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# Atrial fibrillation in stroke-free patients is associated with memory impairment and hippocampal atrophy

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**Aims** To determine whether atrial fibrillation (AF) in stroke-free patients is associated with impaired cognition and structural abnormalities of the brain. AF contributes to stroke and secondary cognitive decline. In the absence of manifest stroke, AF can activate coagulation and cause cerebral microembolism which could damage the brain.

**Methods and results** We cross-sectionally evaluated 122 stroke-free individuals with AF recruited locally within the German Competence Network on AF. As comparator, we recruited 563 individuals aged 37–84 years without AF from the same community. Subjects underwent 3 T magnetic resonance imaging to assess covert territorial brain infarction, white matter lesions, and brain volume measures. Subjects with evidence for stroke, dementia, or depression were excluded. Cognitive function was assessed by an extensive neuropsychological test battery covering the domains learning and memory, attention and executive functions, working memory, and visuospatial skills. Cognitive scores and radiographic measures were compared across individuals with and without AF by stepwise multiple regression models. Stroke-free individuals with AF performed significantly worse in tasks of learning and memory ($\beta = -0.115$, $P < 0.01$) as well as attention and executive functions ($\beta = -0.105$, $P < 0.01$) compared with subjects without AF. There was also a trend ($P = 0.062$) towards worse performance in learning and memory tasks in patients with chronic as compared with paroxysmal AF. Corresponding to the memory impairment, hippocampal volume was reduced in patients with AF. Other radiographic measures did not differ between groups.

**Conclusion** Even in the absence of manifest stroke, AF is a risk factor for cognitive impairment and hippocampal atrophy. Therefore, cognition and measures of structural brain integrity should be considered in the evaluation of novel treatments for AF.

**Keywords** Atrial fibrillation • Cognition, memory • Hippocampus, atrophy

## Introduction

Atrial fibrillation (AF) increases the risk of stroke,[1] and stroke increases the risk of cognitive decline and dementia.[2,3] As a consequence, AF is associated with cognitive decline and dementia.[4–10]

AF leads to a hypercoagulatory state[11,12] that could give rise to subclinical cerebral embolism. Indeed, transcranial Doppler ultrasonography has detected cerebral microemboli in up to 30% of patients with AF.[13,14] Whether AF also increases the risk of cognitive decline and dementia independently of stroke is unclear. Stroke has been the primary outcome measure for randomized trials on anticoagulation that underlie present treatment guidelines for AF.[15,16] If AF also contributes to cognitive decline independently of stroke, future interventional studies—and possible treatment guidelines—would have to consider cognition as an outcome parameter.[17]

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Large studies without brain imaging and small studies, which ruled out stroke by cerebral magnetic resonance imaging (MRI), suggested an independent association between AF and dementia.[10,18,19] Other studies without imaging conducted in old and very old patients found no or no marked influence of AF on cognitive function.[20,21] However, with age there is an accumulation of degenerative and vascular pathology, including hypertension, obesity, impaired glycaemic control, stroke, and cardiac disease. This makes it difficult to discern the relative contribution of single factors to clinically manifest dementia in the elderly.

To test if there is an independent relation between AF and cognitive impairment, we used in-depth neurocognitive evaluation in a cohort of AF patients considerably younger than those in previous studies.[20,21] As a comparator, we recruited a five-time larger cohort without AF from the same community based on matching birth dates. Additionally, we controlled for confounding risk factors, particularly other vascular risk factors and used high-field MRI of the brain to exclude covert territorial brain infarction.

We also used MRI to assess white matter lesions and brain atrophy—particularly atrophy of the hippocampus, since the hippocampus is highly sensitive to vascular and other brain damage.[22,23]

# Methods

A total of 501 adult patients who presented to the local centre of the AF Competence NETwork (AFNET, www.kompetenznetz-vorhofflimmern.de) in Münster, Germany were screened for enrolment. Inclusion criterion was an electrocardiographical documentation of AF in the last 12 months before enrolment. For comparison, individuals without AF from the same community were recruited. The local Ethics Committee approved of the research protocol. Community-living individuals from 35 to 85 years of age were randomly selected based only on dates of birth from the urban population register. Both AF patients and controls were invited by letter to participate in the study and were recruited after giving informed written consent. The time period of recruitment was 27 months (January 2004 to April 2007). Subjects who could not undergo MRI of the brain or psychometric tests were excluded. To reduce possible effects of co-morbidity on cognition, we restricted this study to non-demented and -depressed individuals. We, therefore, excluded participants with scores below 25 points on the Mini-Mental State Examination (MMSE)[24] and those with scores higher than 17 on the Beck Depression Inventory (BDI).[25] As in previous studies, we further excluded the participants with a history or imaging evidence of stroke, other severe neurological conditions or psychotropic medication.[26] Participants who did not complete the neuropsychological evaluation were also excluded from analyses. A detailed list of exclusion criteria is given in *Table 3*.

All participants received a structured clinical face-to-face interview, a physical examination by a physician, blood sampling, a comprehensive neuropsychological assessment, and MRI at 3.0 T.

## Neuropsychological assessment

Trained technicians supervised by a clinical neuropsychologist conducted the neuropsychological assessment. The test battery was designed to assess a full range of cognitive functions. Tests and their particular neurocognitive scope are listed in *Table 1*. A detailed description of each test may be found in Lezak.[27]

**Table 1 Neuropsychological tests**

| Domain | Test | Scope |
|---|---|---|
| Learning and memory | Auditory verbal learning test (German version) | Immediate verbal span<br>Verbal learning<br>Slope of learning<br>Short and long-term retrieval<br>Recognition |
| Attention and executive functions | Colour-word-interference test (Stroop test) | Cognitive flexibility |
| | Digit symbol substitution test | Psychomotor speed<br>Cognitive flexibility |
| | Trail-making test | Cognitive speed<br>Cognitive flexibility<br>Visual search |
| Working memory | Category and letter fluency | Semantic and phonological retrieval |
| | Digit span (Wechsler Memory Scale Revised, German Version) | Immediate numeric span (forward span)<br>Working memory (backward span) |
| Visuospatial skills | Rey-Osterrieth complex figure test | Incident figural memory<br>Constructional ability<br>Planning |

## Magnetic resonance imaging

MRI was performed with a 3 T MRI system (Gyroscan Intera T30, Philips Medical System, The Netherlands) using a head coil with a high-resolution structural T1-weighted 3D turbo-field-echo sequence (matrix $256 \times 205 \times 160$ over a field of view of $25.6 \times 20.5 \times 16$ cm reconstructed after zero filling to $512 \times 410 \times 320$ cubic voxels with an edge length of 0.5 mm), as well as T2-weighted, and fluid-attenuated inversion recovery (FLAIR) imaging. Image files were transferred to a Linux workstation (Red Hat, Research Triangle Park, NC, USA).

Image analysis included a conventional neuroradiological reading. Assessment of leukoaraiosis was based on the detection of white matter hyperintensities (WMH). WMH were graded using axial FLAIR sequences. WMH were calculated semi-quantitatively based on 15 brain regions in the periventricular and deep white matter of both hemispheres, the left and right cerebellum, and the brain stem. For each region (left and right separately), a severity score extending from '0—no lesion' to '5—large confluent lesions' was applied, thus defining a total WMH-score of 0–165.

Intracranial volume was calculated using SIENAX after the segmentation of the T1-weighted MRI using SPM99 (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK).

Hippocampal volumetry was performed in a subset of 122 scans based on random selection from the cohort, because the procedure is highly time-consuming. Two trained, independent operators, who were blinded to group membership and clinical data performed region of interest tracing. Hippocampal volumes were determined in a semi-automated way by outlining the periphery of the hippocampus using a custom-tailored software based on Analyse-software (Brain Imaging Resource, Mayo Clinic, Rochester, MI, USA). Bilaterally, the anterior border of the hippocampus was defined as the first of 0.5 mm-thick slices, in which the pes hippocampal appeared just caudal to the amygdala. The posterior border was defined as the slice just rostral to

where the crus of the fornix appeared as a continuous tract. Measurement of the hippocampus included the hippocampal body, dentate gyrus, uncus, fimbria, alveus, and subiculum. Interrater correlation was 0.97. Data were normalized by dividing hippocampal volume by the intracranial volume resulting in a relative hippocampal volume.

## Independent variables

Blood pressure was measured after a 20–40 min rest period, while subjects sat in an upright position. Three measurements were taken from the left arm, one from the right arm. Blood pressure values were then calculated from the average over the last two measures from the left arm and the measure from the right arm. Education was assessed as categorical variable (5 vs. 7 vs. 9 years of secondary school vs. tertiary education). Body mass index (BMI) was calculated dividing body weight (kg) by the square of the body height ($m^2$). History of arterial hypertension, coronary artery disease, diabetes, dyslipoproteinemia, current smoking status, and the use of antihypertensive or lipid lowering medication were documented as dichotomous variables.

## Statistical analyses

In preanalyses, possible confounders for cognitive performance and hippocampal volume, like age, education, body weight, height, cardiovascular risk factors, and cardiovascular disease were compared between patients with AF and controls without AF. Differences in categorical variables were studied using Fisher's exact test (two-sided) and differences in continuous variables using Student's *t*-test. The significance level was set at $P < 0.05$. To determine meaningful composite scores of cognitive functions, we performed a principal component analysis of single test performances, followed by an oblique (Oblimin with Kaiser-normalization) rotation, including coefficients with absolute values above 0.4. The same test was not included in more than one composite score. The resulting four factors (all with an eigenvalue $>1$) of the principal component analysis were *z*-transformed with a mean score of 0 and a standard deviation of 1, and hence considered as principle cognitive domains (*Table 1*).

Multiple linear regression models were then carried out to test independently the effect of AF on cognitive scores. Adjustment of covariates ranged from a basic set to complex models adjusting for a broad range of confounders (see *Table 2*). The assumption of linearity was evaluated by examining the distribution of residuals in the respective model and was not found to be violated.

The same modelling procedure was applied to assess the relation between AF and hippocampal volume: the basic model included the covariates age, gender, education, and body length, the last being a strong predictor of brain volume.[28] To adjust for well-known confounders, the extended model additionally included diabetes and hypertension as covariates.

Interactions between factors were considered using a stepwise regression analysis. The significance level was set at $P < 0.05$ (hippocampal measurements) and $P < 0.0125$, respectively (cognitive domains after Bonferroni correction for multiple testing).

To test for a possible cognitive effect resulting from the type of AF and from different therapies, we restricted regression models (*Table 2*) to the patient subgroup and additionally adjusted for the type of AF, history of electrical cardioversion, use of anticoagulation, platelet inhibitors, and antiarrhythmics. The analysis was carried out using SPSS version 13 (SPSS Inc., Chicago, IL, USA).

**Table 2 Set of covariates in linear regression models relating atrial fibrillation to cognitive domains**

| Model | Covariates |
|---|---|
| Basic | Age, gender, education |
| Basic + risk factors | Age, gender, education,<br>Systolic blood pressure, body mass index (BMI), hypertension, diabetes, dyslipoproteinemia, smoking, coronary artery disease |
| Basic + risk factors + treatment | Age, gender, education<br>Systolic blood pressure, BMI, hypertension, diabetes, dyslipoproteinemia, smoking, coronary artery disease<br>Anithypertenisve medication, use of statins |

# Results

A total of 563 out of 2200 invited citizens without AF and 122 of 501 patients with documented AF consented to participate. Exclusions left a total of 87 individuals with AF and 446 without AF for the analyses (*Table 3* and *Figure 1*).

Univariate analyses identified the following factors that differed significantly between patients with AF and control subjects without AF: age and education was higher in control subjects, BMI was higher in patients with AF. Male gender, cardiovascular disease (diabetes, coronary artery disease, and hypertension), and the use of antihypertensive or lipid lowering medication were more common in patients with AF. There was no significant difference in the levels of systolic or diastolic blood pressure, in the prevalence of smoking or dyslipoproteinemia and in the extent of WMH (*Table 4*).

In the AF group, 47 individuals suffered from paroxysmal AF, 37 had persistent, or permanent AF. One patient had a single episode of AF and in two patients, the type of AF was not documented explicitly. Patients with chronic AF and paroxysmal AF did not differ significantly in any covariate except gender (more females with paroxysmal AF). Sixty-seven patients were on antiarrhythmic drugs. Thirty patients received antiarrhythmic agents of Class I (sodium channel blockers) and Class III (potassium channel blockers). Sixty patients were treated with Class II (ß blockers) and Class IV (calcium antagonists) antiarrhythmics, either as monotherapy or in addition to a rhythm controlling antiarrhythmic agent. Fifteen patients received cardiac glycosides and 14 had undergone electrical cardioversion (*Table 5*). Again, groups did not differ significantly in any covariate. Oral anticoagulation was used by 45 of 87 AF patients, platelet inhibitors by 20 patients with AF. Subjects on oral anticoagulation were significantly older ($P = 0.041$) and suffered more often from chronic than paroxysmal AF ($P = 0.028$).

Test performance of the four cognitive domains derived from principle component analysis explained 61% of the total variance of all tests and proved theoretically meaningful measures for learning and memory, attention and executive function, visuospatial skills, and working memory. Their explained variance varied between 38.1 (learning and memory) and 5.8% (working memory).

**Table 3 Exclusion criteria**

| Consented | *n* = 685 (100) | | | | Total |
|---|---|---|---|---|---|
| **Exclusion criterion** | **Male, *n* = 342 (50)** | | **Female, *n* = 343 (50)** | | |
| | **No atrial fibrillation (AF), *n* = 246 (36)** | **AF, *n* = 96 (14)** | **No AF, *n* = 317 (46)** | **AF, *n* = 26 (4)** | |
| Magnetic resonance imaging pathology (territorial infarctions, tumours) | 10 | 7 | 8 | 2 | 27 |
| History of ischaemic stroke | 3 | 6 | 0 | 2 | 11 |
| Transient ischaemic attack in history | 2 | 3 | 6 | 2 | 13 |
| Head injury | 3 | 0 | 3 | 1 | 7 |
| History of intracerebal bleeding | 1 | 1 | 0 | 0 | 2 |
| History of brain tumour | 2 | 0 | 0 | 1 | 3 |
| History of meningitis | 2 | 0 | 1 | 0 | 3 |
| Epilepsy | 1 | 0 | 2 | 1 | 4 |
| Psychiatric disorder | 2 | 0 | 0 | 0 | 2 |
| Parkinsońs disease | 1 | 0 | 0 | 0 | 1 |
| Dementia | 2 | 0 | 1 | 0 | 3 |
| Malignancy | 4 | 0 | 2 | 0 | 6 |
| History of kidney transplantation | 0 | 1 | 0 | 0 | 1 |
| Antidepressive medication | 8 | 2 | 16 | 1 | 27 |
| Anticonvulsive medication | 3 | 0 | 3 | 1 | 7 |
| MMSE < 25 | 2 | 1 | 1 | 0 | 4 |
| BDI > 17 | 7 | 4 | 19 | 4 | 34 |
| Symptomatic hypertension on examination (agitation, sensation of heat, nausea) | 2 | 1 | 0 | 0 | 3 |
| Non-German native language | 2 | 0 | 0 | 0 | 2 |
| Study drop-out | 0 | 0 | 1 | 0 | 1 |
| Missing data of neuropsychological assessment | 10 | 3 | 7 | 4 | 24 |
| Sum ('excluded cases') | 67 (10) | 29 (4) | 70 (10) | 19 (3) | 185 (27) |
| Number of excluded individuals[a] | 55 (8) | 24 (3.5) | 62 (9) | 11 (1.5) | 152 (22) |
| Included participants | 191 (28) | 72 (11) | 255 (37) | 15 (2) | 533 (78) |

[a]Some participants fulfilled more than one exclusion criterion, thus the number of 'excluded cases' as listed above exceeds the actual number of excluded participants. Numbers in brackets show percentages.

Presence of AF was significantly and independently related to performance in learning and memory in all regression models (*Table 6* and *Figure 2*). There was also a significant association of AF with attention and executive functions (*Table 6*). There was no significant difference in performance on visuo-spatial abilities or working memory. There was also no significant difference in cognitive domains depending on the type of AF (paroxysmal vs. chronic), but a trend towards worse performance in learning and memory in patients with chronic AF (Student's *t*-test: $P = 0.062$; *Figure 2*). Intake of antiarrhythmic drugs, including betablockers, and history of cardioversion did not show any significant association with cognitive performance. Oral anticoagulation, however, was significantly negatively related with performance in learning and memory ($ß = -0.282$, $SE = 0.186$, $P < 0.01$).

In the 122 subjects with hippocampal volume measurements, the presence of AF was significantly and independently related to hippocampal volume (*Table 7* and *Figure 3*). There was no significant association of AF with total brain volume or WMH.

# Discussion

The main finding of the present study is that learning and memory as well as attention and executive functions are poorer and hippocampal volume is smaller in stroke-free community-dwelling individuals with AF as compared with those without AF even after controlling for other vascular risk factors.

The present study differs from previous studies on cognition in AF by the younger median age of participants and a more extensive and fine-grained neurocognitive assessment. Further strengths are the stepwise adjustment for potential confounders and the rigorous exclusion of strokes by history and brain imaging.[21,29–31] However, other methodological issues deserve mention. Data were obtained from cross-sectional observation. This can introduce variability due to unrelated differences between subjects. Thus, patients with AF were younger than control subjects (*Table 4*). Since younger people perform better on cognitive tests and have larger hippocampi, there may have been masking of impairment in AF.[23] Conversely, although patients with AF

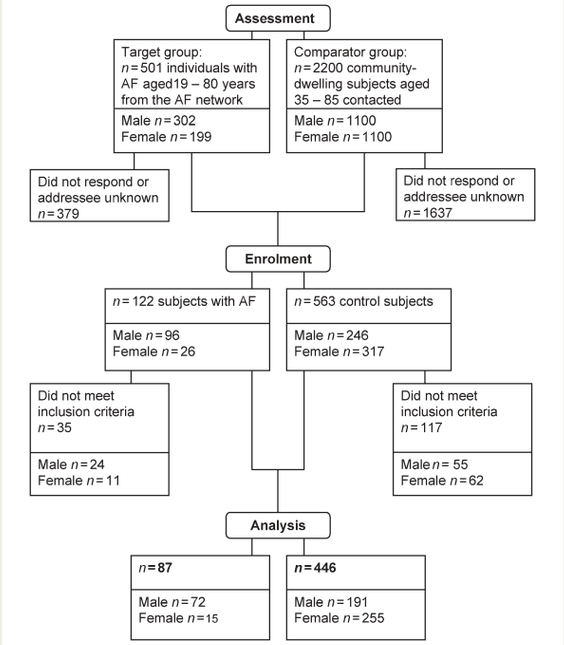


**Figure 1** Diagram showing the flow of participants.

**Table 4 Characteristics of study subjects ($n$ = 533)**

| | AF ($n$ = 87) | No AF ($n$ = 446) |
|---|---|---|
| Age, years* | 60 ± 12 | 64 ± 7[a] |
| Female* | 15 (17.2) | 255 (57.2)[b] |
| Education (5/7/9/+)** | 40/15/14/18 (46/17/16/21) | 142/128/51/125 (32/29/11/28)[c] |
| Systolic blood pressure, mmHg | 140 ± 19 | 144 ± 18[a] |
| Diastolic blood pressure, mmHg | 83 ± 11 | 85 ± 11[a] |
| Hypertension in history** | 41 (47.1) | 154 (34.5)[b] |
| Antihypertensive medication* | 68 (78.2) | 167 (37.4)[b] |
| Use of angiotensin converting enzyme inhibitors* | 26 (29.9) | 60 (13.5)[b] |
| Cigarette smoking | 8 (9.2) | 48 (10.8)[b] |
| Body mass index, kg/m$^2$* | 27.1 ± 4.3 | 25.1 ± 3.2[a] |
| Dyslipoproteinaemia | 33 (37.9) | 144 (32.3)[b] |
| Use of statins* | 25 (28.7) | 59 (13.2)[b] |
| Diabetes* | 9 (10.3) | 15 (3.4)[b] |
| Coronary artery disease* | 15 (17.2) | 27 (6.1)[b] |
| WMH-score | 6.4 ± 10.9 | 7.7 ± 13.5[a] |

Data are shown as means ± SD for continuous variables and as count (percentage) for dichotomous and categorical variables. Variables differing significantly between AF patients and controls are marked (*$P < 0.01$; **$P < 0.05$). Education is assessed as 5 vs. 7 vs. 9 years of secondary school vs. tertiary education (5/7/9/+).
[a]Student's $t$-test; [b]Fisher's exact test (two-sided), [c]univariate ANOVA.

**Table 5 Characteristics of patients with atrial fibrillation (AF) ($n$ = 87)**

| | $n$ | % |
|---|---|---|
| Electrical cardioversion | 14 | 16.1 |
| Anticoagulation | 45 | 51.7 |
| Platelet inhibitors | 20 | 23.0 |
| Antiarrhythmic drugs | | |
| Sodium channel blockers (I)[a] | 12 | 13.8 |
| ß-Blockers (II)[a] | 51 | 58.6 |
| Potassium channel blockers (III)[a] | 18 | 20.7 |
| Calcium antagonists (IV)[a] | 9 | 10.3 |
| Cardiac glycosides | 15 | 17.2 |
| Type of AF | | |
| Paroxysmal AF | 47 | 54.0 |
| Persistent or permanent AF | 37 | 42.5 |
| Other type of AF[b] | 3 | 3.4 |

[a]Classes I, II, III, and IV of the standard classification system (Vaughan Williams).[27]
[b]One patient with a single episode of AF, two with unknown type of AF.

usually are under close medical scrutiny, AF could reflect more severe vascular disease, which may not only become manifest in cardiac arrhythmias, but also in increased brain damage. We attempted to control for the extent of overall vascular pathology by correcting for known contributors to vascular cognitive impairment and by the adjustment for WMH. AF is variable in character concerning duration and treatment regimens. Available information for participants in the present study did not allow for reliable categorization of AF duration. However, cognitive performance showed a trend towards worse performance in patients with chronic as compared with paroxysmal AF. Since chronic AF has usually been present for longer time than paroxysmal AF,[32] this may be taken as suggestive evidence for AF of longer duration to be associated with worse cognition. Treatment regimens other than anticoagulation were not significantly related to cognitive performance. Anticoagulation, however, was associated with poorer cognition—possibly because patients on anticoagulation were older and more often had chronic than paroxysmal AF.

Impairment of learning and memory and atrophy of the hippocampus are highly consistent since learning and memory heavily depend on the hippocampus and its integrity.[33] Several mechanisms may have led to hippocampal damage in AF and subsequent impairment of learning and memory. AF does not only lead to formation of large atrial thrombi, which are responsible for the often severe cardiogenic strokes. AF has also been associated with abnormalities of haemostasis, endothelial damage, platelet dysfunction, and low cardiac output,[34–36] increased rates of dense silent lacunar infarction,[37] spontaneous echo contrast on transesophageal echocardiography,[38] and intermittent microembolization.[13,14,39] All of these mechanisms can impact the brain and impair cognition. Our data suggest that in the absence of large strokes, these or other mechanisms may lead to brain damage that manifests as cognitive impairment.

**Table 6 Regression coefficients (ß) and standard errors (SEs) showing the relation between AF and cognitive performance (z-scores)**

| Cognitive domain | Basic model | | Basic + risk factors model | | Basic + risk factors + treatment model | |
|---|---|---|---|---|---|---|
| | ß | SE | ß | SE | ß | SE |
| Learning and memory | −0.120* | 0.109 | −0.115* | 0.115 | −0.115* | 0.115 |
| Attention and executive functions | −0.102* | −0.102 | −0.105* | −0.109 | −0.105* | −0.109 |
| Visuospatial abilities | 0.041 | | 0.024 | | 0.024 | |
| Working memory | −0.052 | | −0.062 | | −0.062 | |

*$P < 0.01$.

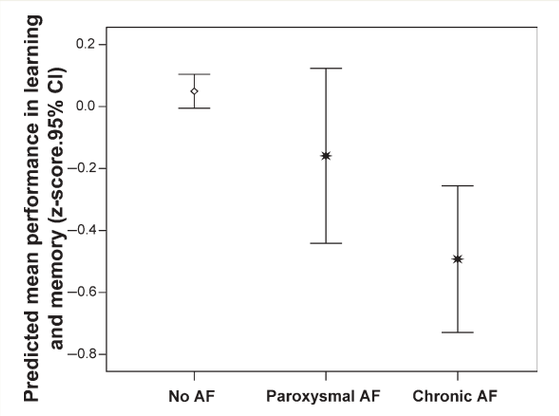


**Figure 2** Learning and memory in paroxysmal and chronic atrial fibrillation (AF). Domains had been determined by principle component analysis. Subjects with AF (stars) performed significantly worse in tasks of learning and memory ($P < 0.01$) than control subjects (diamonds). There was a trend towards worse performance in patients with chronic AF ($P = 0.062$) compared with patients with paroxysmal AF.

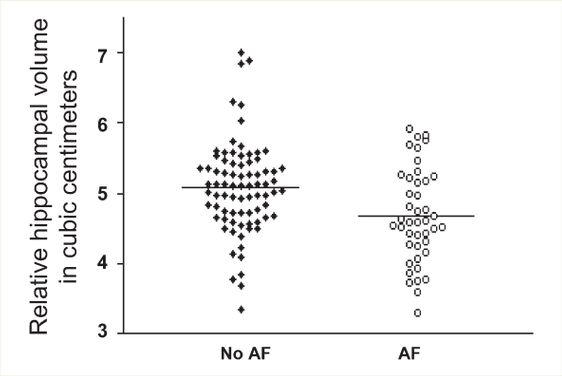


**Figure 3** Scatter column (with mean) of raw relative hippocampal volume in individuals with atrial fibrillation (AF) and without AF (No AF). Subjects with AF showed a significantly lower hippocampal volume, both absolute ($P < 0.01$) and relative to total brain volume ($P < 0.01$).

**Table 7 Regression coefficients (ß) and standard errors (SEs) showing the relation between atrial fibrillation (AF) and hippocampal volumes**

| Hippocampal volume | Basic model | | Basic + risk factors model | |
|---|---|---|---|---|
| | ß | SE | ß | SE |
| Total | −0.272* | 0.129 | −0.272* | 0.129 |
| Left | −0.261* | 0.071 | −0.261* | 0.071 |
| Right | −0.254* | 0.066 | −0.254* | 0.066 |
| Relative | −0.270* | <0.001 | −0.270* | <0.001 |

*$P < 0.01$.

Why are learning and memory as well as attention and executive function impaired in AF rather than working memory or visuospatial and perceptual skills? Occasionally in vascular dementia, visuospatial and perceptual skills seem more affected than learning and memory.[40] These differences in impairment profiles could indicate that the pathophysiology of brain damage in AF, e.g. subclinical cardiogenic microembolization, differs from that of patients with vascular risk factors like hypertension and diabetes.

Why was hippocampal volume decreased in individuals with AF but other radiographic measures did not differ? White matter lesions on MRI are considered as the hallmark of cerebral small vessel disease. So far, no increases in white matter lesions have been reported for patients with AF after correction for associated vascular risk factors.[37] The aetiology of white matter lesions is diverse and not fully understood.[41,42] Age, hypertension, and diabetes have been implicated. However, these factors were controlled for in the present study. A comparable load of white matter lesions in individuals with and without AF suggests that AF does not damage the brain by small vessel pathology but by other mechanisms—possibly microembolism.

Total brain volume (corrected for gender, height, and weight) was insignificantly smaller in participants with AF. If brain damage in AF was related to microembolism, lack of significant brain atrophy in AF patients could indicate that our relatively young patients (mean age, 60 years) still had considerable reserve capacity to compensate the effects of microemboli. Additionally, total brain volume may by too coarse a measure, because it is influenced by several factors that may not act in a fully linear way such as height and weight. Since the relative hippocampal volume is corrected for overall brain volume, these confounders are adjusted for. Therefore, hippocampal volume may have been a more sensitive measure for brain damage. The hippocampus is highly plastic, but also one of the most vulnerable regions of the brain. Thus, hippocampal damage is encountered in Alzheimer's disease, diabetes, hypertension or after brain trauma, hypoxia, and extreme stress.[43–48] We do not believe that AF would affect in isolation the hippocampus and its associated functions memory and learning. Rather the hippocampus and its functions may have been the most sensitive structures and the ones that allowed for best measurement.

The sensitivity of neuropsychological tests used here was considerably higher than those in previous studies on older subjects which heavily relied on the MMSE.[20,21] These studies found no increase in cognitive impairment in AF, which the researchers deemed clinically significant.[20] Therefore, the question arises whether the extent of memory impairment found here is clinically relevant. On average, compared with participants without AF, individuals with AF produced one word less on long-term retrieval (auditory verbal learning test, AVLT—recall trial 7) where the average number of words recalled in our cohort was 11 out of 15. Cognition, particularly memory, is an intermediate endpoint for the development of clinically manifest dementia.[49,50] Additionally, cognition is an endpoint in itself as a major determinant of quality-of-life.[51,52] Vasculogenic impairment of cognition like that related to AF is, above all, critical on a population level because it reduces cognitive reserve. Thus, in a recent study, AF was associated with a greater rate of decline in Alzheimer disease.[53] Reduction of vascular pathology can delay development of dementia. Any delay would lead to a disease compression and thus a reduction of the overall burden of dementia.[54,55]

The lifetime risk for development of AF is 25% for men and women aged 40 and older with a steep increase in prevalence in the old and very old, i.e. in those individuals most at risk of memory decline and dementia.[56] Here, standard treatment of AF involves anticoagulation or platelet inhibitors to prevent thromboembolic (overt) strokes.[16] The present findings indicate that cognitive function may also be impaired by AF independently of stroke. Whether novel antithrombotic or rhythm-control treatments of AF can prevent cognitive decline should be studied in controlled trials.

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**Conflict of interest:** none declared.

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The above article uses a new reference style being piloted by the EHJ that shall soon be used for all articles.