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CLINICAL RESEARCH
Heart failure and cardiomyopathies

Temporal changes in total and hippocampal brain volume and cognitive function in patients with chronic heart failure—the COGNITION.MATTERS-HF cohort study

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Aims We quantified the concurring dynamics affecting total and hippocampal brain volume and cognitive function in patients with chronic heart failure (HF) over a period of three years.

Methods and results A total of 148 patients with mild stable HF entered this monocentric prospective cohort study: mean age 64.5 (10.8) years; 16.2% female; 77% in New York Heart Association functional classes I–II; 128 and 105 patients attended follow-up visits after 1 and 3 years, respectively. The assessment included cardiological, neurological, psychological work-up, and brain magnetic resonance imaging. Total and regional brain volumes were quantified using an operator-independent fully automated approach and reported normalized to the mean estimated intracranial volume. At baseline, the mean hippocampal volume was ∼13% lower than expected. However, the 3-year progressive hippocampal volume loss was small: -62 mm^3 [95% confidence interval (CI) -81 to -42, $P < 0.0001$). This corresponded to a relative change of -1.8% (95% CI -2.3 to -1.2), which was similar in magnitude as observed with physiological aging. Moreover, the load of white matter hypointensities increased within the limits of normal aging. Cognitive function during the 3-year observation period remained stable, with 'intensity of attention' as the only domain declining (LSmean -1.82 points, 95% CI -3.05 to -0.58, $P = 0.004$). After 3 years, performance in all domains of cognition remained associated with hippocampal volume ($r \geq 0.29$).

Conclusion In patients with predominantly mild HF, the markedly reduced hippocampal volume observed at baseline was associated with impaired cognitive function, but no accelerated deterioration in cognition and brain atrophy became evident over a mid-term period of three years.

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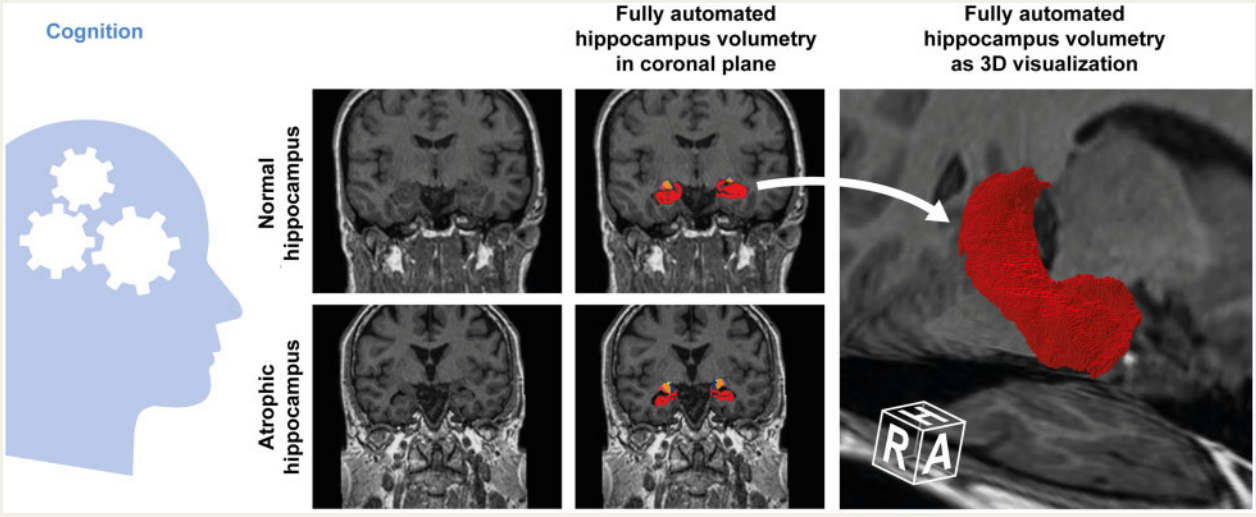
Graphical Abstract



Keywords Chronic heart failure • Cognitive function • Hippocampal atrophy • Brain MRI

Introduction

The number of chronic heart failure (HF) patients is constantly increasing due to aging populations and better survival of patients experiencing an acute coronary syndrome.[1] The mainstay of HF treatment is stabilization of cardiac function, but identification and targeting of disease-modifying comorbidities is a rapidly emerging field in HF research.[1] Numerous cross-sectional studies reported that >40% of HF patients showed cognitive deficits,[2–4] which are thought to relate to adverse outcome. Prevalent and incident cardiovascular disease predicted cognitive decline in middle-aged individuals.[5] However, little is known about the development of cognitive impairment in patients with HF over time, the underlying brain pathology, its long-term impact on survival and rehospitalization rates, and its susceptibility to treatment strategies.[3,4,6,7]

To address these issues, we initiated the prospective cohort study COGNITION.MATTERS-HF.[2] Patients with clinically confirmed chronic HF were investigated over three years, by an interdisciplinary team formed by cardiology, neurology, psychology, and neuroradiology. Data per visit were collected within a narrow two-day interval to enhance its clinical meaningfulness. Recently, we reported that 68% of patients in our cohort showed cognitive impairment at baseline.[2] There, we also observed that HF patients compared to matched controls exhibited a pronounced medial temporal atrophy (MTA) on brain magnetic resonance imaging (MRI), based on a qualitative, visual assessment approach (i.e. the Scheltens score).[2] Furthermore, the load of white matter hyperintensities did not differ.[2]

We here report on the results of the 3-year follow-up examinations of the COGNITION.MATTERS-HF study, which represents the largest and longest prospective assessment of cognitive function and brain morphology in relation to cardiac function in HF patients. We examined, whether cognitive impairment, total brain, and hippocampal atrophy as well as white matter lesions detected in these patients at baseline deteriorate faster than expected with physiological aging.

Methods

Study design and investigations

COGNITION.MATTERS-HF is an investigator-initiated, prospective, monocentric follow-up study. The study protocol was approved by the local Ethical Committee and complies with the Declaration of Helsinki. Written informed consent was obtained from all participants. The study protocol with its selection criteria has been published.[2] In brief, eligible patients were older than 18 years and suffered from stable chronic HF.[1] Patients with major neurological or psychiatric disorders, or a device that impeded brain MRI were not eligible (Supplementary material online, *Tables S1* and *S2*). Investigations at baseline, after 12 and 36 months were performed as detailed in[2]. Investigations included cardiovascular and neurological clinical examination, electrocardiogram, echocardiogram, 24-hour Holter electrocardiogram, 24-hour blood pressure measurement, 6-min walk testing (6-MWT), neurological scales, cerebrovascular ultrasound, routine clinical chemistry, psychological test battery, and brain MRI.

Psychological testing

The test battery was performed between 9 and 11 am. A detailed description is provided in Supplementary material online, *Table S3*, and the baseline manuscript.[2] In brief, the Test Battery of Attentional

Performance (Zimmermann & Fimm 2009, version 2.2), the Visual and Verbal Memory Test (2nd edition, Schellig & Schächtele 2009), the Digit Span Forward and Block Tapping Span Forward tests of the Wechsler Memory Scale revised (Wechsler, 1987), the Regensburger Word Fluency Test (Aschenbrenner, Tucher & Lange, 2000), and the HAMASCH-5-Point-Test revised (Haid, Martl & Schubert, 2004) were applied. The respective influencing effect of age, sex, and educational level has been investigated in validation studies of these tests in healthy volunteers. The test outputs are reported adjusted for respective influencing factors per test, i.e. as standardized *T*-values, with $m = 50$ and SD = 10 as mean reference comparator relative to the reference population.

The interpretation is such that 50% of the reference population perform better and 50% perform worse at the *T*-value of 50. Accordingly, 68.26% of the reference population perform within the *T*-value limits of 60–40 since 34.13% corresponds to a standard deviation. A total of 15.87% each of the reference population perform better than a *T*-value of 60 and worse than a *T*-value of 40, respectively. As such, a *T*-value of <40 indicates performance markedly below average (corresponding to the mostly impaired 15.87%) according to the test-specific reference population compatible with a cognitive deficit irrespective of the test and cognitive domain.

Cerebral magnetic resonance image acquisition and processing

Brain MRI was performed on a 3-T scanner (Siemens MAGNETOM Trio, Erlangen, Germany) using a 12-channel head coil as described[2] previously (Supplementary material online, *Table S4*). All brain MRI scans (MPRAGE data) were processed by the FreeSurfer pipeline for the segmentation of cerebral structures and comprehensive volumetric analysis.[8,9] Measurements of neuro-anatomic structures were determined in mm^3 or ml. Cortical thickness analysis was performed within the longitudinal stream of FreeSurfer, a longitudinal image processing framework based on unbiased, robust, within-subject template creation (http://surfer.nmr.mgh.harvard.edu/). FreeSurfer allows automatic surface reconstruction and segmentation of brain MRI of arbitrarily many time points.[10]

The present study focused on total brain volume (TBV) and regional hippocampal brain volume (HippBV) normalized to the mean estimated intracranial volume of the cohort to test for circumscribed changes over the observation period. This approach was motivated by more advanced MTA detected by visual assessment of Scheltens score at baseline in comparison to matched controls. Visually derived qualitative scores are relatively insensitive to subtle volume changes. Therefore, we now assessed HippBV at baseline and over time (1 and 3 years) quantitatively and by fully automated, operator-independent target region segmentation and volume analysis. For this purpose, the hippocampal subfield module of FreeSurfer was applied rendering hippocampal volume for each hemisphere, per subject and time point.[11] However, baseline Scheltens MTA score (subdivision in pathological and non-pathological MTA at baseline) data[2] of study participants were applied to describe the outcome of the cohort (death and hospitalization for HF) over the time. In patients under 75 years, a mean value of MTA ≥1.5, and in patients over 75 years, a mean value of MTA ≥2 was considered pathological. Moreover, we assessed the dynamics of white matter alterations appearing as hypointense signal alterations on T1-w MRI as well as the number of cerebral lacunes and infarcts over time.

Data analysis

Variables are described using mean (standard deviation, SD), median (quartiles), or count (percent), as appropriate. Associations are described by Pearson's correlation coefficient with 95% confidence interval (CI) and *P*-value. Continuous variables over time were analysed using a mixed model for repeated measures including terms for baseline and visit as fixed effects, and patient and error as random effects (unstructured covariance was assumed). All available data and not only cases with complete data were used, except for the brain MRI evaluation. Complete brain MRI data sets could be analysed from a subset of 81 patients, who provided data for baseline, 1 year, and 3 years. Reasons for selective MRI dropouts were 'claustrophobia' or new implantation of a cardiac device. Least squares means (LSmean) and differences (LSmean difference) with 95% CI were calculated. If analysis targeted subgroups, a subgroup term was included as fixed effect. Only main effects models, i.e. no interactions, were evaluated to reduce risk of bias. A cognitive deficit was defined as *T*-score <40. Five cognitive domains were analysed over time. Furthermore, patients were categorized according to the number of cognitive deficits into three groups: (i) no deficits, (ii) deficits in 1–2, and (iii) deficits in 3–5 domains. The change in mean TBV and HippBV over time was analysed in the subgroup of 81 patients with a complete set of MRI scans.

We conducted several sensitivity analyses exploring (i) subgroups concerning the association between change in cognitive function (five domains) and change in HippBV over time and (ii) the impact of disease duration, atrial fibrillation at baseline, and ischaemic cause of HF on these changes. Time-to-event analyses were described by the Kaplan–Meier product limit estimates and plots. Subgroups were compared using Cox proportional hazards regression, and the hazard ratio (HR) with 95% CI was estimated. Since all analyses are considered exploratory, no adjustment of *P*-values for inflated type I error was made. The statistical software R was used.

Results

Clinical characteristics of study population

In total, 148 patients (64.5 ± 10.8 years; 16.2% female) with systolic and diastolic HF entered the study. The comprehensive baseline characteristics have been described in detail elsewhere,[2] selected parameters are provided in *Table 1*. At study entry, the mean 6-MWT distance was 392 (99) m, and the mean left ventricular ejection fraction (LVEF) was 43 (8)%. Severity of symptoms was mild in the majority of patients, with 77% in New York Heart Association (NYHA) functional class I or II and 44% had suffered from HF for >5 years.

Characteristics of subgroups and their changes over the study period

Follow-up visits including clinical examination and psychological testing were completed after 1 and 3 years by 128 (87%) and 105 (71%) patients, respectively. Main reasons for dropouts were subject's decision ($n = 28$, 19%) and death ($n = 8$, 8%; *Figure 1*). A complete data set of cerebral MRI triplicates performed at baseline and after 1 and 3 years was available in $n = 81$ patients. Reasons for selective MRI dropouts were 'claustrophobia' or new implantation of a cardiac device. Importantly, the basic and follow-up clinical characteristics were similar between the whole study sample ($n = 148$), the subgroup of 81 patients with serial MRIs available, and the remaining 67 patients who either represented study 'dropouts' ($n = 43$) or had remained within the study but had no serial brain MRI ($n = 24$; *Table 1*). Throughout the 3-year observation period, NYHA class II remained the most

Table 1 Selected baseline[a] and 3-year characteristics of study participants

	Total sample		Patients with brain MRI at all 3 time points		Patients with <3 brain MRI scans
	Baseline, *N* = 148	3 years, *N* = 105	Baseline, *N* = 81	3 years, *N* = 81	Baseline, *N* = 67
Age at baseline (years)	64.5 (10.8)	66.5 (10.1)	63.5 (10.7)	–	65.6 (11.0)
Female sex	24 (16.2)	15 (14.2)	11 (13.6)	–	13 (19.4)
Time since diagnosis of HF at baseline					
<2 years	46 (31.1)	35 (33.3)	29 (35.8)		17 (25.4)
2–5 years	37 (25.0)	24 (22.9)	19 (23.5)		18 (26.9)
>5 years	65 (43.9)	46 (43.8)	33 (40.7)		32 (47.8)
Predominant cause of HF at baseline					
Ischaemic	96 (64.9)	73 (69.5)	50 (61.7)		46 (68.7)
Non-ischaemic	52 (35.1)	32 (30.5)	31 (38.3)		21 (33.3)
NYHA functional class					
I	41 (27.7)	38 (36.2)	20 (24.7)	29 (35.8)	21 (31.3)
II	88 (59.5)	40 (38.1)	52 (64.2)	32 (39.5)	36 (53.7)
III	19 (12.8)	29 (27.6)	9 (11.1)	20 (24.7)	10 (14.9)
Blood pressure (mmHg)					
Systolic	138 (19.8)	137 (19)	139 (19)	138 (19)	138 (20)
Diastolic	81 (11)	79 (11)	81 (9)	79.2 (11.1)	81 (13)
Heart rate (beats/min)[b]	65 (11)	64 (10)	64 (10)	66 (11)	66 (11)
LV ejection fraction (%)	43.6 (8.1)	43.7 (11.7)	43.1 (8.6)	44.7 (10.8)	41.9 (7.8)
6-Minute walking distance (m)	392 (99)	400 (104)	410 (90)	402 (113)	370 (105)
Medical history[c] at baseline					
Myocardial infarction	80 (54.1)	55 (52.4)	45 (55.5)		35 (52.2)
Atrial fibrillation	29 (19.6)	24 (22.9)	11 (13.6)		18 (26.9)
Hypertension	118 (79.7)	84 (80.0)	71 (87.7)		47 (70.1)
Diabetes mellitus	43 (29.1)	30 (28.6)	24 (29.6)		19 (28.4)
Renal dysfunction	53 (35.8)	35 (33.3)	27 (33.3)		26 (38.8)
Medication					
ACE inhibitor	87 (58.8)	53 (50.5)	53 (65.4)	44 (54.3)	34 (50.8)
AT1 receptor antagonist	48 (32.4)	46 (43.8)	25 (30.9)	33 (40.7)	23 (34.3)
Beta-blocker	132 (89.2)	93 (88.6)	75 (92.6)	71 (87.7)	57 (85.1)
MRA	55 (37.2)	45 (30.4)	31 (38.3)	30 (37.0)	24 (35.8)
Diuretic	81 (54.7)	57 (54.3)	40 (49.4)	40 (49.4)	41 (61.2)
ASA	80 (54.1)	57 (54.3)	46 (56.8)	42 (51.9)	34 (50.8)
Platelet inhibitor	21 (14.2)	3 (2.9)	13 (16.1)	2 (2.5)	8 (11.9)
Vitamin K antagonist	46 (31.1)	24 (22.9)	22 (27.2)	16 (19.8)	24 (35.8)
Other anticoagulants	1 (0.7)	10 (9.5)	1 (1.2)	9 (11.1)	0 (0.0)
None	18 (12.2)	16 (15.2)	10 (12.4)	14 (17.3)	8 (11.9)

Data are *n* (%) or mean (SD), as appropriate.
[a]The full set of phenotyping variables has been reported.[2]
[b]Heart rate as assessed during clinical examination.
[c]Definitions applied: atrial fibrillation, diagnosed from the electrocardiogram or electrocardiogram; renal dysfunction, estimated glomerular filtration rate <60 mL/min/1.73 m^2.
ACE, angiotensin-converting enzyme; ASA, acetylsalicylic acid; AT1, angiotensin-1; cMRI, cerebral magnetic resonance tomography; COPD, chronic obstructive lung disease; HF, heart failure; LV, left ventricular; MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association.

frequent, and there was no change in the 6-MWT distance nor in LVEF over time in both the complete cohort and the subgroup of 81 HF patients undergoing serial MRI (*Figure 2A–F*).

Clinical outcomes

During the 3-year follow-up period, 4 patients (2.7%) died and 10 patients (6.8%) suffered from at least one episode of worsening of HF requiring hospitalization. The risk for the combined endpoint 'time to death or hospitalization for HF' was comparatively low (*Figure 3A*). A pathological Scheltens score at baseline was not associated with an increased risk of death or hospitalization for HF during the entire follow-up period (HR 1.63, 95% CI 0.54–4.92, $P = 0.385$; *Figure 3B*). Similarly, presence of cognitive deficits at baseline or their degree of severity had no effect on the combined endpoint: HR for 'mild deficits' 1.30 (0.88–1.91, $P = 0.189$); HR for 'severe deficits' 0.95 (0.55–1.65, $P = 0.866$; *Figure 3C*).

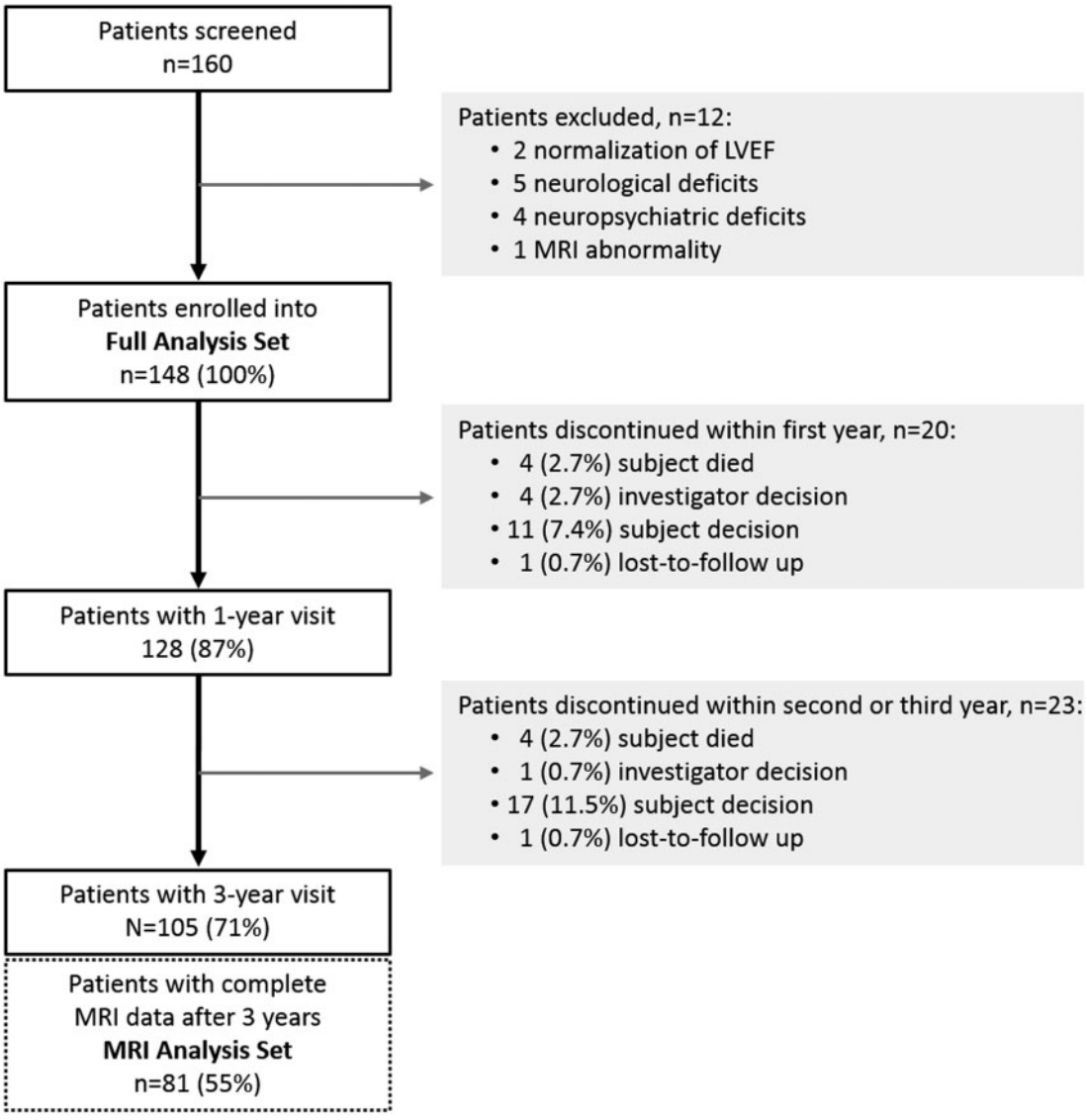


Figure 1 Patient flow showing the number and proportions of screened, enrolled and follow-up patients after 1 and 3 years. Reasons for discontinuation are displayed and the numbers of patients with complete magnetic resonance imaging data are shown.

Cognitive function

We applied a detailed psychological test battery addressing five domains of cognition (*Figure 4A–E* and Supplementary material online, *Table S5*). Within 3 years of observation, intensity of attention was the only domain exhibiting a significant decline: LSmean -1.82 ([-3.05; -0.58], $P = 0.004$) points. In contrast, visual/verbal fluency (0.94, [0.06; 1.82], $P = 0.036$) and visual/verbal memory (3.15, [1.93; 4.37], $P < 0.0001$) even improved over time, while the domains selectivity of attention or working memory remained unchanged. Duration of HF, atrial fibrillation, and ischaemic cause of HF had almost no effect on the longitudinal performance (Supplementary material online, *Table S6*); only improvement in the domain of fluency was more pronounced in non-ischaemic vs. ischaemic patients (LSmean [95% CI] up to 3 years: 2.30 [1.02; 3.59] vs. 0.22 [-0.78; 1.21]; $P = 0.0056$). Studying patients in groups with no, mild, or severe cognitive dysfunction revealed no relevant between-group shifts over time: 47/148 (32%) at baseline vs. 27/105 (26%) at 3-year follow-up had no, 77/148 (52%) vs. 52/105 (50%) had mild, and 23/148 (16%) vs. 15/105 (14%) had severe cognitive deficits. In summary, concordant with the relative stability of HF, detailed psychological testing showed only minor changes over time, with moderate deterioration in intensity of attention, i.e. reaction times, but also subtle improvement in visual/verbal fluency and memory.

Morphological changes on cerebral MRI

Complete brain MRI data sets could be analysed from 81 patients (*Figure 1* and *Table 1*). The normalized TBV in our cohort [1098 (184)

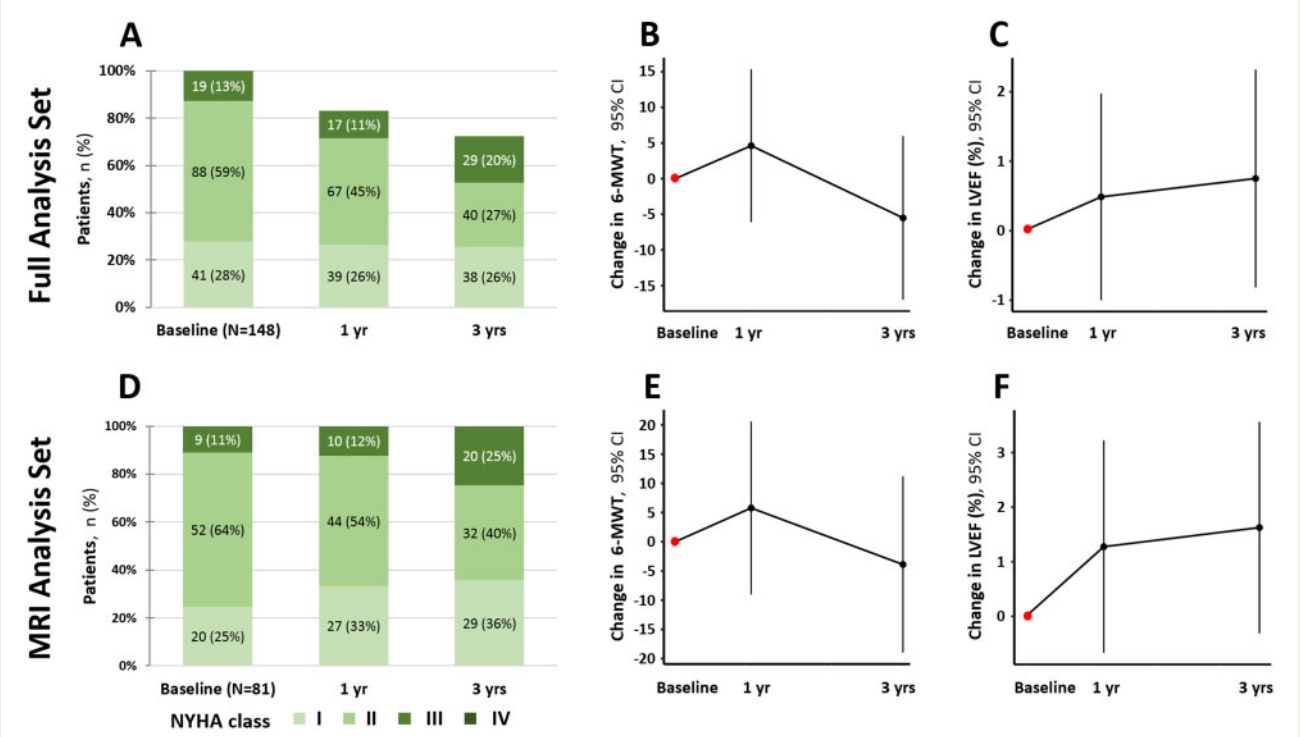


Figure 2 Course of clinical parameters. (*A*) The proportion of patients with New York Heart Association classes I–IV; (*B*) the LSmean change (95% confidence interval) for the 6-min walk testing distance; and (*C*) the LSmean change (95% confidence interval) for the left ventricular ejection fraction, in all analysed patients (n = 105) at baseline, 1 year, and 3 years, respectively. (*D*) The proportion of patients with New York Heart Association classes I–IV; (*E*) the LSmean change (95% confidence interval) for the 6-min walk testing distance; and (*F*) the LSmean change (95% confidence interval) for the left ventricular ejection fraction, in patients with the whole magnetic resonance imaging analysis set (n = 81) at baseline, 1 year, and 3 years, respectively. Overall the clinical cohort remained stable with regard to those parameters, measuring the clinical severity.

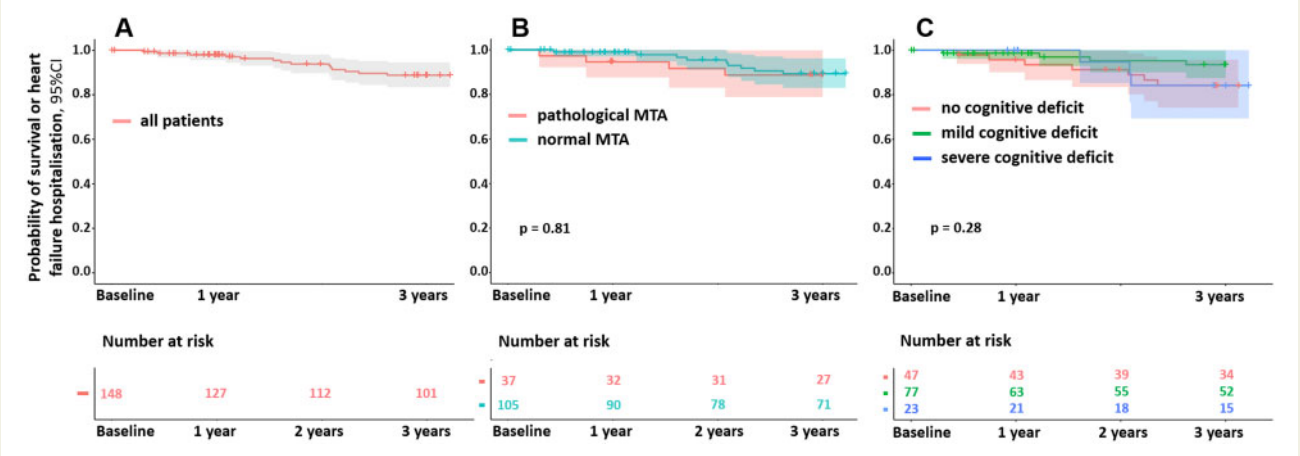


Figure 3 Kaplan–Meier curve for clinical events. Kaplan–Meier product limit estimator (95% confidence interval) for the combined endpoint 'time to death or rehospitalization for heart failure'. (*A*) Events of the total sample. (*B*) Events by the presence of medial temporal atrophy. (*C*) Events by the presence of cognitive dysfunction at baseline.

ml, mean age 64.5 (10.8) years] was comparable to published data in healthy controls [1068 (102) ml, mean age 75.9 (5.2) years].[12] The normalized TBV shrinkage observed in our cohort was 0.34%/year, which is also very close by numerical comparison to the previously reported shrinkage associated with normal aging, i.e. 0.38%/year.[13]

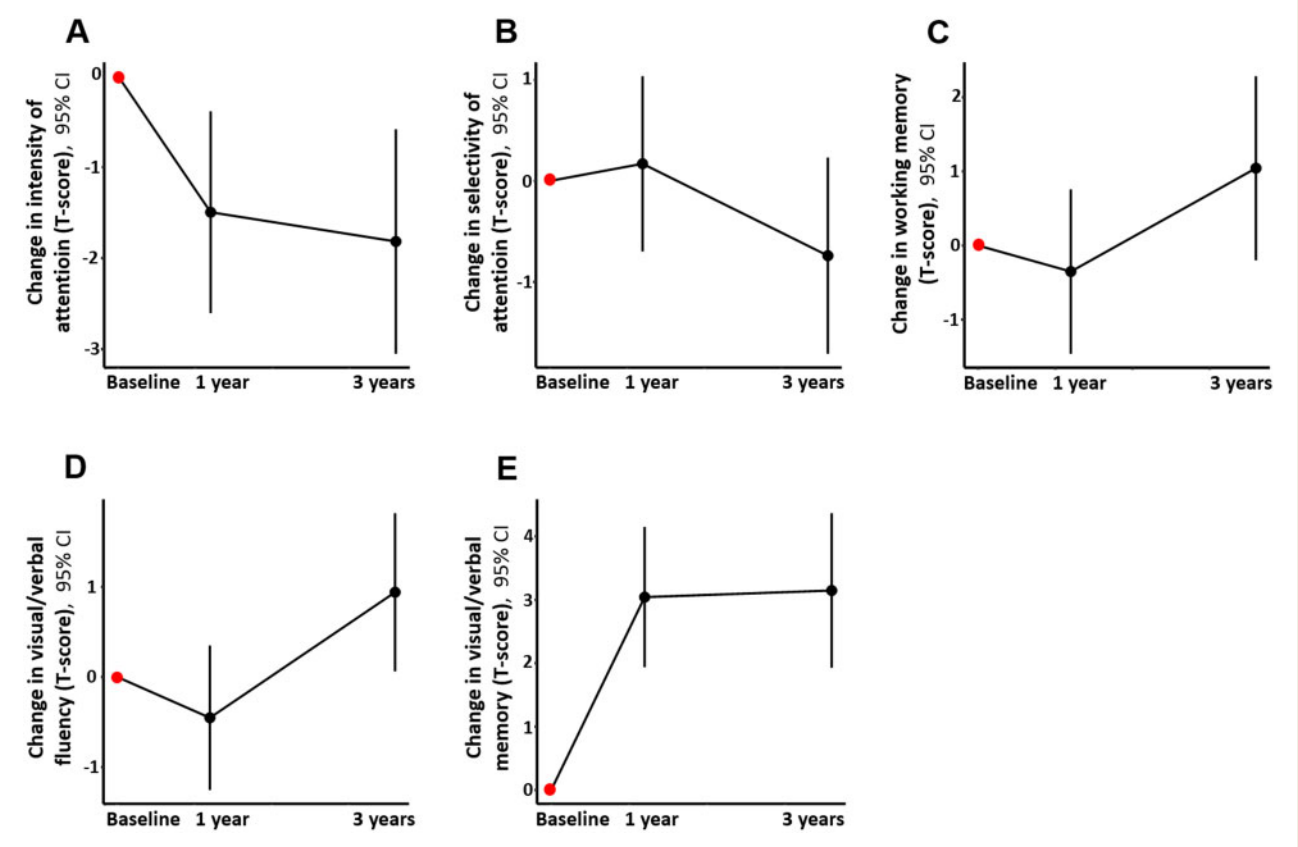


Figure 4 Course of cognitive function parameters. Panels show the LSmean (95% confidence interval) change in *T*-scores for cognitive parameters over the duration of 3 years of follow-up: (*A*) intensity of attention, (*B*) selectivity of attention, (*C*) working memory, (*D*) visual/verbal fluency, and (*E*) visual/verbal memory, as assessed by the psychological test battery.

Table 2 **Changes in hippocampal volume with regard to severity of cognitive dysfunction over the time of 3 years**

Mean hippocampal volume (mm^3)	Visit	Severity of cognitive dysfunction (overall type III *P*-value <0.0001)		
		No (*N* = 27)	Mild (*N* = 42)	Severe (*N* = 12)
Mean (SD)	Baseline	3708.2 (484.8)	3488.6 (508.7)	3140.8 (595.9)
Mean (SD)	12 months	3733.6 (560.1)	3433.7 (477.6)	3241.8 (629.6)
LSmean change [95% CI; *P*-value]		-31.7 [-62.3, -1.16]*	-24.1 [-46.5, -1.68]*	-61.1 [-100.4, -21.9]*
Mean (SD)	36 months	3709.9 (495.5)	3382.2 (577.2)	3184.6 (579.8)
LSmean change [95% CI; *P*-value]		-67.9 [-98.1, -37.7]*	-60.2 [-83.8, -36.7]*	-97.3 [-137.9, -56.7]*

LSmean change (95% CI) for hippocampal volume (mm^3) by cognitive deficits over time in the MRI analysis subset.
*Statistically significant at the 5% level.
CI, confidence interval; MRI, magnetic resonance imaging; SD, standard deviation.

At baseline, we identified atrophy of the medial temporal lobe encompassing the hippocampus and the nucleus amygdala as a predominant morphological feature of brain injury in HF patients compared to healthy controls while total brain volume and the extent of white matter alterations did not differ between groups.[2] This original finding of MTA, which was based on visual assessment using the Scheltens score, could now be corroborated by unbiased automated segmentation and quantitative volumetric measurements of hippocampal brain volume (HippBV). HippBV were 3478 (353) mm^3 on the left and 3566 (354) mm^3 on the right side. This was markedly lower than reported for equally normalized HippBV in healthy controls aged 73.6 (5.5) years: left side 3889 (634) mm^3 and right side 4216 (651) mm^3.[14] Of note, long-term cognitive changes did not differ between the group of all 105 patients, who underwent cognitive

testing after 3 years, and the group of 81 patients with complete sets of three MRI scans (Supplementary material online, *Figure S1*). By averaging the hippocampal volume over both brain hemispheres, the mean HippBV was 3510 (540) mm^3 at baseline and 3449 (553) mm^3 at the 3-year follow-up examination. This corresponded to a 3-year decline of -61.5 mm^3 ([-80.7; -42.2], $P < 0.0001$; Supplementary material online, *Figure S2*), i.e. a 3-year relative change of -1.8% ([-2.3%; -1.2%]). Duration of HF and presence of atrial fibrillation had no significant effect on HippBV changes over time (Supplementary material online, *Table S7*). However, non-ischaemic cause of HF was associated with more pronounced normalized hippocampal shrinkage (LSmean [95% CI] up to 3 years: -89.0 [-116.7; -61.3] mm^3 vs. -44.4 [-67.1; -21.8] mm^3; $P = 0.009$).

Furthermore, the volume of white matter lesions [Supplementary material online, Methods, 2260 (interquartile range (IQR) 1236–3575) mm^3 at baseline vs. 2706 (IQR 1422–4048) mm^3 after 3 years; $P < 0.0008$] increased by 6.2% per year over the observation period but was comparable with the changes in healthy population (6.5% per year).[15] The number and distribution of lacunes (14% of patients) did not change over the time. Only in one patient, clinically silent cerebral infarctions were detected on the 1-year follow-up MRI related to biological valve replacement due to aortic stenosis.

Relation between cognitive function and hippocampal volume

This analysis refers to 81 patients with complete sets of both cognitive testing and MRI and describes the correlation between HippBV and cognitive domains (*T*-values). HippBV was positively correlated with all cognitive domains. At baseline, correlations were weak ($r < 0.30$) yet statistically significant, except for selectivity of attention (Supplementary material online, *Table S8*). In the course of 3 years, correlations of *T*-values in separate cognitive domains and mean HippBV became stronger ($r \geq 0.30$) in all domains except for intensity of attention ($r = 0.29$) (Supplementary material online, *Table S8*). Furthermore, we evaluated the correlations between mean HippBV and cognitive function according to group assignment with no, mild, or severe cognitive deficits. The automated FreeSurfer analysis confirmed findings based on the visual Scheltens score[2]: we observed a significant association between change in mean HippBV and cognitive function (overall type-3 *P*-value <0.0001; *Table 2*). Interestingly, across 3 years of observation, there were no statistically significant differences in mean change of HippBV with regard to cognitive group assignment at baseline and the 3-year follow-up ($P = 0.543$ for mild vs. no cognitive decline; $P = 0.128$ for severe vs. no cognitive decline). Hence, the cognitive status at baseline was not predictive for a more rapid progression of hippocampal atrophy.

Discussion

The present study prospectively assessed cognitive function in patients with chronic HF over 3 years applying a comprehensive psychological test battery. Region-specific brain volume was serially quantified in a fully automated fashion, i.e. excluding the operator's influence on brain region segmentation or volumetric measurements. Surprisingly, cognitive function in HF patients, although exhibiting relevant deficits at baseline, remained relatively stable with only a moderate decline in reaction times. Stable cognitive function over time was paralleled by only minor progression of total brain and hippocampal atrophy, which was in a range observed with normal ageing.[16,17]

The 3-year longitudinal analysis was based on the remaining 105 out of 148 patients at baseline, which was higher than anticipated by the original power calculation of the study.[2] The 43 patients leaving the study prematurely exhibited similar HF characteristics as the remaining 105 patients; this argues for representativeness of the subjects studied long term. Overall outcome was better than previously published.[1] Different to 'real-world' conditions, our cohort received optimal HF treatment. Furthermore, we had selected patients with relatively mild HF. Importantly, NYHA stage distribution, 6-MWT, and LVEF remained stable over 3 years.

It was unexpected that neither impaired cognitive function nor pathological hippocampal volume loss were associated with the risk of death or rehospitalization. A recent meta-analysis including 8 studies with 3318 participants reported an overall increased mortality risk (HR 1.64), and cognitive decline in 29% of cases. However, heterogeneous study populations had been included, with different test systems addressing cognitive decline.[18]

Changes in cognition over time

While it is accepted that a significant proportion of HF patients develops cognitive deficits,[2–4] few studies prospectively addressed the evolution of cognitive function over time.[19–21] Recently, the WARCEF reported an annual 2-point decrement in the mini-mental state examination (MMSE) in patients with HF, which was associated with higher baseline MMSE score, higher age, non-white ethnicity, and lower education.[22] However, 11% of patients had suffered from a previous cerebrovascular event, and 27% of the entire cohort experienced such an event (or death) during follow-up. Hence, the worsening in cognitive function observed in WARCEF was confounded by incident stroke as there is a 50 times higher incidence of dementia in the year after a major stroke compared to the general population.[23] We attempted to avoid this confounder by increasing the detail and depth of psychological testing and particularly, by strictly excluding patients with any history of stroke at baseline. In the entire study population, during three years of follow-up, only two clinically apparent cerebrovascular events occurred, e.g. transitory ischaemic attacks. In one patient clinically silent infarctions were found at follow-up MRI after 1 year, which further supports our notion that impairment in cognitive function in HF patients may occur independent from cerebrovascular events or their cumulative burden. To enhance long-term adherence of study patients, we compiled a psychological test battery, which reliably covered various relevant cognitive function domains, minimized repetition and habituation effects, and still did not put undue strain on study participants. Intensity of attention was the only cognitive domain deteriorating within the 3-year period. Unexpectedly, we even observed median improvements in visual/verbal fluency and memory in our study. Similar results were reported in a cohort of 115 HF patients completing neuropsychological testing at baseline and after 12 months. There, attention/executive function and language remained stable, while memory performance improved.[19] Stable neuropsychological test results were also noted in 279 HF patients re-examined after

6 months.[21] Thus, it appears that cognitive function may remain stable if HF is not progressing (this study and reference[19]).

Morphological changes in cerebral MRI

As a unique feature of our study, we prospectively acquired cerebral follow-up MRI scans in addition to neuropsychological testing in a relevant number of HF patients ($n = 81$). Since this subgroup resembled the total sample, we may generalize findings of structural brain MRI to the entire cohort under study. Initially, we had used the Scheltens score to assess MTA, i.e. the recommended morphological hallmark of cognitive dysfunction in HF patients in previous studies.[24] Visual rating of MTA is reliable in discriminating between a normal population and patients developing minimal cognitive impairment (MCI) and Alzheimer's disease (AD).[25] However, it is sensitive to operator bias, non-quantitative and may miss subtle changes of neuronal loss over time in other settings of secondary neurodegeneration such as HF. Therefore, all MRI scans were also quantitatively analysed by the FreeSurfer processing pipeline. Thereby, we could show that the TBV did not significantly differ between our HF cohort and published controls and that the annual loss of 0.34% was within the limits reported for normal aging. In contrast, the mean HippBV assessed by FreeSurfer analysis in our cohort was 3510 mm^3, which is significantly less than in healthy controls (4052 mm^3) according to previously published data from a healthy population using a comparable method.[14] These findings are in accordance with a small study showing reduced HippBV in 17 HF patients compared to 34 healthy controls[26] and our own data on visual assessment of the hippocampal region by the Scheltens score as a semi-quantitative measure of atrophy at baseline.[2] Interestingly, a population-based cohort study showed that HF is associated with an increased risk of developing AD, a condition where temporal lobe atrophy also predominates.[27] As a note of caution, it is likely that additional brain regions are affected by HF as suggested by a cross-sectional MRI study of 35 HF patients[3] and widespread regional reductions of cerebral blood flow in HF patients.[28]

Importantly, in our study the mean hippocampal volume decreased by 62 mm^3 in 3 years corresponding to a relative reduction of 1.8% over 3 years. It is well known that normal individuals also exhibit reductions in cognitive abilities and undergo brain atrophy upon physiological aging.[29,30] Previous volumetric analyses revealed medial temporal volume shrinkage of ~0.8–2.2% per year in healthy cohorts,[16,17] which means that the magnitude of shrinkage of HippBV over time in our study population was comparable to the healthy population and much lower than reported in patients with MCI[31] and AD.[12] Complete assessment of regional brain volumes by FreeSurfer analysis in our cohort of HF patients is under way. It will allow to identify in an unbiased manner, whether additional brain areas are selectively affected by HF, and illustrate their respective dynamics over time.

Conclusion

The current prospective study observed a high prevalence of cognitive dysfunction and marked hippocampal tissue loss in patients with optimally treated HF. Over a period of three years, cognitive function and hippocampal shrinkage remained relatively stable and did not affect hospitalization or death rates. The hippocampus may be regarded as a major target brain region for research on the widely unknown pathological heart-brain interactions underlying HF-related cognitive decline.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Data availability

Data will be made available upon request in adherence with transparency conventions in medical research and through requests to the corresponding authors.

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