversely associated with total cerebral brain volume, frontal brain volume, and temporal brain volume. After further adjustment for vascular risk factors and APOE4, AF remained associated with frontal brain volume.

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Conflicts of Interest:

None.

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Conclusion—After accounting for vascular risk factor burden, prevalent AF was associated with lobar indices of vascular brain aging but not with expected white matter changes.

Keywords

Imaging; brain volume; atrial fibrillation; MRI; Framingham

Introduction

Atrial fibrillation (AF) is a serious cardiovascular condition that is associated with a significant degree of morbidity and mortality. The incidence and prevalence of AF is expected to more than double in the next three decades[1] with a prevalence of 16% in those 85–89 years of age.[2] AF is associated with increased risk of stroke, heart failure, and all-cause mortality.[3] The adverse association of AF with global cognition, daily functioning,[4] learning, attention, memory,[5] abstract reasoning, executive functioning,[6] and AF's association with increased risk for dementia[7–10] have been well documented.

There is a paucity of research investigating the impact of AF on brain structure and morphology. Structural brain anomalies such as white matter hyperintensities (WMH), global and regional atrophy, and silent cerebral infarcts (SCI) are known to be significantly associated with cognitive dysfunction[11–14] but it is not known whether AF operates through these mechanisms.

A recent Icelandic study found AF to be associated with reduced total brain volume[15] whereas 3 previous studies had found this association to be insignificant.[5,16,17] Permanent, or persistent, AF was more strongly associated with global brain atrophy than paroxysmal AF, suggesting a cumulative effect. One case-control study demonstrated decreased hippocampal volume in participants with AF compared to those without.[5] Furthermore, a Japanese study reported that the frequency of SCIs and the severity of WMH were greater in individuals with nonvalvular AF compared to referents.[18] However, no study to date that has examined a spectrum of brain imaging parameters, including WMH volumes, in addition to global and regional brain volumes, to provide a more comprehensive understanding of the association of AF with brain anatomy.

Our study investigated the associations between AF and measures of structural brain anomalies on magnetic resonance imaging (MRI) in the Framingham Offspring cohort. We hypothesize that AF is associated with decreased total and lobar brain volumes and increased WMH volume.

Methods

Study Sample

The Framingham Heart Study (FHS) is a community-based study that began prospective examination of the Original cohort in 1948. The Offspring cohort was recruited in 1971 and is comprised of people who had a least one biological parent who was a member of the Original Framingham Study cohort and their spouses.[19]

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The present study includes participants from the Offspring cohort, which underwent periodic physical and medical examinations to identify risk factors for cardiovascular and cerebrovascular diseases. The initial Offspring cohort consisted of 5124 men and women; 88% of survivors (3,539 of 4,031) participated in Examination 7 in 1998 to 2001. As part of a large ancillary study, Offspring participants who survived to the 7th examination and attended at least one evaluation among the 5th, 6th, or 7th examinations (n = 3,623) were invited to undergo volumetric brain MRI (1999–2005). We included 2,229 individuals who had a baseline MRI within one year before and five years after their examination date. We excluded 85 participants with documented clinical stroke, clinical dementia, or other neurological disorders at the time of baseline MRI assessment, resulting in a final sample size of 2,144 for our cross-sectional analysis.

We invited all participants included in the original ancillary study to undergo a second brain MRI that we performed between 2005 and 2011, and at least 1 year after the first MRI. A subset of 1,546 participants underwent a second MRI scan. We excluded 13 participants who had a new diagnosis of other neurological disorders that may have affected the MRI measurements, resulting in a sample of 1,533 participants for the analysis of longitudinal change in MRI measures. The mean time between the baseline and follow-up MRI was 6.5±1.3 years.

The Boston University Medical Center Institutional Review Board approved the study protocol and all participants provided written informed consent.

Ascertainment of AF and Covariates

We routinely ask FHS participants about AF at examinations and biennial health history updates. If participants report a diagnosis of AF, we seek outside records. In addition, we systematically solicit and review all cardiovascular, cancer, neurological, and hip fracture records. Presence of AF among FHS participants is determined from multiple sources: 12-lead electrocardiograms obtained at each FHS exam, and from all CVD-related hospitalizations and clinician visits. Cases of suspected new-onset AF undergo rigorous adjudication by two FHS cardiologists. We adjusted for incident cases of AF because we are investigating longitudinal associations. Therefore, the key exposure variables are prevalent AF and no AF.

MRI Acquisition Parameters

The imaging parameters, measurement protocols, and reproducibility of these measures have been described in a prior publication.[20] MRIs were obtained with a Siemens Magnetom (Siemens Medical Solutions, Malvern, PA) 1 or 1.5 tesla field strength machine using a double spin-echo coronal imaging sequence of 4 millimeter contiguous slices from nasion to occiput. All analyses were performed using QUANTA 6.2, a custom-designed image analysis package, operating on an Ultra 5 workstation (Sun Microsystems, Santa Clara, CA). A segmentation threshold for WMH was determined as 3.5 SDs in pixel intensity greater than the mean of the fitted distribution of brain parenchyma. WMHV and TBV were computed using a previously validated method.[20] As hippocampal volume at the second MRI was available only in a small subset of participants at this time, change in hippocampal

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size was estimated using change in temporal horn volume (THV), and is considered a surrogate marker of hippocampal volume.

MRI volumetric measures included total cerebral brain volume (TCBV), frontal (FBV), temporal (TBV), hippocampal (HPV), temporal horn (THV), and white matter hyperintensity (WMHV) brain volumes. Total and lobar volumes were analyzed as percentage of TCV, to correct for differences in head size. THV and WMHV were natural log (ln) transformed for all analyses. Extensive WMHV (EXT_WMH) was defined as having a z-score of >1 for 5-year age group specific z-scores. Annualized raw change in MRI brain volume measures was calculated by taking the difference between the follow-up and baseline MRI brain volume measures and dividing by the time interval between the baseline and follow-up MRI scans. DeCarli et al. provides a detailed description of the quantification of all brain volumes.[20]

Statistical Analysis

Baseline descriptive statistics were calculated for participants with and without prevalent AF. Linear regression was used to examine the cross-sectional association between prevalent AF and each brain volumetric measure separately. We constructed normal quantile-quantile (Q-Q) plots of the residuals and plots of the residuals versus the predicted values to assess the assumptions of normality, linearity, and heteroscedasticity for each of the MRI brain volume outcome measures; no violations were observed. Model 1 was adjusted for age at MRI, age at MRI-squared, and sex. Model 2 was additionally adjusted for time between covariate measurement and MRI, vascular risk factors (systolic blood pressure, diastolic blood pressure, antihypertensive treatment, current smoking, ln-transformed homocysteine, diabetes, prevalent myocardial infarction, prevalent heart failure), and presence of the APOE4 allele. Logistic regression was used for the categorical outcome of extensive white matter hyperintensity.

We also constructed linear regression models to examine the association between prevalent atrial fibrillation and annualized change in each MRI brain volume measure. Model 1 was adjusted for age at MRI, age at MRI-squared, and sex. We tested for age-squared as a covariate for all analyses with MRI volumes as outcomes since the relationship between age and MRI volumes has been shown to be non-linear.[20] Model 2 was additionally adjusted for time between covariate measurement and MRI, vascular risk factors (as described above), presence of the APOE4 allele, and interim AF between baseline and follow-up MRI. Model 3 was additionally adjusted for baseline MRI brain volume measures.

Analyses were performed using Statistical Analyses System software Version 9.4 (SAS Institute, Cary, NC). A two-sided p-value of <0.05 was considered statistically significant.

Results

Table 1 describes the baseline characteristics for the Framingham Offspring participants in our study sample. Participants' (N=2,144) mean age was 61.8±9.3 years and 54% were women. At the time of the MRI 73 (3.4%) participants had prevalent AF. Overall,

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participants with prevalent AF were older, more likely to be men, and had a higher prevalence of vascular risk factors as compared to those without AF.

Table 2 summarizes the regression results for the cross-sectional association between prevalent AF and MRI brain volume measures. The age-squared term was statistically significant for all models so it was included as a covariate. In age/sex-adjusted models (Model 1), AF was inversely associated with total cerebral brain volume (Beta±standard error [SE])= −1.18±0.33, p<0.001), frontal brain volume (Beta±SE= −1.12±0.35, p=0.001), and temporal brain volume (Beta±SE= −0.31±0.10, p=0.002). After further adjustment for vascular risk factors and APOE4 in Model 2, AF remained associated with only frontal brain volume (Beta±SE= −0.82±0.38, p=0.03). There was no association between prevalent AF and temporal horn, hippocampal,, or white matter hyperintensity brain volumes.

Table 3 shows the linear regression results for the association between prevalent atrial fibrillation and longitudinal change in MRI brain volume measures (N=1,533 participants, N=40 prevalent AF cases). The beta coefficient from these models represents the mean difference in annualized change in MRI brain volume measurements between those with and without atrial fibrillation at baseline.

In age/sex-adjusted models (Model 1), prevalent AF was statistically significantly associated with a reduction in temporal horn volume during follow-up compared to participants without AF (Beta±standard error [SE])= −0.0022±0.0010, p=0.03). However, there was no statistically significant association after further adjustment for vascular risk factors and APOE4 in Model 2 or baseline MRI brain volume measures in Model 3.

Discussion

While AF was associated with decreased total and lobar volumes as initially hypothesized, these associations were no longer present after accounting for vascular risk factors. In our sample, participants with AF had a significantly greater burden of vascular risk.

There are several potential explanations to our findings. AF may cause cerebral hypoperfusion or small cerebral emboli, which may subsequently lead to smaller brain volumes.[21,22] However, AF and brain atrophy share similar causes, namely hypertension and diabetes. Hypertension has been associated with smaller total brain and hippocampal volumes[23] whereas diabetes has been linked to reduced total brain and grey matter volumes.[24]

Only a few studies have investigated the association of AF with brain structure and morphology. AF was linked to reduced total brain, white, and gray matter volumes,[15] decreased hippocampal volume,[5] greater frequency of SCIs, and increased severity of WMH.[18] However, all of these studies relied on cross-sectional study design or examined few MRI measures (e.g., total brain, white, and gray matter volume,[15] hippocampal volume,[5] SCIs, and WMH[18]). By comparison, our study included change in mean across multiple MRI measures. We also adjusted for APOE4, which independently has been linked to smaller brain volumes, greater brain atrophy, and increased WMH.[25]

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The strengths of our study are its prospective, community-based design, with volumetric MRI measures at baseline and follow-up. There are, however, several limitations. The study participants were predominantly white, and educated, which may limit the generalizability of the study. Only 1.5 T MRIs were used to examine brain volumes. The prevalence of AF in our sample was low (about 3.4%), which may have limited power to detect associations. Further, since we examined prevalent AF at the time of MRI, we are unable to account for the duration effects of exposure to AF. We were also unable to report on other markers of chronicity of AF (such as left atrial size or reduced left atrial appendage velocities) because they were not measured at baseline. As stated, one study found that persistent rather than paroxysmal AF was more strongly associated with global brain atrophy.[15] In addition, we cannot exclude misclassification of AF status, as AF may be clinically unrecognized. We were unable to include indexes of diastolic heart function in our analysis. Future research should examine indexes of diastolic heart function as a link between promoting atrial fibrillation and decreased cerebral volume despite correction for vascular risk. Lastly, we cannot infer causality from our results.

In conclusion, although our findings suggest that AF was associated with smaller frontal lobe volumes, given the small prevalence of AF in the study population, further exploration of the association between AF and brain morphology, particularly MRI metrics of vascular brain aging, and its subsequent effect on cognition, is warranted to substantiate these results.

Acknowledgments

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Table 1

Study sample characteristics for Framingham Heart Study Offspring Cohort participants at baseline (exam 7).

	Prevalent Atrial Fibrillation at Baseline MRI	
	No (N=2071)	**Yes (N=73)**
Continuous characteristics, mean (SD)		
Age at MRI, years	61.5 (9.3)	69.5 (6.7)
Years between exam 7 and baseline MRI	0.77 (0.79)	0.70 (0.69)
Systolic blood pressure, mm Hg	125 (18)	133 (21)
Diastolic blood pressure, mm Hg	74 (10)	70 (9)
Homocysteine, median (25^{th}, 75^{th} percentile)	7.8 (6.5, 9.5)	8.4 (7.4, 10.9)
Categorical characteristics, n (%)		
Women	1128 (54.5)	25 (34.3)
Education level		
<High school degree	62 (3.0)	5 (6.9)
High school degree	1195 (57.7)	42 (57.5)
≥College degree	814 (39.3)	26 (35.6)
Diabetes	191 (9.4)	22 (31.0)
Prevalent MI	62 (3.0)	18 (24.7)
Prevalent heart failure	6 (0.29)	12 (16.4)
Current smoker	260 (12.6)	4 (5.5)
Antihypertensive treatment	593 (28.7)	43 (58.9)
Anticoagulant use	11 (0.53)	22 (30.1)
Heavy alcohol use*	338 (16.3)	17 (23.3)
APOE4	461 (22.7)	11 (15.5)
*Baseline MRI Brain Volume Measures*** *, median (25^{th}, 75^{th} percentile)*		
Total cerebral brain volume, %	79.8 (77.5, 81.9)	76.6 (74.1, 79.8)
Frontal lobe brain volume, %	36.5 (34.2, 38.9)	33.8 (31.7, 35.3)
Temporal lobe brain volume, %	10.5 (9.9, 11.1)	9.9 (9.5, 10.5)
Temporal horn volume, %	0.041 (0.024, 0.064)	0.058 (0.038, 0.107)
Hippocampal brain volume, %	0.337 (0.300, 0.371)	0.317 (0.287, 0.337)
White matter hyperintensities volume, %	0.045 (0.025, 0.086)	0.086 (0.037, 0.222)
Extensive white matter hyperintensities volume, n (%)	264 (12.8)	15 (20.6)

*Defined as >14 drinks/week for men and >7 drinks/week for women

**All brain volume measures expressed as a percentage of total cranial volume

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Table 2

Regression results for the cross-sectional association between prevalent atrial fibrillation and MRI brain volume measures (N=2144).

MRI Outcome Measure	Model 1*			Model 2**		
	Adjusted R-square	Beta (SE)	P-value	Adjusted R-square	Beta (SE)	P-value
Total cerebral brain volume, %	**0.34**	**−1.18 (0.33)**	**0.0004**	0.35	−0.35 (0.36)	0.34
Frontal lobe brain volume, %	**0.29**	**−1.12 (0.35)**	**0.001**	**0.31**	**−0.82 (0.38)**	**0.03**
Temporal lobe brain volume, %	**0.13**	**−0.31 (0.10)**	**0.002**	0.14	−0.18 (0.11)	0.10
Temporal horn volume†, %	0.21	0.13 (0.085)	0.13	0.22	0.072 (0.092)	0.44
Hippocampal brain volume, %	0.066	−0.0060 (0.0064)	0.35	0.067	−0.0055 (0.0071)	0.44
White matter hyperintensities volume†, %	0.28	0.15 (0.11)	0.17	0.27	0.17 (0.12)	0.16
	C-statistic	**OR (95% CI)**	**P-value**	**C-statistic**	**OR (95% CI)**	**P-value**
Extensive white matter hyperintensities volume (Yes vs. No)	0.57	1.59 (0.88–2.89)	0.12	0.61	1.70 (0.87–3.30)	0.12

Abbreviations: SE, standard error; OR, odds ratio; CI, confidence interval

Note: Beta represents the mean difference in MRI brain volume measurements between those with and without atrial fibrillation at baseline. All brain volume measures are expressed as a percentage of total cranial volume.

*Model 1 is adjusted for age at MRI, age at MRI squared, and sex.

**Model 2 is adjusted for model 1 covariates plus time between exam 7 and MRI, systolic blood pressure, diastolic blood pressure, antihypertensive treatment, diabetes, prevalent MI, prevalent CHF, current smoking, ln-transformed homocysteine, and APOE4.

†Natural log (ln) transformed

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Table 3

Linear regression results for the association between prevalent atrial fibrillation and annualized change in MRI brain volume measures (N=1533 participants, 40 prevalent AF cases).

Annualized change in MRI brain volume measure (%/ year)	Model 1*			Model 2**			Model 3***		
	Adjusted R-square	Beta (SE)	P-value	Adjusted R-square	Beta (SE)	P-value	Adjusted R-square	Beta (SE)	P-value
Total cerebral brain volume	0.10	−0.092 (0.062)	0.14	0.11	−0.087 (0.066)	0.19	0.17	−0.085 (0.064)	0.18
Frontal lobe brain volume	0.021	0.012 (0.069)	0.87	0.027	−0.0041 (0.074)	0.96	0.22	−0.062 (0.066)	0.35
Temporal lobe brain volume	0.016	−0.0091 (0.020)	0.66	0.014	0.00016 (0.022)	0.99	0.17	−0.0087 (0.020)	0.67
Temporal horn volume†	**0.16**	**−0.0022 (0.0010)**	**0.03**	0.17	−0.0013 (0.0011)	0.22	0.18	−0.0013 (0.0011)	0.23
Hippocamp al brain volume	0.0034	0.0024 (0.0024)	0.33	0.0059	0.0031 (0.0026)	0.24	0.19	0.0033 (0.0024)	0.16
White matter hyperintensities volume†	0.14	0.0040 (0.0049)	0.42	0.15	−0.00058 (0.0053)	0.91	0.29	0.00065 (0.0048)	0.89

Abbreviations: SE, standard error

Note: Beta represents the mean difference in annualized change in MRI brain volume measurements between those with and without atrial fibrillation at baseline. All brain volume measures are expressed as a percentage of total cranial volume.

*Model 1 is adjusted for age at MRI, age at MRI squared, and sex.

**Model 2 is adjusted for model 1 covariates plus time between exam 7 and MRI, systolic blood pressure, diastolic blood pressure, antihypertensive treatment, diabetes, prevalent MI, prevalent CHF, current smoking, ln-transformed homocysteine, interim AF between baseline and follow-up MRI, and APOE4.

***Model 3 is adjusted for model 2 covariates plus the baseline MRI brain volume measures

†Natural log (ln) transform

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