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Atrial Fibrillation and Cognitive Decline in the Framingham Heart Study

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Abstract

BACKGROUND—There is a paucity of longitudinal research investigating the relations between AF and domain-specific cognitive performance.

OBJECTIVE—Our study investigated the association between AF and cognitive performance cross-sectionally and longitudinally.

METHODS—Eligible participants were dementia- and stroke-free at the time of baseline neuropsychological (NP) assessment, and underwent at least one additional NP assessment with a one year or greater inter-test interval. AF status was examined as a two-level variable (prevalent AF, no AF) in cross-sectional analyses, and then separately as a three-level variable (prevalent AF, interim AF, no AF) in longitudinal analyses. We examined the association between AF status and cognitive performance with linear regression. We first adjusted models for age and sex, and then for vascular risk factors and *APOE4*.

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RESULTS—We studied 2682 participants of the Framingham Heart Study Original and Offspring cohorts. At the baseline neuropsychological assessment, 112 (4.2%) participants had AF (mean age=72±9 years, 32% women). After adjustment for vascular risk factors and *APOE4*, prevalent AF was significantly associated with poorer attention; sex differences were also noted with men performing worse on tests of abstract reasoning and executive function, while women did better on a measure of executive functioning. Prevalent AF was significantly associated with longitudinal decline in executive functioning in the Original cohort and interim AF was significantly associated with longitudinal decline in executive function in the Offspring cohort.

CONCLUSION—After accounting for vascular risk factor burden and *APOE4*, AF was associated with a vascular profile of change in cognitive function.

Keywords

atrial fibrillation; neuropsychological assessment; cognition; cognitive decline; Framingham Heart Study

Introduction

Atrial fibrillation (AF) is a serious cardiovascular condition that is associated with significant morbidity and mortality. The prevalence of AF is 16% in those 85–89 years of age,[1] and the incidence and prevalence of AF is expected to more than double in the next three decades.[2] AF is associated with an increased risk of stroke, heart failure, and all-cause mortality.[3]

The association of AF with cognitive and functional decline[4–6] has been documented, however, the evidence is much more robust for AF's association with an increased risk for dementia.[7–9] In case control studies compared with sinus rhythm, AF was associated with significantly poorer performance on neuropsychological testing.[10, 11] In a recent meta-analysis of more than 30,000 patients, Kalantarian et al. found that AF was associated with a 40% increased risk of cognitive impairment in participants without a history of stroke.[12] Verbal memory, attention, and executive function may be particularly vulnerable in patients with AF.[5, 10]

Most community-based studies that have reported an association between AF and lowered cognitive performance have relied on the Mini-Mental State Examination (MMSE), a brief composite measure of cognitive status.[13, 14] A post-hoc analysis of two randomized controlled trials with more than 30,000 patients found that patients with AF were significantly more likely to decline 3 or more points on the MMSE over a nearly 5-year follow-up period.[4] However, the use of the MMSE to assess cognitive function has limitations and may be too crude and insensitive to detect subtle changes in the various domains of cognitive function, particularly in those with higher education.

The Framingham Heart Study (FHS) extended the study of AF and cognition beyond the MMSE to domain-specific tests and previously reported that within its middle to young old aged cohort, AF was associated with significantly lower scores on tests of reasoning, attention and spatial abilities.[15] Among men, AF was associated with poorer performance in

tests of global cognition, immediate and delayed memory, attention and executive function.[6] These results were consistent with those of case-control studies, but were similarly limited by cross-sectional design and restricted age ranges of the study population.

There is a dearth of longitudinal studies that have investigated the association between AF and change in cognitive function. Studies of such a design may help identify specific domains of cognition that are preferentially affected and, in doing so, illuminate the potential mechanisms that underlie the relationship. For our study, we examined the association between prevalent and interim AF and concurrent level of cognitive function as well as longitudinal decline in cognitive function in a community-based sample with a broad age range. We hypothesized that AF is associated with poorer baseline cognitive performance and longitudinal decline in cognitive function.

Methods

Study Sample

The FHS is a single-site, community-based, prospective cohort study that was founded in 1948 to investigate risk factors for cardiovascular disease. The Original study cohort consisted of 5209 participants aged 28 through 74 years residing in Framingham, MA, U.S.A. between 1948 and 1953. The Framingham Offspring Study cohort is a community-based sample of 5124 participants (or their spouses) who had at least one biological parent who was a member of the Original cohort who have been followed since 1971.[16] The cohorts had clinic examinations approximately every two (Original cohort) or four-eight (Offspring cohort) years. The sample for the present study consists of members from both the Original and Offspring cohorts. To be considered for the study, participants had to be dementia-free at the time of baseline neuropsychological (NP) assessment between 1999 and 2001 (examination 26 for the Original cohort and examination 7 for the Offspring cohort), and had to undergo at least one additional NP assessment with at least one year inter-test interval. The mean follow-up time in years (median Q1,Q3) for Original cohort was 3 years (2,3) and for Offspring cohort 6 years (6,7). The protocol for diagnosing participants in the Framingham Heart Study with dementia and stroke have been previously described.[17] Participants younger than 40 years were excluded from the analyses (n=16). All participants with a history of clinical stroke were further excluded.

The study was in accordance with the Helsinki Declaration of 1975. The Boston University Institutional Review Board approved the study protocol and all participants provided written informed consent.

Atrial Fibrillation Assessment

The presence of AF (or atrial flutter) is determined by asking participants about AF during examinations and biennial health history updates, which include routine questions about AF. If AF is reported, records are sought. Presence of AF among FHS participants is confirmed from multiple sources: 12-lead electrocardiograms obtained at each FHS exam, and from all cardiovascular disease-related hospitalizations and clinician visits. Cases of suspected new-onset AF undergo rigorous adjudication by two FHS cardiologists.

AF was examined as a two-level variable (prevalent AF, no AF) in cross-sectional analyses. Separately, it was analyzed as a three-level variable (prevalent AF, interim AF, no AF) in longitudinal analyses, with no AF as referent. Prevalent AF was defined as AF at the baseline examination; participants who developed AF between the baseline examination and the follow-up NP assessment were classified as having interim AF.

Neuropsychological Measures

The test battery is administered using standardized testing protocols and scoring procedures, details of which have been described previously.[18] The battery is comprised of tests measuring performance across major cognitive domains (see Table 1). The tests included Visual Reproduction (Immediate and Delayed Recall), which tests visual memory; Wechsler Adult Intelligence Test Similarities, which tests abstract reasoning; Hooper Visual Organization, which tests visuospatial organization and executive function; and Trail Making Test – A and – (B-A), which test attention and executive function respectively. For the Trail Making Test – (B-A), a difference score was calculated. This derived score may reflect a purer measure of the executive abilities required to complete the Trail Making Test – B by subtracting out the simple sequencing and psychomotor demands common to both Trail Making Test – A and – B. The Hooper Visual Organization test, Trail Making Test – A, and Trail Making Test – (B-A) were natural log transformed to normalize their skewed distributions. To aid consistency of interpretation, these values were re-signed such that higher scores reflect superior task performance.

Statistical Analysis

The cross-sectional association between AF and cognitive function at baseline was assessed using multivariable linear regression relating AF to each of the aforementioned tests of the NP test battery. The first model was adjusted for age, sex, education, time between baseline examination and NP testing, and cohort. The second model was additionally adjusted for systolic blood pressure, diastolic blood pressure, antihypertensive medications, smoking, myocardial infarction, heart failure, and apolipoprotein ε4 (*APOE4*) status. Secondary analyses were performed using interaction terms to assess effect modification by cohort and sex.

The longitudinal association between AF and cognitive function was assessed using multivariable linear regression relating AF to annualized change in each of the NP tests. The first model was adjusted for age, sex, education, time between baseline examination and NP testing, and cohort. The second model was additionally adjusted for systolic and diastolic blood pressure, antihypertensive medications, smoking, myocardial infarction, heart failure, and *APOE4* status. Secondary analyses were performed using interaction terms to assess effect modification by sex and cohort.

Two-sided significance was set at $p<0.10$ for analyses assessing effect modification and at $p<0.05$ for all other analyses. All data were analyzed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

Table 2 describes the baseline characteristics for participants in the NP study sample (N=2682) by AF status. At time of baseline neuropsychological assessment, 112 (4.2%) participants had AF (mean age=72±9 years, 32% women). Compared to those without AF at baseline, participants with prevalent AF were older, more likely to be men, had higher prevalence of cardiovascular risk factors and disease, but did not have significantly different Apoe4 ε4 levels.

Table 3A summarizes the multivariable linear regression results for the cross-sectional association between prevalent AF and neuropsychological test performance. In Model 1, prevalent AF was associated with poorer performance on the Visual Reproduction: Immediate Recall, Similarities, and Trail Making Test – A tests. After adjustment for several vascular risk factors and *APOE4* (Model 2), prevalent AF remained associated with poorer performance on the Similarities (β±SE= −0.96±0.33, p=0.004) and Trail Making Test – A (β ±SE= −0.07±0.03, p=0.03). In Model 2 analyses, a sex interaction was observed for Similarities (p=0.01), and Trail Making Test – A (p=0.007). There were no significant cohort interactions with Model 2 analyses.

Table 3B summarizes the association between prevalent AF and neuropsychological test performance stratified by sex for the tests that demonstrated a significant sex interaction. After adjustment for several vascular risk factors and *APOE4*, prevalent AF was associated with better test performance on Trail Making Test – (B-A) in women (β±SE= 0.08±0.04, p<0.04). However, prevalent AF was associated with poorer performance on the Similarities (β±SE= −1.60±0.42, p<0.001) and Trail Making Test – (B-A) (β±SE= −0.07±0.03, p=0.02) in men.

Table 4A describes the multivariable linear regression results for the longitudinal association between AF and cognitive function, comparing prevalent and interim AF to the referent category, no AF. In Model 1, prevalent AF was associated with greater decline in performance on Trail Making Test – (B-A). In Model 2, prevalent (β±SE= −0.31±0.06, p<0.001) and interim (β±SE= −0.10±0.04, p=0.03) AF was associated with greater decline in performance on Trail Making Test – (B-A).

A significant cohort interaction was observed for Similarities and Trail Making Test – (B-A) in Model 2 analyses (Similarities: p=0.098; Trail Making Test – (B-A): p<0.001).

Table 4B describes the multivariable linear regression results for the longitudinal association between AF and cognitive function stratified by cohort for the tests that demonstrated a significant cohort interaction. There was no significant association between AF and annual change in NP performance on the Similarities test in either cohort. Prevalent AF was associated with significant decline in performance on Trail Making Test – (B-A) (β±SE= −1.24±0.33, p<0.001) in the Original cohort and interim AF was associated with significant decline in performance on Trail Making Test – (B-A) (β±SE= −0.09±0.03, p<0.001) in the Offspring cohort.

Discussion

Atrial fibrillation status was predominantly associated with poorer performance on tests of executive function in the Framingham Original and Offspring cohorts. In the cross-sectional analyses, prevalent AF was significantly associated with poorer attention. When looking at performance by sex, prevalent AF in men was associated with poorer abstract reasoning and executive function skills whereas women demonstrated better executive function. Prevalent AF and interim AF were associated with greater decline in executive function but these results were cohort specific; prevalent AF was a significant predictor in the Original cohort, whereas interim AF was a significant predictor in the Offspring cohort. Attention, executive function, and abstract reasoning are cognitive domains associated with frontal lobe atrophy, stroke, and increased white matter hypertensities.[19–25] Taken together, and in the absence of other cognitive deficits, the impact on these domains reflects a vascular profile of change.

In our sample, participants with AF had a significantly greater burden of vascular risk factors, were older, and were more likely to be men. The stronger cross-sectional association of AF to cognitive deficits in men compared to women is consistent with a prior cross-sectional FHS study of AF in men,[6] however, it should be noted that there was no analysis looking at women in that study. These results should be interpreted with caution due to the small sample size of female participants with AF, and could be due to chance or residual confounding. While it has not been described in individuals with AF, a higher cardiovascular risk was associated with a greater decline in reasoning in men but not women in the Whitehall II study.[26] To our knowledge, there has been no previous literature that identifies this sex interaction on the association of atrial fibrillation with cognition.

There are several potential explanations for our results. AF may cause cerebral hypoperfusion or small cerebral emboli, which may impact certain vascular beds and subsequently lead to smaller brain volumes.[27, 28] It should also be noted that AF and brain atrophy share similar predisposing factors, including hypertension and diabetes. Hypertension has been associated with smaller total brain and hippocampal volumes[29] whereas diabetes has been linked to reduced total brain and grey matter volumes.[30] Therefore, the insignificance of associations following adjustment for vascular risk may be explained by confounding due to these comorbid risk factors. A recent study within the FHS Offspring cohort found that AF was associated with smaller frontal lobe volumes.[31] Past research has found a link between frontal lobe volume, specifically prefrontal cortex volume, and executive function task performance[19] as well as complex cognitive behavior and decision making.[20] This could propose an explanation for why participants with AF did worse on tests of abstract reasoning (Similarities) and executive function (Trail Making Test – (B-A)), all tests associated with the frontal lobes. We posit that the longitudinal association between AF and decline in executive function further corroborates cross-sectional findings that the association between AF and cognition may be mediated by decrease in frontal lobe volumes.

The strengths of our study are its prospective, community-based design, with multiple cognitive assessment measures at baseline and follow-up. Few studies have investigated the association of AF with domain-specific neuropsychological test performance. For this study,

we examined the association between baseline AF and concurrent level of cognitive function and longitudinal decline in cognitive function across a community-based sample with a broader age range than what has been published previously.[15] Additionally, our study included multiple cognitive assessment measures. We adjusted for several cardiovascular risk factors, which have been associated with cognitive decline in young, middle-aged, and elderly individuals.[32] We also adjusted for *APOE4*, which independently has been linked to sporadic late onset Alzheimer's disease,[33] as well as smaller brain volumes, greater brain atrophy, and increased white matter hyperintensities.[34]

There are, however, several limitations. The study participants were predominantly of European ancestry and most had at least some college education, which may limit the generalizability of the study. We were not able to adjust for all major cardiovascular risk factors, including diabetes, body mass index, depression and anxiety, alcohol use, and homocysteine levels. The prevalence of AF in our sample was low (about 4.2%), which may have limited power to detect additional associations. Further, since we examined prevalent AF at the time of neuropsychological assessment, we are unable to account for the duration of AF exposure. 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. We were not able to characterize AF status based on type of AF, particularly as certain types of AF have been more strongly associated with global brain atrophy,[35] and additionally, were not able to classify participants by anticoagulation status. We cannot exclude misclassification of AF status, as AF may be clinically unrecognized. Lastly, with an observational cohort-based study design, we cannot exclude residual confounding and we cannot infer causality from our results.

In conclusion, AF was significantly associated with poorer performance on tests of executive function, particularly in men. Furthermore, AF was associated with significant longitudinal decline in executive function when compared to those without AF. Future research is warranted to further investigate the sex disparity in cognitive impairment identified by our study in addition to research that utilizes neuroimaging and biomarkers of brain aging to characterize the mechanisms by which atrial fibrillation is associated with executive dysfunction.

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Table 1

Description of neuropsychological tests.

Test	Description	Cognitive Domain
Visual Reproductions: Immediate & Delayed Recall	Participants are shown a drawing for 10 seconds and asked to draw them from memory and then asked to draw them again after a time delay.	Visual memory
Similarities	Participants are asked how a list of paired items are alike.	Abstract reasoning
Hooper Visual Organization Test	Participants are asked to recognize pictures of objects that have been cut up and rearranged.	Visuoperceptual organization
Trail Making Test – A	As quickly as possible, participants are asked to draw a line connecting numbers that are randomly placed on a page in sequence.	Attention
Trail Making Test – B	As quickly as possible, participants are asked to draw a line alternating between numbers and letters that are randomly placed on a page in sequence.	Executive function

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Table 2

Baseline characteristics of NP study sample by atrial fibrillation status and cohort (Framingham Heart Study Original & Offspring cohorts ages 40 years or more).

	Original			Offspring		
Characteristic	**Atrial Fibrillation (N=29)**	**No Atrial Fibrillation (N=215)**	***p***	**Atrial Fibrillation (N=83)**	**No Atrial Fibrillation (N=2355)**	***p***
Age, years, mean±SD *	83±3	83±3	0.4991	68±7	61±9	**<0.0001**
Female, n (%) *	13 (45)	140 (65)	**0.0339**	23 (28)	1296 (55)	**<0.0001**
Education, n (%)			0.6961			0.0856
No HS degree	3 (10)	39 (18)		6 (7)	76 (3)	
HS degree only	13 (45)	93 (43)		29 (35)	659 (28)	
Some college	8 (28)	45 (21)		21 (25)	719 (31)	
College degree	5 (17)	38 (18)		27 (33)	901 (38)	
Medical History, n (%)						
Myocardial infarction *,‡	4 (14)	16 (7)	0.2719 **	22 (27)	72 (3)	**<0.0001** **
Heart Failure *,‡	4 (14)	6 (3)	**0.0206** **	13 (16)	7 (0.3)	**<0.0001** **
Systolic Blood Pressure, mmHg mean±SD *	137±20	140±20	0.4207	131±21	126±18	**0.0234**
Diastolic Blood Pressure, mmHg, mean±SD *	66±10	69±12	0.1216	70±9	74±10	**<0.0001**
Treatment with Antihypertensives, n (%) *	19 (66)	116 (54)	0.2500	49 (59)	701 (30)	**<0.0001**
Current smoking, n (%) *	1 (3)	10 (5)	1.000 **	4 (5)	299 (13)	**0.0324**
Apoe4 ε4, n (%)	5 (17)	41 (19)	0.8046	14 (17)	521 (23)	0.2601
Time between neuropsych measures, years median (Q1,Q3)	2 (1,3)	3 (2,3)	0.1915	7 (6,7)	6 (6,7)	0.6119
Visual Reproductions: Immediate *	5±3	6±3	0.4832	7±4	9±3	**<0.0001**
Visual Reproduction: Delayed Recall *	4±3	4±3	0.6536	7±4	8±3	**<0.0001**
Similarities (abstract reasoning) *	13±5	14±4	0.1673	15±4	17±4	**<0.0001**
Hooper Visual Organization test, median, (Q1,Q3) *	21 [17,23]	21 [17,23]	0.5117	25 [22,26]	26 [24,27]	**0.0004**
Trail Making Test - A, median (Q1,Q3) *	1 (1,1)	1 (1,1)	0.1809	1 (0,1)	1 (0,1)	**<0.0001**
Trail Making Test - (B-A), median (Q1,Q3) *	1 (1,3)	2 (1,2)	0.9545	1 (1,1)	1 (0,1)	**0.0075**

* IQR=interquartile range; variable log transformed for testing

** using Fisher's exact test

Table 3A

Association between prevalent atrial fibrillation and neuropsychological test performance.

Cognitive Measure	Model 1*			Model 2**			Sex Interaction p	Cohort Interaction p
	β	SE	*p*	β	SE	*p*		
Visual Reproduction: Immediate Recall	−0.67	0.28	**0.02**	−0.40	0.30	0.17	0.12	0.98
Visual Reproduction: Delayed Recall	−0.51	0.30	0.09	−0.29	0.31	0.36	0.16	0.93
Similarities (abstract reasoning)	−1.02	0.31	**0.001**	−0.96	0.33	**0.004**	**0.01**	0.48
Hooper Visual Organization test***	−0.04	0.05	0.41	−0.03	0.05	0.57	0.15	0.89
Trail Making Test – A***	−0.09	0.03	**0.007**	−0.07	0.03	**0.03**	0.42	0.79
Trail Making Test – (B-A) ***	−0.02	0.02	0.35	−0.009	0.02	0.70	**0.007**	0.84

*Adjusted for age, sex, education, time between baseline examination and NP testing, and cohort.

**Additional adjustments for systolic BP, diastolic BP, antihypertensive medications, myocardial infarction and heart failure, smoking status, and ApoE ε4.

***measures natural log transformed

Table 3B

Association between prevalent atrial fibrillation and neuropsychological test performance by sex.

	Women*			Men*		
Cognitive Measure	**β**	**SE**	***p***	**β**	**SE**	***p***
Similarities (abstract reasoning)	0.22	0.54	0.69	−1.60	0.42	**<0.001**
Trail Making Test – (B-A) **	0.08	0.04	**0.04**	−0.07	0.03	**0.02**

*Adjusted for age, education, time between baseline examination and NP testing, cohort, systolic BP, diastolic BP, antihypertensive medications, myocardial infarction and heart failure, smoking status, and ApoE ε4.

**this was natural log transformed.

Table 4A

Association between prevalent and interim atrial fibrillation and annual change in neuropsychological test performance (Interim AF N=140: Original=31; Offspring=109).

Cognitive Measure	Model 1*			Model 2**			Cohort Interaction p
	β	SE	*p*	β	SE	*p*	
Visual Reproduction: Immediate Recall							
noAF	Ref			Ref			0.76
prevAF	0.01	0.07	0.856	−0.01	0.08	0.897	
intAF	−0.009	0.06	0.878	−0.03	0.06	0.573	
Visual Reproduction: Delayed Recall							
noAF	Ref			Ref			0.86
prevAF	−0.07	0.08	0.371	−0.10	0.08	0.221	
intAF	−0.04	0.06	0.454	−0.07	0.06	0.267	
Similarities (abstract reasoning)							
noAF	Ref			Ref			**0.098**
prevAF	−0.06	0.09	0.503	−0.004	0.10	0.964	
intAF	0.05	0.07	0.467	0.02	0.07	0.737	
Hooper Visual Organization test							
noAF	Ref			Ref			0.13
prevAF	−0.07	0.07	0.367	−0.02	0.08	0.802	
intAF	−0.11	0.06	0.050	−0.09	0.06	0.129	
Trail Making Test – A							
noAF	Ref			Ref			0.66
prevAF	−0.03	0.02	0.075	−0.01	0.02	0.548	
intAF	0.008	0.01	0.514	0.009	0.01	0.463	
Trail Making Test – (B-A)							
noAF	Ref			Ref			**<0.001**
prevAF	−0.25	0.06	**<0.001**	−0.31	0.06	**<0.001**	
intAF	−0.08	0.04	0.071	−0.10	0.04	**0.03**	

*Adjusted for age, sex, education, time between baseline examination and NP testing, and cohort.

**Additional adjustments for systolic BP, diastolic BP, antihypertensive medications, myocardial infarction and heart failure, smoking status, and ApoE ε4.

Table 4B

Association between atrial fibrillation and annual change in neuropsychological test performance by cohort (The Framingham Heart Study Original and Offspring cohorts ages 40 years or more).

	ORIGINAL			OFFSPRING		
	Model 1*			Model 1*		
Cognitive Measure	**β**	**SE**	***p***	**β**	**SE**	***p***
Similarities (abstract reasoning)						
noAF	Ref			Ref		
prevAF	−0.15	0.42	0.72	−0.03	0.08	0.72
intAF	0.54	0.39	0.16	−0.06	0.06	0.29
Trail Making Test – (B-A)						
noAF	Ref			Ref		
prevAF	−1.03	0.32	**0.002**	0.006	0.03	0.87
intAF	−0.04	0.27	0.88	−0.09	0.02	**<0.001**

	ORIGINAL			OFFSPRING		
	Model 2**			Model 2**		
Cognitive Measure	**β**	**SE**	***p***	**β**	**SE**	***p***
Similarities (abstract reasoning)						
noAF	Ref			Ref		
prevAF	−0.21	0.42	0.62	0.03	0.08	0.68
intAF	0.20	0.39	0.62	−0.04	0.06	0.53
Trail Making Test – (B-A)						
noAF	Ref			Ref		
prevAF	−1.24	0.33	**<0.001**	−0.008	0.04	0.82
intAF	−0.16	0.28	0.58	−0.09	0.03	**<0.001**

*Adjusted for age, sex, education, and time between baseline examination and NP testing.

**Additional adjustments for systolic BP, diastolic BP, antihypertensive medications, myocardial infarction and heart failure, smoking status, and ApoE ε4.