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Is Hippocampal Volume a Relevant Early Marker of Dementia?

Mélissa Gentreau, Ph.D., Jerome J. Maller, Ph.D., Chantal Meslin, Ph.D., Fabienne Cyprien, MD, Ph.D., Jorge Lopez-Castroman, MD, Ph.D., Sylvaine Artero, Ph.D.

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ABSTRACT

Objective: *Hippocampal volume (HV) is a key imaging marker to improve Alzheimer's disease risk prediction. However, longitudinal studies are rare, and hippocampus may also be implicated in the subtle aging-related cognitive decline observed in dementia-free individuals. Our aim was to determine whether HV, measured by manual or automatic segmentation, is associated with dementia risk and cognitive decline in participants with and without incident dementia.* ***Methods:*** *At baseline, 510 dementia-free participants from the French longitudinal ESPRIT cohort underwent magnetic resonance imaging. HV was measured by manual and by automatic segmentation (FreeSurfer 6.0). The presence of dementia and cognitive functions were investigated at each follow-up (2, 4, 7, 10, 12, and 15 years). Cox proportional hazards models and linear mixed models were used to assess the association of HV with dementia risk and with cognitive decline, respectively.* ***Results:*** *During the 15-years follow-up, 42 participants developed dementia. Reduced HV (regardless of the measurement method) was significantly associated with higher dementia risk and cognitive decline in the whole sample. However, only the automatically measured HV was associated with cognitive decline in dementia-free participants.* ***Conclusion:*** *These results suggest that HV can be used to predict the long-term risk of dementia but also cognitive decline in a dementia-free population. This raises the question of the relevance of HV measurement as an early marker of dementia in the general population.* (Am J Geriatr Psychiatry 2023; 31:932–942)

From the Institute of Functional Genomics (MG, FC, JLC, SA), University of Montpellier, CNRS, INSERM, Montpellier, France; Monash Alfred Psychiatry Research Centre (JJM), Melbourne, Victoria, Australia; General Electric Healthcare (JJM), Richmond, Melbourne, Victoria, Australia; Centre for Mental Health Research (CM), Australian National University, Canberra, Australia; Department of Adult Psychiatry (JLC), Nimes University Hospital, Nimes, France; and the Centro de Investigación Biomédica en Red de Salud Mental (JLC), Madrid, Spain. Send correspondence and reprint requests to Sylvaine Artero, Ph.D., Institute of Functional Genomics, Hôpital La Colombière, 39 avenue Charles Flahault, BP 34493, Montpellier Cedex 5, 34093 France. e-mail: sylvaine.artero@inserm.fr

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Highlights

- **What is the primary question addressed by this study?**
  The study addressed a question whether hippocampal volume (HV), a key imaging marker in dementia prediction, is associated with dementia risk but possibly with aging-related cognitive decline without dementia in general population.
- **What is the main finding of this study?**
  Reduced HV is associated with higher dementia risk but predicts also cognitive decline without dementia Associations of HV with cognitive performance are method-dependent.
- **What is the meaning of the finding?**
  This study raises the question of the relevance of one HV measurement as an early marker of dementia in the general population.

INTRODUCTION

Hippocampus is a plastic brain structure with a central role in human cognition, memory, learning, and spatial navigation.[1,2] Despite its plasticity, it can be damaged by a variety of exogenous stimuli, including diet, air pollution, sleep alterations, inactivity and stress but also endogenous conditions such as depression leading to a decreased volume.[3] Hippocampal volume (HV) is correlated with local neuronal density,[4] and its reduction is likely to be preceded by cellular changes, such as synaptic loss and neuronal degeneration, that cannot be detected by conventional volumetric measurements.

A smaller HV has been associated with the risk of dementia and Alzheimer's disease (AD). It has been shown that patients with AD or mild cognitive impairment have a smaller HV compared with healthy aging controls.[5] Consequently, HV is of utmost interest in AD research, and has been proposed as a possible surrogate biomarker to facilitate early diagnosis. However, most evidence comes from epidemiological studies with short follow-up periods, and the role of HV reduction in predicting the long-term AD risk remains unclear.[6]

HV also decreases progressively with age in dementia-free older adults,[7,8] but the functional consequences of this age-related volumetric loss are not well characterized. Previous research has produced controversial findings on hippocampus role in dementia-free older adults with cognitive decline. While some studies found a significant association between HV and cognitive performance,[9-13] others did not.[14–16] Thus, the relationship between HV and cognitive decline in dementia-free older adults remains poorly understood. Inconsistencies among studies are not surprising, because most of them had a cross-sectional design or a short follow-up, and did not include information on the participants' cognitive outcome. In other words, it was not known whether the included participants developed dementia during the follow-up.

HVs are generally investigated using brain magnetic resonance imaging (MRI) volumetric data. The use of different measurement methods limits the comparisons between studies and explains, at least partly, their discrepancies. Manual tracing is still considered the "gold standard" for volumetric studies due to the hippocampus complex shape and ambiguous boundaries.[17] Unfortunately, this approach is time-consuming when analyzing large MRI databases. To cope with these limitations, automated segmentation methods based on software tools such as FreeSurfer have been developed. It is yet unknown whether the association between HV and dementia risk or cognitive decline could vary depending of the HV measurement method. No study to date has assessed this issue in a cohort of older adults.

In summary, changes in cognitive performance during dementia screening and cognitive assessment measures in patients with mild cognitive impairment and AD have been associated with smaller HV. Conversely, it is unclear whether in the general population 1) HV predicts the long-term risk of dementia; 2) this marker is specific to the dementia stage or whether subtler variations in HV might be observed also during dementia-free aging; and 3) the association between HV and cognitive performance is

affected by the segmentation method used to measure HV.

The aim of this study was to determine whether lower HV at baseline (measured using manual and automatic segmentation methods) is associated with dementia risk and cognitive performance changes with and without incident dementia during a 15-years follow-up in a longitudinal population-based cohort of French older adults.

MATERIALS AND METHODS

Study Sample

The ESPRIT study is a longitudinal study of neuropsychiatric disorders in community-dwelling French older adults and is part of the Three-City multicenter cohort study (Bordeaux, Dijon and Montpellier).[18] Eligible (≥65-years-old and non-institutionalized) participants were recruited from the electoral rolls between 1999 and 2001. The Bicêtre University Hospital Ethics Committee (France) approved the Three-City protocol, and all participants signed an informed consent. Interviews were administered by trained staff (nurses, psychologists, neurologists) at baseline and at 2, 4, 7, 10, 12, and 15 years of follow-up. From the 1,863 participants recruited, only those younger than 80 years were invited for an MRI at baseline. For the present analysis, 760 participants were randomly selected, among whom 537 had complete data (including MRI). From this group, 28 participants were excluded due to a diagnosis of dementia at baseline (n = 11), of dementia with Lewy bodies (n = 4) or Parkinson's disease dementia (n = 1) during the follow-up, and absence of follow-up (n = 12). Thus, 510 participants were retained. Participants were not taking any prescribed medications for dementia.

Cognitive Function Evaluation

At each follow-up visit, trained neuropsychologists administered a battery of cognitive tests to evaluate different cognitive domains. The mini mental state examination (MMSE) was used as a global measure of cognitive function.[19] The Benton's visual retention test (BVRT) evaluates visual memory and psychomotor speed.[20] The trail making test, forms A and B (TMTA and TMTB), assesses attention and visual motor processing speed (executive function).[21] The score is the time (in seconds) needed to execute the task: higher scores correspond to lower cognitive performance. The TMTA and B were not filled in at the 2-years follow-up visit. The Isaacs set test (IST) measures verbal fluency and semantic memory.[22] Fluency corresponds to the total score: the sum of the number of words generated for each semantic category in 15 seconds.

Dementia Diagnosis

At each follow-up visit, participants with suspected dementia (on the basis of their neuropsychological test results) were examined by a neurologist. Then, an independent committee of neurologists reviewed all potential cases of dementia to obtain a consensus on the diagnosis and etiology based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.[23] The date of dementia onset was the middle of the interval between the last follow-up without the event and the first follow-up with the event. The follow-up duration for each participant was calculated from the baseline examination to death, diagnosis of dementia, or end of follow-up, whichever came first.

MRI Data Analysis

At baseline, participants underwent MRI at the Gui De Chauliac Hospital (Montpellier, France). A 1.5T GE Signa Imaging system (General Electric Medical Systems, Milwaukee, WI) was used to acquire a contiguous AC-PC aligned axial IR-prepared SPGR T1-weighed sequence for volumetric estimations (TR = 12, TE = 2.8, IT = 6,000, matrix, size = 256×256, pixel spacing = 0.9375 × 0.9375 mm, NEX = 1, slice thickness = 1.0 mm).

Manual Segmentation of Hippocampus

Hippocampus regions of interest were manually outlined on consecutive coronal slices and the axial and sagittal orientations were verified.[24] According to the protocol described by Watson et al,[25] the area from the anterior tip of the hippocampus to the slice before the opening of the crus of the fornix corresponded to the hippocampus head and body and included the subiculum, CA1-4 areas, and dentate

gyrus.[25] The hippocampus tail was measured from the slice immediately posterior to the last slice. The tail internal structure is the same as that of head and body. The CA areas and dentate gyrus have a homogeneous structure. From the coronal plane perspective, measuring the hippocampus until the crus of the fornix represents the part of the tail that coincides with the coronal section of the pulvinar (which is situated in an upper-medial position). Voluminous choroidal plexuses occupy portions of this region; hence, care was taken to exclude them laterally from the volumetric estimates. The hippocampus was then followed posteriorly. On the initial slices, the tail appears bulgy as an ovoid mass of gray matter on the lower-medial part of the lateral ventricle, and more posteriorly it lies flattened on the superior surface of the parahippocampal gyrus. The tail was outlined up to the point where the fasciolar gyrus becomes the subsplenium gyrus, curving around the splenium posteroinferior margin. The upper border was easy to differentiate from the crus of the fornix. The medial and inferior limits were also easily drawn because of the contrast between gray and white matter. Images from standard atlases were used to ensure a consistent reference to the boundaries and relevant landmarks.

Automatic Segmentation of the Hippocampus

Regional reconstruction and segmentation were performed with the FreeSurfer 6.0 image analysis suite (http://surfer.nmr.mgh.harvard.edu/), as previously described.[26] The standard FreeSurfer automated subcortical segmentation protocol for the hippocampus is based on a probabilistic atlas.[27]

Intracranial Volume Measurement

Using the segment m-file in SPM5 (Wellcome Department of Cognitive Neurology, London, UK), the intracranial volume (gray + white matter + cerebrospinal fluid) was calculated and used as covariate in the models to minimize the effect due to global brain-size differences.

Covariates

The standardized interview included information on sociodemographic data, education level (no school, primary school, high school, or graduate level), medical history, and medication intake. History of cardiovascular disease included myocardial infarction, coronary surgery, coronary angioplasty, and arterial surgery of the legs for arteritis. Daily activity impairment was assessed with the Instrumental Activities of Daily Living (IADL) scale. Impairment was defined as increased difficulty in at least one IADL item.[28] Self-reported information was also obtained on health and sleep quality, appetite loss, social isolation, alcohol consumption (categorized as no drinking, drinking), and smoking status (never, past, or current). Apolipoprotein E genotyping was described elsewhere.[29] APOE4 carriers had at least one $\varepsilon 4$ allele.

Statistical Analyses

The participants' socio-demographic and clinical characteristics were analyzed with Cox proportional hazards models (adjusted for sex, education, age). Variables with $p<0.20$ were included in the multivariate models. Because the left hippocampus is generally more impacted than the right hippocampus in the dementia process,[5,30] we assessed the asymmetric association between HV and risk of dementia or cognitive decline by analyzing left and right HV separately.

Cox proportional hazards models with delayed entry were used for the longitudinal analysis of dementia onset during the 15-year follow-up, taking age as the timescale.[31] HVs were normally distributed and the assumption of hazard log-linearity was checked for each HV measurement.

Linear random-effect models, with random intercept and slope (follow-up time), were used to evaluate the association between baseline HVs and cognitive performance (each test) over time. To normalize the distributions, the MMSE and TMT scores were transformed using $(30\text{-MMSE})^{1/2}$ and the natural logarithm of TMT. For each cognitive test, the HVs x time interaction was tested. This represents the difference in the cognitive change slope for one-unit increase in the baseline HV. As no interaction was significant, this interaction was not included in the final model. In this model, the β coefficient for HV represents the association of HV with the mean cognitive performance during the 15-years follow-up. For BVRT and IST, a positive β coefficient indicates a

reduced mean cognitive performance during the 15-years follow-up for 1 cm^3 decrease in the baseline HV. For MMSE and TMT, a negative β coefficient indicates a reduced mean cognitive performance during the 15-years follow-up for 1 cm^3 decrease in the baseline HV. Finally, for each confounding factor, the interaction with time was tested and was added to the models when significant (i.e., age x time, sex x time, intracranial volume x time). These analyses were repeated after exclusion of the participants who developed dementia during the 15-years follow-up (n = 42).

The degree of agreement between manual and automatic methods was assessed with Bland-Altman plots.[32] The difference between volumes for all participants were plotted against the mean of both measurements on a graph.

All statistical analyses were performed in SAS 9.4 and the graphs were plotted in R 3.4.3.

RESULTS

In the selected ESPRIT study sample (n = 510), the participants' mean age at baseline was 71.3 (±4) years and 52.8% were women. Among all participants, 42 developed dementias during the 15-years follow-up. They were more likely to be older and were more often APOE4 carriers (Table 1).

Reduced HV is Associated With Higher Risk of Dementia

Reduction of right and left HV was associated with higher risk of dementia over the 15-years follow-up (Table 2). Results were similar regardless of the HV measurement method, although a larger effect size was observed with the automatic method (Fig. 1).

Reduced HV, Manually and Automatically Measured, is Associated With Lower Cognitive Performance in the Sample Including Participants With Incident Dementia

Using the manual method, a reduced right HV was significantly associated with reduced BVRT (by 0.36 points) and IST (by 1.51 points) performance over the 15-years follow-up. Similar results were obtained for the left HV (Table 3).

Using the automatic method, reduced HV (right and left sides) was associated with lower performance in all cognitive tests. The effect size was larger for the right hippocampus (Table 3). Indeed, a reduced right HV was associated with lower MMSE (by 0.50 points), BVRT (by 0.67 points), TMTA (by 7.55 seconds), TMTB (by 12.8 seconds), and IST (by 3.17 points) scores during the 15-years follow-up. Reduced HV, automatically measured, is associated with lower cognitive performance in dementia-free participants

Then, the association between HVs and cognitive performance in each test over time was investigated after exclusion of participants with incident dementia (n = 42). Using the manual method, HV was no longer associated with the BVRT and IST scores. Conversely, using the automatic method, the results for the right hippocampus were similar to those obtained in the analysis including participants with incident dementia, although the effect size was slightly weaker (Table 4). Specifically, reduced right HV was associated with a decrease in the MMSE (by 0.45 points), BVRT (by 0.49 points), TMTA (by 5.32 seconds), TMTB (by 8.58 seconds), and IST (by 2.92 points) performance during the 15-years follow-up.

HVs Are Larger With the Automatic Method Than With the Manual Method

The HVs obtained with the automatic method were larger than those obtained by manual measurement (Fig. 1). The right and left HVs were, on average, 0.35 cm^3 and 0.13 cm^3 larger with the automatic method compared to the manual method. This difference increased slightly (but not significantly) with the participants' age.

DISCUSSION

In this longitudinal analysis of a population-based cohort, we found that reduced baseline HVs were associated with higher risk of dementia and decreased cognitive performance during the 15-years follow-up. However, the association between HV and cognitive performance remained only for the automatically measured HVs when participants with incident dementia were excluded. These results suggest that 1) HV is a predictor of cognitive decline also in

TABLE 1. Baseline Demographic and Clinical Characteristics of the Study Participants

Baseline Characteristics	Total Sample n = 510	Incident Dementia n = 42	Dementia-Free n = 478	p Value[a]
Age, mean (SD)	71.3 (4.0)	73.2 (4.5)	71.1 (3.9)	0.012
Women, % (n)	52.8 (269)	52.4 (22)	52.5 (251)	0.64
Education level, % (n)				0.10
No formal education	25.3 (129)	35.7 (15)	24.4 (114)	
Primary	28.4 (145)	16.7 (7)	29.5 (138)	
Secondary	19.8 (101)	21.4 (9)	19.7 (92)	
Higher	26.5 (135)	26.2 (11)	26.5 (124)	
Hypertension[b], % (n)	48.0 (245)	50.0 (21)	47.9 (224)	0.80
Hypercholesterolemia[c], % (n)	52.0 (265)	59.5 (25)	51.4 (240)	0.30
Diabetes[d], % (n)	9.9 (50)	9.8 (4)	9.9 (46)	0.71
History of head trauma, % (n)	10.1 (51)	7.1 (3)	10.4 (48)	0.70
Cardiovascular history, % (n)	6.7 (34)	7.1 (3)	6.6 (31)	0.33
History of stroke, % (n)	3.5 (18)	2.4 (1)	3.6 (17)	0.94
Depressive symptomatology[e], % (n)	15.4 (78)	14.3 (6)	15.5 (72)	0.92
Antidepressants, % (n)	3.9 (20)	7.1 (3)	3.6 (17)	0.17
APOE4 carriers, % (n)	21.6 (109)	36.6 (15)	20.3 (94)	<0.001
Anticholinergic drugs, % (n)	4.3 (22)	2.4 (1)	4.5 (21)	0.64
Alcohol use, % (n)	85.0 (431)	90.5 (38)	84.5 (393)	0.21
Tobacco use (current or past), % (n)	44.3 (226)	40.5 (17)	44.6 (209)	0.83
Insomnia, % (n)	18.5 (91)	20.0 (8)	18.3 (83)	0.52
Good subjective health, % (n)	95.9 (488)	97.6 (41)	95.7 (447)	0.75
Appetite loss, % (n)	7.1 (36)	7.3 (3)	7.1 (33)	0.75
Living alone, % (n)	19.5 (99)	19.1 (8)	19.5 (91)	0.65
Difficulty with at least 1 IADL, % (n)	1.4 (7)	2.4 (1)	1.3 (6)	0.40
Hippocampal volume (cm^3): manual method				
Right, mean (SD)	2.76 (0.37)	2.77 (0.37)	2.64 (0.42)	-
Left, mean (SD)	3.01 (0.42)	3.02 (0.40)	2.81 (0.54)	-
Hippocampal volume(cm^3): automatic method				
Right, mean (SD)	3.12 (0.36)	3.13 (0.35)	2.99 (0.43)	-
Left, mean (SD)	3.14 (0.36)	3.15 (0.36)	2.98 (0.34)	-

Abbreviations: SD: standard deviation; APOE4: apolipoprotein ε4; MMSE: mini mental state examination; IADL: Instrumental activities of daily living; CESD-S: centre for epidemiologic studies of depression scale.

[a] Cox models with delayed entry were performed with age as the basic timescale and birth as the time origin, and adjusted for sex and education level, (except for age, sex, and education level). The p values were determined using the Wald Chi-square test with 1 degree of freedom (df) expect for education level (df = 3).

[b] Blood pressure greater than 140/90 mm Hg or treated.

[c] Cholesterol level greater than 6.2 mmol/L. or treated.

[d] Fasting blood glucose greater than7.0 mmol/L or treated.

[e] Depressive symptomatology: CESD-S ≥17 for men and ≥23 for women.

dementia-free older adults; 2) the segmentation method influences the results.

Manual segmentation, a laborious time-consuming task, is usually considered the gold standard, but many manual tracing protocols are now available. A recent article showed that FreeSurfer and manual tracing provide similar estimations of hippocampal atrophy in terms of biological interpretation, but, in agreement with our observations, volumes were larger with FreeSurfer. The proportion of overlapping voxels between manual tracing and FreeSurfer was 78%.[33] Comparison between manual tracing and FreeSurfer (version 5.3) suggests that FreeSurfer delineation differs by the border location between the hippocampus and the amygdala, and by including boundary voxels along the lateral and dorsal surfaces that contains mixture tissue (grey, white, or cerebrospinal fluid).[34] Moreover, FreeSurfer might also tend to over-segment larger hippocampi than smaller ones.[35] However, the routine use of FreeSurfer has considerable advantages. As FreeSurfer is an algorithm-based software, it cannot be influenced by the brain general shape, unlike clinicians and investigators.[36] FreeSurfer is less time-consuming than manual

TABLE 2. Association Between Baseline Hippocampal Volumes and Risk of Dementia During the 15-Years Follow-up

Hippocampus (cm^3)	Model 1[a] n = 510		Model 2[b] n = 501	
	HR[c] (CI)	p Value	HR[c] (CI)	p Value
Manual method				
Right	1.93 (1.24–2.99)	0.004	1.69 (1.09–2.61)	0.019
Left	2.09 (1.49–3.01)	<0.0001	1.88 (1.36–2.61)	0.0001
Automatic method: FreeSurfer 6.0				
Right	2.45 (1.45–4.34)	0.009	2.18 (1.19–3.99)	0.012
Left	2.92 (1.75–4.55)	<0.0001	2.70 (1.56–4.70)	0.0004

Cox proportional hazard models with delayed entry and age as the time scale were adjusted for:
[a] Sex, education level, and intracranial volume.
[b] Model 1 + antidepressant intake, alcohol use, APOE4 carriers.p values were obtained using the Wald Chi-square test with 1 degree of freedom.
[c] HR, hazard ratio for one standard deviation decrease in hippocampal volume.

FIGURE 1. Bland-Altman plots showing the differences in the mean hippocampal volumes obtained with the two segmentation methods (top). Differences between manual and automatic (FreeSurfer 6.0) tracing according to the participants' baseline age (bottom). Left panels: differences between right (R) hippocampal volumes. Right panels: differences between left (L) hippocampal volumes. Solid lines represent the mean difference between manual and automatic (FreeSurfer 6.0) volumes. Dashed lines represent the upper and lower 95% limits of agreement.

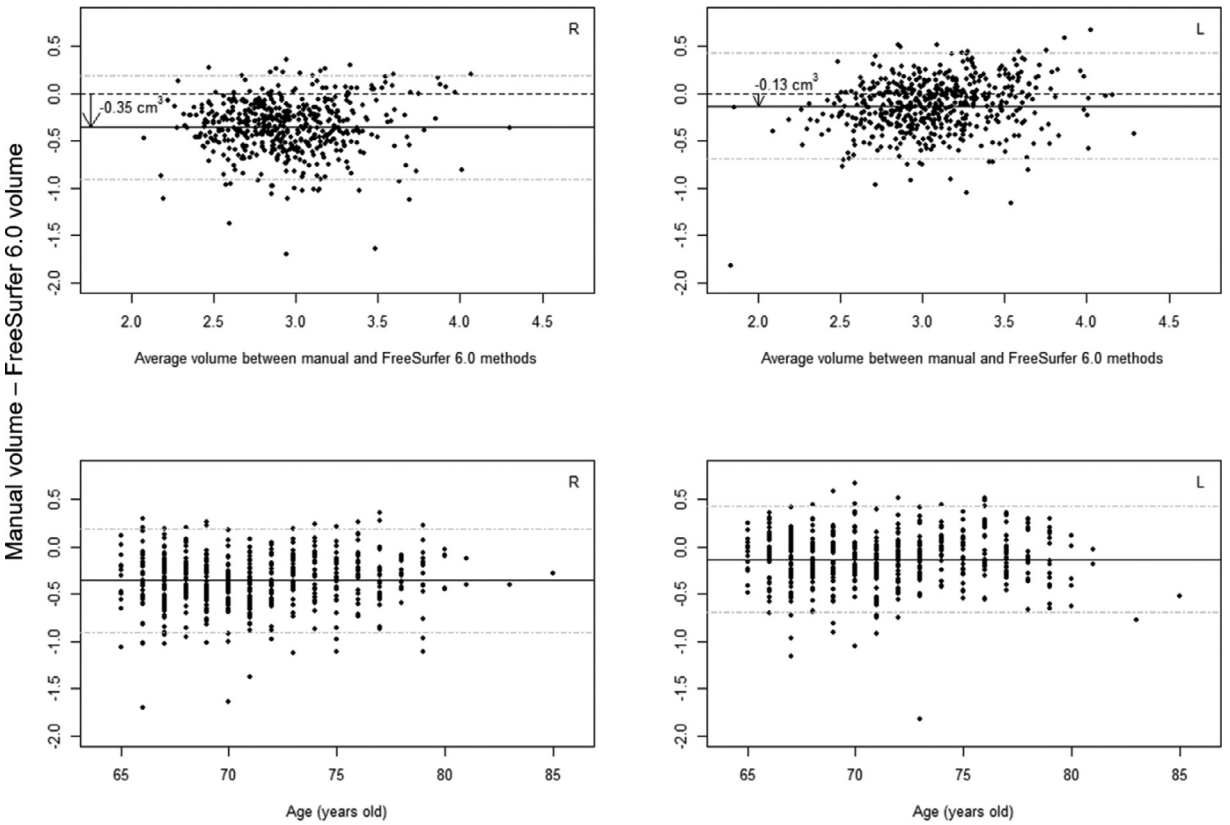

TABLE 3. Association Between Baseline Hippocampal Volumes and Cognitive Performance During the 15-Years Follow-up

	MMSE $\sqrt{30-MMSE}$ n = 482		BVRT n = 482		TMT A $log(TMTA)$ n = 437		TMT B $log(TMTB)$ n = 428		IST n = 483	
Hippocampus (cm^3)	**β (SE)**	**p Value**	**β (SE)**	**p Value**	**β (SE)**	**p Value**	**β (SE)**	**p Value**	**β (SE)**	**p Value**
Manual segmentation										
Right	−0.089 (0.063)	0.15	0.361 (0.173)	**0.037**	−0.056 (0.039)	0.15	−0.060 (0.040)	0.14	1.513 (0.630)	**0.017**
Left	−0.053 (0.056)	0.34	0.300 (0.154)	0.052	−0.059 (0.034)	0.086	−0.043 (0.036)	0.23	1.301 (0.564)	**0.02**
Automatic segmentation: FreeSurfer 6.0										
Right	−0.190 (0.071)	**0.007**	0.665 (0.195)	**0.0007**	−0.149 (0.044)	**0.0007**	−0.133 (0.046)	**0.004**	3.174 (0.709)	**<0.0001**
Left	−0.129 (0.071)	0.069	0.556 (0.837)	**0.004**	−0.115 (0.044)	**0.009**	−0.117 (0.045)	**0.01**	2.929 (0.704)	**<0.0001**

BVRT: Benton visual retention test; IST: Isaacs set test; MMSE: mini mental state examination; SE: standard error; TMT: trail making test.

Linear mixed models adjusted for time, age, sex, education level, intracranial volume, antidepressant intake, alcohol use, APOE4 carrier, and interaction terms (age x time, sex x time, intracranial volume x time). The p values were obtained using the Student's t-test with respectively 1,305, 1,288, 734, 785, and 1,267 degrees of freedom for MMSE, BVRT, TMTA, TMTB, and IST.

To transform back to the original scale:

MMSE: $-\beta^2 - (2\beta\sqrt{30 - m_{MMSE}})$ where $m_{MMSE} = 28$.

TMTA et TMTB: $\exp(\beta)m_{TMT} - m_{TMT}$ where $m_{TMTA} = 47\ sec$ and $m_{TMTB} = 90\ sec$.

m is the median of the cognitive score in the sample.

tracing and facilitates comparisons between studies. Our results also suggest that FreeSurfer can detect subtle HV changes during normal cognitive aging, compared with the manual method.

Many studies have shown a reduction in HV in AD and dementia. A meta-analysis of 23 cross-sectional studies found a decrease of the right and left HVs by 23.2% and 24.2%, respectively, in patients with AD compared with healthy controls.[5] Hippocampus is generally considered as the main target of AD hallmarks: neurofibrillary tangles, amyloid plaques, and neuronal loss. Thus, it has been incorporated in AD diagnostic criteria.[37,38] However, few studies have reported smaller HVs as a risk factor of dementia in longitudinal analyses. Our results are in line with the prospective analysis by the Rotterdam Scan Study showing that smaller HVs are associated with higher risk of dementia during a 10-years follow-up.[30]

We also found that reduced baseline HVs were associated with lower performances in all cognitive domains during the 15-years follow-up. However, when we excluded participants with incident dementia, only the right HV was associated with lower cognitive performance in global cognition, visual

TABLE 4. Association Between Baseline Hippocampal Volumes and Cognitive Performance During the 15-Years Follow-up in the Sample Without Participants With Incident Dementia (n = 42)

	MMSE $\sqrt{30-MMSE}$ n = 442		BVRT n = 442		TMT A $log(TMTA)$ n = 400		TMT B $log(TMTB)$ n = 392		IST n = 443	
Hippocampus (cm^3)	**β (SE)**	**p Value**	**β (SE)**	**p Value**	**β (SE)**	**p Value**	**β (SE)**	**p Value**	**β (SE)**	**p Value**
Manual segmentation										
Right	−0.061 (0.065)	0.35	0.221 (0.175)	0.21	−0.034 (0.040)	0.40	−0.022 (0.041)	0.59	1.180 (0.662)	0.07
Left	0.010 (0.059)	0.87	0.124 (0.179)	0.45	−0.038 (0.037)	0.31	−0.005 (0.038)	0.90	1.049 (0.609)	0.09
Automatic segmentation: FreeSurfer 6.0										
Right	−0.170 (0.074)	0.021	0.488 (0.199)	0.014	−0.123 (0.046)	0.008	−0.092 (0.048)	0.054	2.915 (0.748)	0.0001
Left	−0.092 (0.072)	0.203	0.390 (0.194)	0.047	−0.083 (0.045)	0.066	−0.069 (0.046)	0.14	2.587 (0.732)	0.0004

BVRT: Benton visual retention test; IST: Isaacs set test; MMSE: mini mental state examination; SE: standard error; TMT: trail making test.

Linear mixed models adjusted for time, age, sex, education level, intracranial volume, antidepressant intake, alcohol use, APOE4 carrier, and interaction terms (age x time, sex x time, intracranial volume x time). The p values were obtained using the Student's t-test with respectively 1200, 1,189, 677, 731, and 1,170 degrees of freedom for MMSE, BVRT, TMTA, TMTB, and IST.

To transform back to the original scale:

MMSE: $-\beta^2 - (2\beta\sqrt{30 - m_{MMSE}})$ where $m_{MMSE} = 28$.

TMTA et TMTB: $\exp(\beta)m_{TMT} - m_{TMT}$ where $m_{TMTA} = 46\ sec$ and $m_{TMTB} = 89\ sec$.

m is the median of cognitive score in the sample.

memory and psychomotor speed, attention and visual-motor processing speed, and semantic memory. This suggests that the right HV could be a better predictor of cognitive decline in dementia-free older adults. The strongest and most robust association was between HV and semantic memory. Therefore, semantic memory may be the first cognitive function altered upon HV reduction during normal cognitive aging.

Although several studies assessed the association between HV and cognitive decline in dementia-free individuals, they were limited by a short follow-up or small sample size. A cross-sectional study suggested the possible role of hippocampus in executive function and processing speed.[9] The authors also showed a role of aging-related HV changes in episodic memory and verbal learning. In another study, total HV (measured with FreeSurfer 6.0) was associated with all cognitive tests, except verbal learning, during a mean follow-up of 5.5 years.[39] Unlike our study, another population-based study did not find any significant association between HV and cognitive performance during the follow-up.[40] This discrepancy can be explained by the shorter follow-up (5 years vs. 15 years) and the use of data collected only at one follow-up visit, whereas we considered the changes in cognitive performance over several assessments. Another study also found that in a sample of 40 women, reduced HV was associated with a decline in executive functions, but not episodic memory.[41]

According to our results, the HV alone does not identify individuals who will develop dementia, but might help to detect individuals at risk of cognitive decline, particularly when using FreeSurfer as a segmentation method. The fact that HV also predicts cognitive decline during dementia-free aging is not a surprising result. Indeed, because of the high neuroplasticity of the hippocampus, HV correlates with many environmental conditions and pathologies that can also affect cognition. HV changes combined with other biomarkers, such as amyloid Aβ_{42} and tau concentration in cerebrospinal fluid and in brain (PET imaging),[38] might allow differentiating individuals at risk of dementia and AD from those with stable cognitive decline.

The major strengths of our study are the prospective population-based design, the important number of participants for an MRI-based study and the long follow-up period with regular diagnosis of incident dementia and cognitive testing during the follow-up. Our study also presents some limitations. We did not perform a longitudinal brain MRI assessment to monitor hippocampal atrophy. HVs, adjusted only to intracranial volume, may not provide an entirely valid index of hippocampal atrophy because of the wide range of such volumes.[42] Another measurement of the HV later in the follow-up could have refined our results. Then, some HV subfields (e.g., the subiculum) have been associated with the risk of dementia and executive function impairment.[39] However, we did not assess the association between HV subfields and the risk of dementia or cognitive decline because manual measurements could not be compared with FreeSurfer automatic measurements. Finally, we did not adjust for multiple testing which increase the type I error but prevent the increase of type II error.[43–45]

Reduced HV was significantly associated with the risk of dementia but also cognitive decline during aging in our study. The use of the FreeSurfer automatic method to measure HV could help to better identify older adults at risk of cognitive decline. Thus, one single measure of HV is not a relevant early marker of dementia in general population, but individuals with a reduced hippocampus also constitutes a high-risk population for age-related cognitive decline, which can lead to disabilities. Thus, all individuals with a reduced hippocampus should benefit from targeted preventive measures to slow down or prevent cognitive decline.

AUTHOR CONTRIBUTIONS

Conceptualization: SA; methodology: MG, JJM, CM; software: MG, JJM, CM; validation: SA; formal analysis: MG; investigation: MG; resources: SA; data curation: SA; writing—original draft preparation: MG, SA: writing—review and editing: MG, SA, FB, CM, JJM, JLC; visualization: MG; supervision: SA; project administration: SA; funding acquisition: SA.

DATA STATEMENT

The data have been presented as a poster at a scientific meeting (AAIC, virtual conference, July 2020).

DISCLOSURES

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