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Longitudinal trajectories of hippocampal volume in middle to older age community dwelling individuals

Mark A. Fraser [a,*], Erin I. Walsh [a,b], Marnie E. Shaw [c], Walter P. Abhayaratna [d], Kaarin J. Anstey [a,e,f], Perminder S. Sachdev [g], Nicolas Cherbuin [a]

[a] Centre for Research on Ageing, Health and Wellbeing, Research School of Population Health, Australian National University, Canberra, Australian Capital Territory, Australia
[b] Population Health Exchange, Research School of Population Health, Australian National University, Canberra, Australian Capital Territory, Australia
[c] ANU College of Engineering & Computer Science, Australian National University, Canberra, Australian Capital Territory, Australia
[d] College of Health & Medicine, Australian National University, Canberra, Australian Capital Territory, Australia
[e] Ageing Futures Institute, University of New South Wales, Sydney, New South Wales, Australia
[f] Neuroscience Research Australia, Sydney, New South Wales, Australia
[g] Centre for Healthy Brain Ageing (CHeBA), School of Psychiatry, University of New South Wales, Sydney, New South Wales, Australia

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ABSTRACT

Understanding heterogeneity in brain aging trajectories is important to estimate the extent to which aging outcomes can be optimized. Although brain changes in late life are well-characterized, brain changes in middle age are not well understood. In this study, we investigated hippocampal change in a generally healthy community-living population of middle ($n = 421$, mean age 47.2 years) and older age ($n = 411$, mean age 63.0 years) individuals, over a follow-up of up to 12 years. Manually traced hippocampal volumes were analyzed using multilevel models and latent class analysis to investigate longitudinal aging trajectories and laterality and sex effects, and to identify subgroups that follow different aging trajectories. Hippocampal volumes decreased on average by 0.18%/year in middle age and 0.3%/year in older age. Men tended to experience steeper declines than women in middle age only. Three subgroups of individuals following different trajectories were identified in middle age and 2 in older age. Contrary to expectations, the subgroup containing two-thirds of older age participants maintained stable hippocampal volumes across the follow-up.

1. Introduction

It is important to understand brain changes that can be attributed to the typical aging process across the lifespan to guide prevention and population health. Yet, neuroimaging research tends to focus on clinically relevant neuropathology (e.g., Alzheimer's disease [AD], Parkinson's disease) in older adults or psychopathology (e.g., schizophrenia, depression) in the young. As a result, the precise dynamics of age-related brain changes across the adult lifespan are not well understood, particularly those taking place in middle age.

The hippocampus is a bilateral brain structure that provides a sensitive and practical measure of brain change over time. The hippocampus plays an important role in memory and mood regulation with many factors shown to affect hippocampal structure and function including genetic vulnerabilities (Li et al., 2016), modifiable lifestyle factors (Cherbuin et al., 2015; Durazzo et al., 2013; Erickson et al., 2011), environmental exposure (Hanson et al., 2011), and neuropathology (Braak et al., 1996). Typical hippocampal volume change across the adult lifespan is thought to exhibit a nonlinear trajectory that follows a weakly declining slope until around 50 years of age when the trajectory trends downward at an accelerating rate (Coupé et al., 2017; Fjell et al., 2013; Fraser et al., 2015). This trajectory has been demonstrated by a number of comprehensive cross-sectional studies investigating age-related change in brain structure across the adult lifespan (Coupé et al., 2017; Potvin et al., 2016). However, large longitudinal studies investigating the trajectories of age-related hippocampal volume change have tended to focus on groups older than 55 years of age (Armstrong et al., 2019; Cespedes et al., 2017; Leong et al., 2017; Schuff et al., 2012), and the few longitudinal studies that have covered both middle and older age groups tend to have relatively small sample sizes (Narvacan et al., 2017; Pfefferbaum and Sullivan, 2015; Raz et al., 2005, 2010; Taylor et al., 2014). Thus, although the typical hippocampal aging trajectory across the adult lifespan has

* Corresponding author at: Centre for Research on Ageing, Health and Wellbeing, Australian National University, Florey Building 54, Mills Road, Canberra, Australian Capital Territory 2601, Australia. Tel.: +61 2 61256338; fax: +61 2 61259123.
E-mail address: mark.fraser@anu.edu.au (M.A. Fraser).

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been extensively characterized from cross-sectional research, the paucity of longitudinal evidence in middle age represents a gap in the evidence base.

The contribution of several individual characteristics on neurodegeneration trajectories are also insufficiently understood. Hemispheric asymmetry, where the right hippocampus is larger than the left hippocampus by as much as 5.8% in individuals free of neurological disorder (Shi et al., 2009), combined with asymmetric atrophy rates (Ardekani et al., 2019), suggest possible differences in the trajectories of left and right hippocampal volumes. Moreover, although when no adjustment for head size is applied, men demonstrate larger hippocampal volumes than women (Coupé et al., 2017; Goodro et al., 2012; Nobis et al., 2019; Potvin et al., 2016), after controlling for head size this difference often becomes non-significant or reversed (Coupé et al., 2017; Goodro et al., 2012; Narvacan et al., 2017; Nobis et al., 2019; Shen et al., 2019; Taylor et al., 2014). In addition, some longitudinal studies have found no sex differences in atrophy rates (Narvacan et al., 2017; Raz et al., 2010; Taylor et al., 2014), whereas others found higher hippocampal atrophy in elderly women aged 74.7 years (Shen et al., 2019), or higher atrophy in men over 50 years (Armstrong et al., 2019; Nobis et al., 2019). Individual characteristics and varying exposure to risk factors may also interact with sex and individual behaviors to differentially impact hippocampal trajectories (Head et al., 2012; Li et al., 2016; Morra et al., 2009; Shen et al., 2019).

The typical aging trajectory involving an overall population level decline in hippocampal volumes assumes a homogenous population. However, evidence of differences in cognitive aging related to education and ethnicity (Zelinski and Jacobucci, 2017), multiple trajectories of cognitive change in pre-clinical AD (Small and Bäckman, 2007), and multiple trajectories of terminal well-being decline (Burns et al., 2014) suggest the possibility of heterogenous aging trajectories. We hypothesized that there could be multiple subpopulation trajectories of hippocampal aging that may suggest new combinations of risk factors for future investigation.

To address these questions, we used multilevel models (MLM) and multilevel latent class analysis to investigate longitudinal hippocampal volume aging trajectories in middle and older age community-living individuals, over a follow-up of up to 12 years. The study aims were to determine the typical hippocampal volume aging trajectory across middle age to older age, to explore hemispheric and sex trajectory differences, and to identify subgroups of individuals following heterogeneous aging trajectories and to investigate their characteristics.

2. Materials and methods

2.1. Participants

Study participants were from the Personality and Total Health Through Life (PATH) project, a large longitudinal study investigating aging, health, cognition, and individual characteristics across the adult lifespan described in detail elsewhere (Anstey et al., 2012; Cherbuin et al., 2009; Maller et al., 2007). Briefly, prospective participants were randomly selected from the electoral rolls of the adjacent cities of Canberra and Queanbeyan, Australia, and as enrollment to vote is compulsory in Australia, this approach provides cohorts that are representative of the population. At baseline, the project surveyed 2404 young adults (YA) aged 20–24 years, 2530 middle aged adults (MA) aged 40–44 years, and 2551 older age adults (OA) aged 60–64 years, representing participation rates (PR) of 58.6%, 64.6%, and 58.3% of those invited. A randomly selected subsample of the 2 older cohorts was invited to undergo magnetic resonance imaging (MRI) scans. At wave 1, 478 OA participants (PR = 76.8%) underwent a baseline MRI scan and at the second wave of data collection 431 MA participants (PR = 85.7%) received their baseline MRI scan. MRI substudy participants were invited to have further scans at each subsequent wave of data collection (Supplementary Fig. S1). Participants with epilepsy, stroke, Parkinson's disease, mild cognitive impairment, or dementia at any wave were excluded from the current study, leaving 421 MA participants and 411 OA participants with a baseline scan. The study sample did not differ from the overall PATH cohort in age, body mass index (BMI), sex, hypertension, diabetes, or *APOE-ε4* genotype at the time of the baseline scan. However, the study OA participants had higher education levels (0.40 years, 95% confidence interval [CI] 0.12, 0.68) and fewer smokers (−4%, 95% CI 0.01, 0.07) compared to OA participants in the overall PATH cohort (Supplementary Table S1). All participants provided written informed consent. The Human Research Ethics Committee of The Australian National University approved the study protocol.

2.2. MRI scan acquisition and pre-processing

T1-weighted 3-dimensional structural MRI scans were acquired for all participants. Detailed parameters and methods have been extensively reported elsewhere (Shaw et al., 2017) and are reported in more detail in the Supplementary Material. In brief, for the first 2 waves, all participants were imaged with a 1.5 Tesla Philips Gyroscan ACS-NT scanner (Philips Medical Systems, Best, The Netherlands) for T1-weighted 3-dimensional structural MRI using a fast-field echo sequence. Due to scanner changes all participants were scanned with a Siemens Avanto scanner (Siemens Medical solutions) at wave 3, and with a Siemens Espree scanner (Siemens Medical solutions) at wave 4. Intensity normalization and B1 inhomogeneity correction (Sled et al., 1998) were applied on all images using the MINC imaging toolbox (MINC; http://en.wikibooks.org/wiki/MINC).

2.3. Volumetric measurement

Manual hippocampal volumes were measured by experienced neuroscientists (CM, JM, MF) tracing the left and right hippocampus on each slice of a T1-weighted scan in coronal orientation using Analyze Software (Brain Imaging Resource; Mayo Clinic, Rochester, MI). The protocol used for the hippocampal volume measurement has been described in detail elsewhere (Maller et al., 2006; Watson et al., 1992, 1997). Wave 3 and wave 4 scans were resized to 1.0 mm^3 voxels prior to tracing. Mean reliability measured by intra-class correlation coefficient (Shrout and Fleiss, 1979), measured on 10 randomly selected retraced scans, was $\geq$0.88 across all waves (Fraser et al., 2018; Maller et al., 2006, 2007). The hippocampal volumes were normalized to adjust for differences in total intracranial volume (ICV) using the residual method (adjusted volume = raw volume$-\beta \times$ [ICV−mean ICV]; where β is the slope of the regression of the region of interest volume on the ICV) with the estimated total ICV for each participant calculated from the FreeSurfer 5.3 cross-sectional pipeline (Buckner et al., 2004; Pintzka et al., 2015; Raz et al., 2004; Sanfilipo et al., 2004). Total hippocampal volume was calculated as the sum of left and right hippocampal volume for each participant. Scanner related variance in hippocampal volumes was estimated and removed via an established and published orthogonalization method (Shaw et al., 2016b). This process was carried out prior to statistical analysis and on the entire PATH data set of MRI scans corresponding to participants aged 44–78 years old, for the purpose of minimizing the correlation between the scanner covariate and participant age. The distributions of hippocampal volumes for each time point and age group were then examined and univariate outliers ($Z > 3.29$) were excluded (Tabachnick et al., 2007).

2.4. Participant characteristics

Age, sex, education, diabetes, and smoking were measured by self-report. BMI was calculated as weight (kg)/[height (m)]^2. Blood pressure was objectively measured. Participants with blood pressure above 140 mm Hg systolic or 90 mm Hg diastolic (average of 2 seated measures), or who reported taking blood pressure medication were classified as "hypertensive." *APOE-ε4* genotype was assessed using DNA collected by cheek swab at wave 1 (Cherbuin et al., 2011). Only OA participants were assessed using the Mini Mental State Examination (MMSE) as this test is not designed to provide cognitive data on middle age adults.

2.5. Statistical analysis

Statistical analysis was performed using R version 3.5.1 (R Core Team, 2018). MLM, using lme4 (Bates et al., 2015) and lmerTest (Kuznetsova et al., 2017) packages, were used to examine longitudinal changes in hippocampal volumes over time. Significance of fixed effects was assessed with 95% CIs, random effects significance was assessed using χ^2 tests, and pseudo R^2 was determined using the approach suggested by Nakagawa and Schielzeth (2013). Although MLM analyzes group and individual trajectories, and are tolerant of missing observations and differences in the timing of longitudinal observations, MLM assumes that all participants are drawn from a single population with common parameters. Therefore, we used the lcmm package (Proust-Lima et al., 2017) to identify subpopulations (latent classes) with aging trajectories that differ from the overall group trajectory. Significance of sample characteristic differences was assessed using *t*-tests, χ^2 tests, or Wilcoxon signed-rank tests. Missing hippocampal data (no more than one missing occasion per participant), representing 1.37% of total measured volume were singly imputed using the R Amelia-II package (Honaker et al., 2011).

2.5.1. Hippocampal volume trajectories

Trajectories of hippocampal volume change were investigated using MLM with the trajectories for the MA and OA cohorts combined investigated first. A linear model with total hippocampal volume as the outcome variable and age, centered at the sample minimum age (44 years), as the predictor was compared using analysis of variance to a quadratic model that included a quadratic age term. Next, the effects of hemisphere and sex were investigated. A fully specified linear model with age, hemisphere, and sex predictors including 2 and 3-way interactions was compared to a model that included quadratic age predictors (age, age^2, hemisphere, sex) with 2 and 3-way interactions. Backward deletion using the lmerTest step function (Kuznetsova et al., 2017) was applied to each model before comparison. Model fit of the optimal linear and quadratic models, measured by Akaike information criterion (AIC; Akaike, 1974), was compared using analysis of variance with optimal models selected based on model fit and ease of interpretation where model fit was very similar. The process was repeated for the MA cohort with age centered at the sample minimum age (44 years) and then for the OA cohort with age centered at the sample minimum age (60 years).

2.5.2. Latent class analysis

The presence of latent classes (subgroups) was investigated using latent class analysis separately for each hemisphere of the MA and OA cohorts (Proust-Lima et al., 2017). Latent classes were modeled using a linear function with age as the predictor. The results were analyzed, and the best fitting latent class sets were selected based on model fit (AIC), stable allocation of individuals to the classes (>50% of members of each class with posterior probability >0.7), and at least 20 individuals in each class.

The best fitting latent class sets for the left hippocampus and right hippocampus in each cohort were examined for class differences. In each latent class set containing multiple classes, the participant characteristics, measured at baseline, of the smaller classes in each set were compared to the participant characteristics of the largest class.

2.5.3. Post hoc analysis

The modeled trajectories were projected back to 20 years of age to test consistency with previous literature that investigated hippocampal volumes in other age groups including young adults. This was achieved by centering age at 80 years and running models backwards in time with the lme4 simulate function used to simulate hippocampal volumes for a cohort of young adults based on the MA data points (Bates et al., 2015). The projected volumes and rates of atrophy were then compared to the results of previous studies that included participants from across the adult lifespan.

3. Results

Baseline participant characteristics are shown in Table 1. Both cohorts had high levels of education with more education in the MA cohort. As expected, the OA cohort had more medical comorbidity and smaller hippocampi at baseline. The intra-class correlations

Table 1
Participant characteristics at baseline

Characteristic	All	Middle age	Older age	Middle vs. older age
Sample, no.	832	421	411	
Age (y) (SD)	55.02 (8.05)	47.20 (1.38)	63.03 (1.43)	<0.001[a]
Age (y), range	44.66–65.98	44.66–49.80	60.32–65.98	
Male, *n* (%)	402 (48.32)	189 (44.89)	213 (51.82)	0.045[b]
Years of education (SD)	14.51 (2.42)	14.82 (2.24)	14.19 (2.57)	<0.001[a]
BMI (kg/m^2) (SD)	26.75 (4.57)	27.07 (4.82)	26.43 (4.28)	0.051[a]
Hypertension, *n* (%)	362 (43.51)	115 (27.32)	247 (60.10)	<0.001[b]
Diabetes, *n* (%)	42 (5.05)	10 (2.38)	32 (7.79)	<0.001[b]
APOE-ε4 carrier, *n* (%)	215 (25.84)	118 (28.03)	97 (23.60)	0.145[b]
Smoker, *n* (%)	95 (11.42)	66 (15.68)	29 (7.06)	<0.001[b]
Hippocampus volume				
Left (mm^3) (SD)	3287 (367)	3345 (330)	3226 (395)	<0.001[a]
Right (mm^3) (SD)	3350 (367)	3426 (307)	3269 (407)	<0.001[a]
Total (mm^3) (SD)	6638 (692)	6771 (590)	6494 (763)	<0.001[a]

Key: BMI, body mass index; SD, standard deviation.
[a] *t*-test.
[b] χ^2 test.

indicated a moderate proportion of variance between individuals (MA = 52%–55%, OA =40%–44%, all = 47%–49%) and this level of between-subject variability was suitable for using random individual intercepts. However, insufficient variability in slope was detected across time and therefore random slopes were excluded from the models.

For the combined cohorts, mean hippocampal volume change was −17.3 [95% CI −20.7, −13.9] mm^3/y (−0.25%/year) for the total hippocampus, −11.7 [95% CI −13.5, −9.8] mm^3/y (−0.34%/year) for the left, and −5.8 [95% CI −7.6, −3.9] mm^3/y (−0.17%/year) for the right. For the MA cohort, hippocampal volume change was −12.2 [95% CI −20.3, −4.1] mm^3/y (−0.18%/year) for the total hippocampus, −12.6 [95% CI −17.1, −8.0] mm^3/y (−0.36%/year) for the left, and 0.5 [95% CI −3.9, 4.9] mm^3/y (<0.1%/year) for the right. For the OA cohort, hippocampal volume change was −21.3 [95% CI −28.2, −14.5] mm^3/y (−0.30%/year) for the total hippocampus, −18.7 [95% CI −22.2, −15.1] mm^3/y (−0.51%/year) for the left, and −2.7 [95% CI −6.5, 1.2] mm^3/y (< −0.1%/year) for the right.

3.1. Hippocampal volume trajectories

The total hippocampal volume trajectory was non-linear for both the combined and OA cohorts (Supplementary Table S2, Models S1–S3, and Fig. S2). When the effects of hemisphere and sex were included, hippocampal volume followed a non-linear trajectory for the combined and MA cohorts, with a linear trajectory for the OA cohort (Table 2, Models 1–3, and Fig. 1). MA men had significantly larger hippocampal volume and greater rates of volume change compared to women. Furthermore, the right hippocampus was significantly larger compared to the left hippocampus and the rate of volume loss was significantly lower for the right hippocampus when compared to the left. In OA, the rate of volume loss was significantly lower for the right hippocampus when compared to the left.

3.2. Latent class analysis

We estimated up to 5 class models for each structure and examined the model fit, stability, and class sizes to determine whether the optimal class sets had been identified. We did not estimate 6 or more class models as it was clear that the optimal class sets involved 1–3 classes. Goodness-of-fit characteristics of the latent class sets are shown in Supplementary Table S3, the latent class trajectories are shown in Fig. 2, and latent class comparisons are shown in Supplementary Table S4.

3.2.1. MA left hippocampus

A three-class model produced the best fit with groups predominantly differentiated by their baseline volume (low, medium, high). The largest class, Class 1 ($n = 287$) representing 68.5% of the population, had an intercept of 3413.42 [95% CI 3356.01, 3470.83] mm^3 and volume change of −11.05 [95% CI −17.03, −5.07] mm^3/y (−0.32%/year), the next largest class (Class 2, $n = 100$, 23.9%) had a smaller intercept of 3052.97 [95% CI 2971.87, 3134.07] mm^3, volume change of −16.49 [95% CI −25.53, −7.45] mm^3/y (−0.54%/year), and the smallest class (Class 3, $n = 32$, 7.6%) had the largest intercept of 3931.80 [95% CI 3775.59, 4088.01] mm^3, and volume change of −14.12 [95% CI −30.17, 1.93] mm^3/y (−0.36%/year). There were no significant differences between Class 1 and Class 2 at baseline. Compared to Class 1, Class 3 was older by 0.82 [95% CI 0.25, 1.38] years and had a 26% [95% CI 7, 45] greater proportion of males.

3.2.2. MA right hippocampus

A two-class model produced the best fit with groups differentiated by baseline volume (low, high) and slope of volume change. The largest class (Class 1, $n = 216$, 51.6%) had an intercept of 3536.38 [95% CI 3432.93, 3639.83] mm^3 and volume change of 7.08 [95% CI −0.27, 14.43] mm^3/y (0.20%/year), and the smaller class (Class 2, $n = 203$, 48.4%) had a smaller intercept of 3284.28 [95% CI 3196.02, 3372.54] mm^3 and volume change of −6.98 [95% CI −15.35, 1.39] mm^3/y (−0.21%/year). When the 2 classes were compared at baseline, there were no significant differences.

3.2.3. OA left hippocampus

A two-class model produced the best fit with groups differentiated by both baseline volume and slope (high-declining, low-stable). The largest class (Class 1, $n = 258$, 63.5%) had an intercept of 3097.64 [95% CI 3048.64, 3146.64] mm^3 and volume change of −2.18 [95% CI −12.16, 7.80] mm^3/y (−0.07%/year), and the smaller class (Class 2, $n = 148$, 36.5%) had an intercept of 3534.36 [95% CI

Table 2
Trajectory models

Predictors	All HCV (Model 1)			MA HCV (Model 2)			OA HCV (Model 3)		
	Estimates	95% CI	*p* value	Estimates	95% CI	*p* value	Estimates	95% CI	*p* value
(Intercept)	3223.75	3166.91, 3280.60	**<0.001**	3271.15	3202.25, 3340.05	<0.001	3275.04	3234.62, 3315.46	**<0.001**
Age	5.63	−1.16, 12.42	0.104	0.99	−17.30, 19.28	0.915	−18.27	−21.81, −14.73	**<0.001**
Age^2	−0.40	−0.59, −0.20	**<0.001**	−0.50	−1.69, 0.68	0.406			
Right side	177.63	124.67, 230.59	**<0.001**	73.57	30.62, 116.51	**0.001**	20.85	−23.98, 65.68	0.362
Male	190.46	110.02, 270.91	**<0.001**	265.17	169.78, 360.56	**<0.001**			
Age × right	−7.24	−14.12, −0.37	**0.039**	10.90	5.31, 16.50	**<0.001**	15.32	10.57, 20.07	**<0.001**
Age × male	−15.85	−24.38, −7.32	**<0.001**	−59.82	−85.81, −33.83	**<0.001**			
Right × male	−66.14	−126.55, −5.73	**0.032**						
Age^2 × male	0.31	0.08, 0.54	**0.008**	3.31	1.59, 5.03	**<0.001**			
Age^2 × right	0.25	0.05, 0.45	**0.016**						
Age × right × male	3.66	0.44, 6.89	**0.026**						
Random effects									
σ^2	66,282.42			54,818.19			74,091.46		
τ_{00}	$63,653.00_{Individual}$			$65,949.94_{Individual}$			$62,038.99_{Individual}$		
ICC	0.49			0.55			0.46		
N	825			419			406		
Observations	4222			1958			2264		
Marginal R^2/conditional R^2	0.095/0.538			0.064/0.5750			0.063/0.490		

Model 1 shows impact of age, sex, and hemisphere on hippocampal volume; Model 2 shows impact of age, sex, and hemisphere on MA hippocampal volume; Model 3 shows impact of age and hemisphere on OA hippocampal volumes.
Key: σ^2, residual random variance; τ_{00}, individual intercept random variance; All, both cohorts combined; HCV, hippocampal volume; ICC, intra-class correlation between individuals; MA, middle age cohort; OA, older age cohort; Bolded values represent statistical significance at $p < 0.05$.

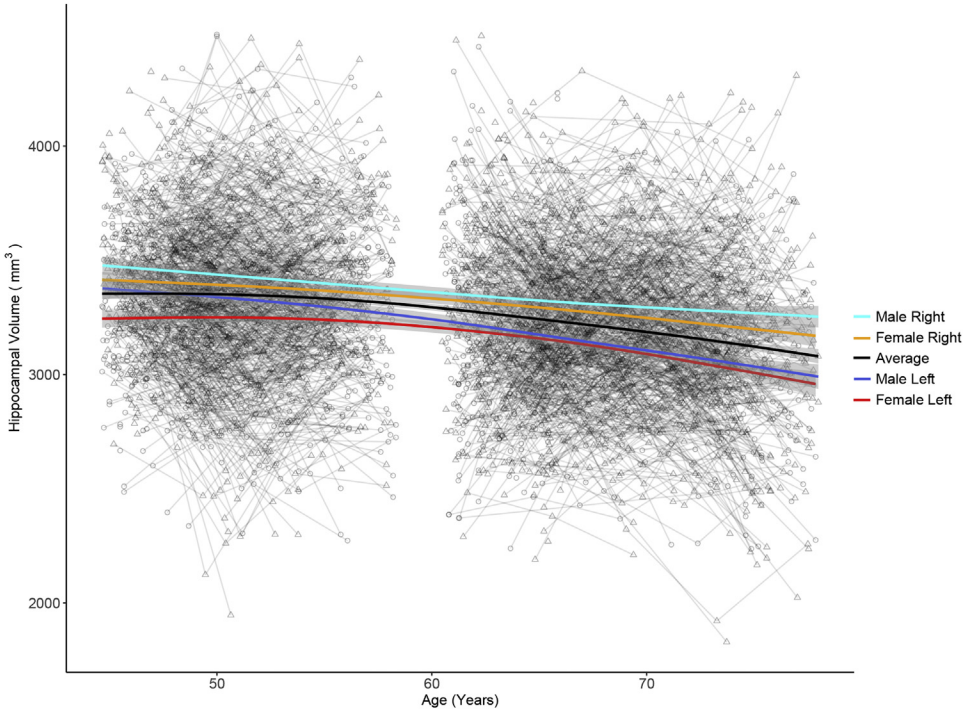

Fig. 1. Hippocampal volume trajectories in middle and older age. The black line is the average of the trajectories, light blue is the male right hippocampus, orange is the female right hippocampus, dark blue is the male left hippocampus, and red is the female left hippocampus. The gray shadows around the trajectories represents the 95% confidence intervals. The individual data points for females are represented by circles and males by triangles. Longitudinal data points for each participant are connected by lines. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

3389.46, 3679.26] mm^3 and volume change of −41.43[95% CI −55.23, −27.63] mm^3/y (−1.17%/year). When the 2 classes were compared at baseline, there were no significant differences.

3.2.4. OA right hippocampus

A two-class model met the criteria in terms of lowest AIC and all class sizes greater than 20 but failed the stability criteria with class 2 having <50% of members with a posterior probability >0.7. Thus, the single class model was selected.

3.3. Sensitivity analysis

Although individuals with neurological disorders were not included in this study, latent class analysis was repeated for the OA cohort with low MMSE participants (MMSE <27; 3.7%) excluded to assess the impact of prodromal neurocognitive disorders. The analysis produced the same latent class structure and characteristics (Supplementary Table S5).

3.4. Post hoc analysis

The trajectory models and observed MA and OA data were used to estimate hippocampal volumes for younger adults from 20 years of age and estimate atrophy rates by decade from 20 to 80 years. The maximum total hippocampal volume of 6866 mm^3 was estimated to occur at 26 years of age, and the model predicted a 10.9% volume loss by age 80 (Supplementary Fig. S3, Table S6).

4. Discussion

We investigated longitudinal hippocampal aging trajectories in samples of middle age and older age adults living in the community. Particularly notable findings were that, while a consistent and progressive decrease in volume was observed across the age range considered, the atrophy rates were lower than would have been predicted based on previous literature (Barnes et al., 2009; Fraser et al., 2015), especially in the older aged cohort. Furthermore, subgroup analysis demonstrated that hippocampal volumes remained stable for most older age adults with volume decline identified in only a third of this population. This novel finding augments the limited existing evidence of heterogeneous aging outcomes (Burns et al., 2015, 2019; Small and Bäckman, 2007).

4.1. Trajectories

Hippocampal volumes followed a non-linear trajectory across middle age and older age, remaining non-linear when effects of hemisphere and sex were included, consistent with previous cross-sectional (Allen et al., 2005; Coupé et al., 2017; Potvin et al., 2016; Walhovd et al., 2011; Ziegler et al., 2015) and longitudinal research (Fraser et al., 2015; Pfefferbaum and Sullivan, 2015; Schmidt et al., 2018; Schuff et al., 2012). When the older age cohort was examined separately, the trajectory appeared non-linear for the combined hippocampus, but linear when independent hemisphere contributions were included in the model. Left hippocampal volumes were smaller and experienced higher atrophy compared to the right. This suggests that linear hemispheric trajectory differences may appear non-linear when left and right hippocampal volumes are combined. Results from earlier longitudinal studies of total hippocampal volumes using smaller samples and fewer time points produced equivocal results with respect to linearity (Leong et al., 2017; Narvacan et al., 2017; Raz et al., 2010; Schuff et al., 2012). However, the present findings in a large sample with long follow-up demonstrates that while the hippocampal volume trajectories are non-linear across middle and older age, there is significant heterogeneity related to hemisphere and sex.

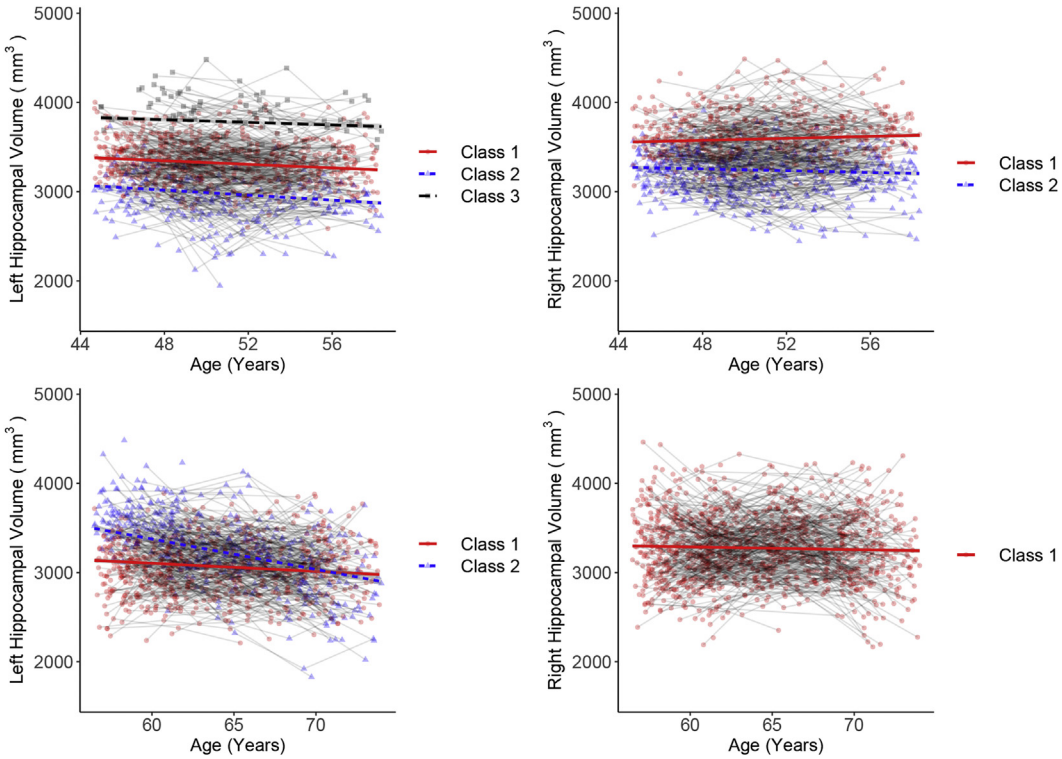

Fig. 2. Hippocampal trajectories corresponding to different subgroups of individuals identified by latent class analysis. Upper left = MA left hippocampus (Class1 $n = 287$, Class2 $n = 100$, Class 3 $n = 32$), Upper right = MA right hippocampus (Class1 $n = 216$, Class2 $n = 203$), Lower left = OA left hippocampus (Class1 $n = 258$, Class2 $n = 148$), Lower right = OA right hippocampus (Class1 $n = 406$). Class 1: Trajectory is represented by a solid line and the data points by circles, Class 2: Trajectory is represented by short dashed line and data points by triangles, Class 3: Trajectory is represented by long dashed line and data points by squares. Longitudinal data points for each participant are connected by lines.

Middle but not older aged women had a smaller mean normalized left hippocampal volume and a lower atrophy rate compared to men. This finding is consistent with that of a recent large ($n = 19{,}793$) cross-sectional study (Nobis et al., 2019; Sudlow et al., 2015) that found that the rate of volume loss is lower in women between 50 and 60 years of age after which men and women have similar mean bilateral hippocampal volumes and follow a similar trajectory. It is possible that the lower rates of atrophy in women are related to the effects of lifestyle factors, or reduced estrogen levels after menopause (Barth et al., 2016; Raz et al., 2004; Wnuk et al., 2012; Zárate et al., 2017), or to greater convergence of risk factors after mid-life (e.g., obesity, sedentary lifestyle). Earlier trajectory studies, which did not separately model the effects of sex or hemisphere, identified an inflection point in hippocampal volume change around 50 years of age (Coupé et al., 2017; Fjell et al., 2013). Thus, it is possible that there may be different inflection points in hippocampal trajectories for men and women, and this question warrants future investigation of sex differences across the third to the seventh decades.

When compared to meta-analysis benchmarks, the estimated total atrophy rates from the current study were lower than Barnes et al. (2009) and within the CI range of a later meta-analysis of 27 studies characterizing hippocampal atrophy in normal aging (Fraser et al., 2015). The relatively low rates of hippocampal atrophy in the current study are consistent with the corresponding rates of age-related cortical thinning from the same cohort samples (Shaw et al., 2016a, 2016b).

When we estimated hippocampal volumes from 20 to 80 years, the models suggested that volumes peaked in the mid-20s consistent with previous development and aging studies (Allen et al., 2005; Fjell et al., 2013; Lupien et al., 2007; Uematsu et al., 2012; Wellington et al., 2013), and in agreement with a large longitudinal developmental study in children and young adults aged 5–25 years (Fish et al., 2019), but earlier than Coupe et al. (2017). Predicted volumes from the models were consistent with previous literature taking into account differences in volumetry methods used (Allen et al., 2005; Scahill et al., 2003; Uematsu et al., 2012). We projected that total hippocampal volume would have declined by almost 11% from 20 to 80 years of age, slightly lower than the 13% decline reported by Allen et al. (2005).

4.2. Latent class analysis

We identified subgroups of individuals with distinct hippocampal trajectories. In middle age, the main difference between the subgroups related to baseline hippocampal volume. This indicates that differences in hippocampal volume were larger between people than over time, and can be interpreted as evidence that different subgroups of hippocampal atrophy over time may be difficult to differentiate in middle age.

In older age, we identified 2 subgroups for the left hippocampus with the largest group having a smaller hippocampus at baseline and stable volume at a life stage when mean volumes are expected to decline. When we looked at the trajectories of the right hippocampus for the 2 subgroups, we found a similar pattern with right hippocampal volumes declining in the smaller subgroup and not declining in the larger subgroup (Supplementary Fig. S4). We compared demographic characteristics of the subgroups at baseline, but no significant differences or consistent trends were identified (Livingston et al., 2017). We considered the possibility that sample attrition with healthier/unhealthy participants dropping out in one or the other group, contributed to these findings. Although the participants who dropped out from the stable group were 7 months older than those who remained in the study, they

did not differ in sex ratio, education, BMI, hypertension, diabetes, *APOE-ε4* genotype, or smoking status. For the declining group, apart from somewhat more women than men dropping out, the participants who dropped out were not significantly different to those who remained. Given that there were no significant sex differences in the older cohort trajectories, the small age difference is unlikely to explain the different subgroup trajectories (Supplementary Table S7). Similar heterogeneous trajectories have previously been found for MMSE scores and for terminal decline in mental health and well-being in older adults (Burns et al., 2015; Small and Bäckman, 2007). This suggests that average trajectories may not be representative of the majority of the population. The implication here is that previous research may have overestimated the rate of decline for much of population while underestimating decline for a minority. This could be explored by larger studies focusing on detecting subgroups with enough statistical power to identify differences between the stable and declining groups.

4.3. Laterality

We found that left hippocampal volumes were smaller and experienced higher atrophy rates compared to the right. Such rightward hippocampal volumetric asymmetry has been reported from childhood, continues throughout adult life (Giedd et al., 1996; Potvin et al., 2016; Uematsu et al., 2012; Woolard and Heckers, 2012), and is thought to be related to hemispheric functional specialization (Reuter-Lorenz et al., 2000; Toga and Thompson, 2003). Increased left hippocampal atrophy in normal aging may be related to the left hippocampus being more vulnerable to cardiovascular factors such as chronic hypoperfusion, increased thickness of the carotid artery, and increased incidence of stroke (Cherbuin et al., 2010; Giannakopoulos et al., 2007). Left hippocampal atrophy in normal aging appears to be ameliorated by the recruitment of right hemisphere regions resulting in less asymmetric cognitive processing (Reuter-Lorenz et al., 2000). However, rightward volumetric asymmetry decreases in adults experiencing subjective cognitive decline (Yue et al., 2018) or AD (Shi et al., 2009). In AD, increasing gray matter loss in the right hemisphere coincides with significant cognitive deficits (Giannakopoulos et al., 2007; Thompson et al., 2003). Hence increasing rightward asymmetry appears to be associated with normal aging, while asymmetry reduction appears to be associated with later-stage AD. In the current study, while the population demonstrates a typical asymmetric normal aging pattern, the largest subgroup appears to have stable hippocampal volumes with little age-related decline suggesting that this group may have a lower risk of developing dementia in later life.

4.4. Strengths and limitations

The main strengths of this study include the large sample size, narrow age cohorts of middle age and older aged community-living adults, longitudinal follow-up of up to 12 years, manual tracing of left and right hippocampal volumes, and precise modeling of both hemisphere and sex. Limitations include possible sample selection biases and attrition over time. The number of sequential scans was limited, with up to 3 for the middle age and 4 for the older aged cohort. To our knowledge, this is the largest manually traced longitudinal study of hippocampal aging in middle age and older age populations investigating both hemisphere and sex.

5. Conclusions

In this study, we found that hippocampal volumes followed a non-linear trajectory declining in middle age by 0.18% per year increasing to 0.30% per year in older age. Left hippocampal volumes were lower and demonstrated greater atrophy compared to the right. We also found that middle age women had smaller left hippocampal volume and lower rates of atrophy compared to middle age men. However, these sex differences dissipated at older ages, suggesting that there may be different critical ages for hippocampal aging in men and women. Finally, the population contained a number of subgroups that differed in terms of baseline hippocampal volume and rates of change. Most striking was that the largest older age group demonstrated stable hippocampal volumes across the period of the study suggesting that there is no one-size-fits-all normative trajectory of hippocampal change in aging.

Disclosure statement

The authors report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurobiolaging.2020.10.011.

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