# Evaluating the position of the uncal apex as a predictor of episodic memory across the adult lifespan

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## Abstract

Structural decline of the hippocampus occurs in heterogeneous patterns across its spatial extent, and is an important determinant of episodic memory dysfunction in aging. However, evidence indicate that the anatomical landmark uncal apex, used to demarcate anterior and posterior hippocampal subregions, changes position as the hippocampus atrophies. This emphasizes a risk of misclassifying gray matter into the incorrect subregion when using standard demarcation methods, contributing to over- and underestimation of age effects on anterior and posterior hippocampal volume. Yet, it remains unexplored whether inter-individual differences in uncal apex position predict episodic memory performance in itself. Here, we manually identified the uncal apex in anatomical MRI data from a healthy adult-lifespan sample (n=180; 20-79 years), assessed age differences in its position, and associations with word recollection performance. Increasing age was linked to a more anteriorly located uncal apex (retracting ~0.041 mm/year). Importantly, a more anterior uncal apex position was linked to lower memory performance. Whereas anterior hippocampal volume remained stable with increasing age, posterior volume displayed non-linear decline with an infliction point at approximately 45 years. Neither anterior nor posterior hippocampal volumes predicted memory performance, but the ratio of posterior to anterior volume showed a significant association with memory when taking the position of the uncal apex into account. These results indicate that uncal apex position may provide an estimate of hippocampal integrity sensitive to inter-individual differences in memory, independent of limitations associated with different segmentation methods.



**Key words:** aging, anatomical landmark, anterior hippocampus, episodic memory, longitudinal axis, posterior hippocampus

Age-related decline in episodic memory has several biological sources, among them changes in the structural integrity of the hippocampus (Fjell et al., 2014; Gorbach et al., 2017). Over the years, it has become increasingly evident that age-related hippocampal decline and its role in memory must be considered in light of the anatomical and functional heterogeneity characterizing the hippocampus longitudinal axis (Poppenk et al., 2013; Strange et al., 2014). To this end, many studies assess gray matter atrophy and associations with memory performance separately for anterior and posterior hippocampal subregions (Chauveau et al., 2021; Langnes et al., 2020; Malykhin et al., 2017; Nordin et al., 2018; Snytte et al., 2022). However, a recent study observed that the anatomical landmark most commonly used for segmenting the hippocampus into anterior and posterior subregions – the uncal apex – alters position in aging, increasing the risk of misclassifying anterior hippocampal tissue as part of the posterior hippocampus in an age-dependent manner (Poppenk, 2020).

Using cross-sectional data from several large-scale samples, Poppenk (2020) demonstrated an anterior displacement of the uncal apex by approximately 0.03 mm/year across the adult lifespan, and by 0.05-0.06 mm/year in older age (>60 years). Whereas this observation has limited implications for segmentation of the anterior and posterior hippocampus in healthy young adults, it suggests that an uncal apex landmark-based approach may be inappropriate for demarcating anterior and posterior subregions in samples where anatomical hippocampal alterations occur. The current understanding posits that, as the uncal apex retracts anteriorly, it exposes the sub-uncal area – which in older and some clinical samples would risk being misclassified as posterior tissue – whereas still accurately classified as anterior tissue in healthy young adults. In line with this, Poppenk (2020) reported overestimated anterior, while underestimated posterior, volume loss when volumes were based on uncal apex landmark-segmentation as compared to when they were based on segmentation in normalized space at the Montreal Neurological Institute (MNI) coordinate of y = -21. Critically, age-related variation

in the position of the uncal apex would risk misclassification of any hippocampal feature estimated using anterior and posterior hippocampal masks (e.g., gray matter, functional activation and connectivity, molecular markers).

The main aim of this study was to evaluate individual differences in uncal apex position across the adult lifespan as a hippocampus-based predictor of memory in itself, avoiding limitations associated with demarcating anterior and posterior subregions for volumetric estimation. We predicted that a more anteriorly located uncal apex, likely conveying reduced hippocampal structural integrity, would be linked to lower levels of memory function. Furthermore, we wanted to assess the impact of uncal apex position on associations of anterior and posterior hippocampal volumes with episodic memory, hypothesizing that accounting for uncal apex position would contribute to predicting memory performance by reducing noise and increasing specificity in subregional volume estimates from landmark-based segmentation. Specifically, we assessed effects in relation to verbal recollection memory, a domain in which longitudinal decline is highly dependent on the hippocampus (Gorbach et al., 2017).

Whereas a recent large-scale longitudinal lifespan study indicated a primary link between anterior hippocampal volume and verbal recollection (Langnes et al., 2020), cross-sectional data from the adult lifespan, in contrast, support a main role of the posterior hippocampus in verbal recollection memory (Hoang et al., 2024; Malykhin et al., 2024). This is in line with recent findings of an anterior-posterior division between decline in recognition and recollection memory, respectively (N. Persson & Andersson, 2022). Notably, previous findings in young adults emphasize a role of posterior-to-anterior volume ratios in predicting recollection memory (Poppenk & Moscovitch, 2011; Snytte et al., 2020). Since this measure is directly linked to the position of the uncal apex, and therefore susceptible to age-related differences therein, it should warrant particular consideration of inter-individual differences in uncal apex position when used to predict recollection memory in an aging sample.

Here, we manually identified the uncal apex in anatomical MRI data from a healthy adult-lifespan sample (n=180; 20-79 years) and created two estimates of uncal apex location. The first corresponded to the measure used by Poppenk (2020), constituting y-plane coordinates transformed to MNI space, whereas the second was a native-space alternative, expressed as the distance in mm between the manually identified uncal apex and the most anterior point of the hippocampus.

## 2. Materials and methods

This study included data from the DopamiNe, Age, connectoMe, and Cognition (DyNAMiC) study, which has previously been described in detail elsewhere (Johansson et al., 2023; Nordin et al., 2022). Here, we include the materials and methods directly relevant to the current study. The DyNAMiC study was approved by the Regional Ethical board of Umeå, Sweden. All participants provided written informed consent prior to testing.

### 2.1 Participants

The initial DyNAMiC sample included 180 participants (20-79 years; mean age = 49.8±17.4; 90 men and 90 women equally distributed within each decade). Recruitment was done via postal mail to a randomly selected sample from the population register of Umeå in northern Sweden. Exclusion criteria implemented during the recruitment procedure included brain pathology, impaired cognitive functioning (Mini Mental State Examination < 26), medical conditions and treatment that could affect brain functioning and cognition (e.g. dementia, diabetes, and psychiatric diagnosis), and magnetic resonance imaging (MRI) contraindications (e.g. metal implants). All participants were native Swedish speakers.

### 2.2 Episodic memory

Episodic memory was measured using a task testing word recollection (Nevalainen et al., 2015; Nordin et al., 2022). In this task, participants were presented with 16 Swedish concrete nouns

that appeared successively on a computer screen. Each word was presented for 6 s during encoding with an inter-stimulus interval (ISI) of 1 s. After encoding, participants reported as many words as they could recall by using the keyboard. Two trials were completed, yielding a maximum score of 32. Raw scores were transformed into T-scores (M = 50; SD = 10).

### 2.3 Structural MR Imaging

Brain imaging was conducted at Umeå University Hospital, Sweden. Structural MRI data were acquired with a 3T Discovery MR 750 scanner (General Electric, WI, USA), using a 32-channel head coil. Anatomical T1-weighted images were acquired with a 3D fast-spoiled gradient-echo sequence, collected as 176 slices with a thickness of 1 mm. Repetition time (TR) was 8.2 ms, echo-time (TE) = 3.2 ms, flip angle = 12º, and field of view (FOV) = 250 × 250 mm.

### 2.4 Manual identification of the uncal apex

The uncal apex, defined as the most posterior coronal slice in which the uncus is visible (Dalton et al., 2017; Malykhin et al., 2007; Poppenk, 2020), was for each participant manually identified in left and right hemispheres using anatomical T1-weighted images. To ensure reliability of manual ratings, two independent raters underwent training on how to recognize the landmark and established a common protocol. The raters independently completed an initial round of manual identification using a set of 10 randomly selected participants (i.e., 20 hippocampi). Reliability of ratings in this first round was determined as high based on a DICE coefficient at 0.85 and an inter-class coefficient (ICC) at 0.986, which increased to 0.996 after a second round was completed. Subsequently, one of the raters completed the manual landmark identification in the rest of the DyNAMiC sample. Cases marked as difficult during this procedure were revisited and discussed before a final coordinate was determined.

Following the methods of the original report (Poppenk, 2020), the uncal apex coordinates identified in native space were, for each participant and hemisphere, transformed to standard MNI space using linear normalization (here, in Statistical Parametric Mapping,

SPM12: Wellcome Trust Centre for Neuroimaging http://www.fil.ion.ucl.ac.uk/spm/). The resulting left- and right-hemisphere y-plane MNI coordinates were taken to denote *uncal apex position* (Figure 1A). Manual identification resulted in estimates of uncal apex position for a total of 173 participants (left hemisphere: M = -19.75, SD = 2.88; right hemisphere: M = -19.22, SD = 2.73), excluding 7 individuals due to problematic ratings and outlier values following normalization.

### 2.5 Hippocampal segmentation and volumetric assessment

Individual anatomical T1-weighted images were submitted to automated segmentation in FreeSurfer version 6 (Fischl et al., 2002, 2004). The resulting native-space hippocampal segmentations were divided into anterior and posterior segments using the manually identified native space uncal apex projected on an axis from the most anterior to the most posterior points of the hippocampus. Volume values were corrected for FreeSurfer's estimated total intracranial volume (eTIV; the sum of volumes for gray matter, white matter, and cerebrospinal fluid). Adjusted volumes were equal to the raw volume - $b$(eTIV - $\overline{eTIV}$), where $b$ is the regression slope of volume on eTIV (Buckner et al., 2004; Jack et al., 1989). A total of 3 participants were excluded based on exhibiting extreme volume values (1.5$^{*}$interquartile range).

### 2.6 Hippocampal length and native space uncal apex distance estimates

Using the subject-specific segmentations from FreeSurfer, we additionally calculated the total length of the hippocampus and the distance in mm between the most anterior point of the hippocampus and the position of the manually identified uncal apex projected on the axis between the most anterior and most posterior points of the hippocampus. This was done as to obtain an estimate of uncal apex position independent of normalization to standard space, henceforth referred to as *uncal apex distance* (Figure 1 A; left hemisphere: M = 19.57 mm, SD

= 1.55; right hemisphere: M = 19.07 mm, SD = 1.52). A total of 3 participants were excluded based on outlier values in this measure, resulting in 167 remaining participants.

### 2.7 Statistical analyses

Statistical analyses were conducted in SPSS version 28.0 and in R version 4.1.3 (R Core Team, 2021). We considered both linear and non-linear associations between age and hippocampal measures (i.e., uncal apex position, distance, and hippocampal gray matter) using data-driven generalized additive models (GAM), which delineate the best fit of the data without any *a priori* assumptions of linearity. With GAM, the smoothness of the age curve is estimated as part of the model fit and allows for the effective degrees of freedom (edf) to be taken as an estimate of deviation from linearity (Zuur et al., 2009). We used simple linear regression to estimate the average annual displacement of the uncal apex and difference in volume where significant effects of age were evident. Hierarchical regression analyses were used to test uncal apex estimates and hippocampal volume as predictors of episodic memory performance over covariates (e.g., sex, age). In R, GAM was performed with the mgcv package version 1.8-40 (Wood, 2011). Statistical significance is reported using both unadjusted p-values and false discovery rate (FDR) adjusted p-values.

## 3. Results

### 3.1 Age-related anterior retraction of the uncal apex

#### *3.1.1 Uncal apex position*

There was a significant correlation between uncal apex position in left and right hemispheres ($r$ = 0.80, $p$ < 0.001, $p_{FDR}$ = 0.004), on par with previous observations in a similar lifespan sample (Poppenk, 2020: $r$ = 0.72). This allowed us to combine left- and right-hemisphere y-plane MNI coordinates into a measure of mean uncal apex position (M = -19.44, SD = 2.61). GAM revealed that uncal apex position was significantly related to age across the sample (F =

12.67, edf = 1.00, $p < 0.001$, $p_{FDR} = 0.002$). Simple linear regressions estimated that the uncal apex was on average located 0.041 mm more anteriorly per year across the sample (R = 0.267, $R^2 = 0.071$, $\beta = 0.041$), Figure 1B. For consistency with the previous report (Poppenk, 2020), we also estimated the effect of age across segments of individuals below and above 40 years separately. Uncal apex position did not show significant age-related variation before the age of 40 years (R = 0.149, $R^2 = 0.022$, $F_{(1, 53)} = 1.19$, $\beta = 0.059$, $p = 0.281$, $p_{FDR} = 0.390$), but an average anterior displacement by 0.063 mm after the age of 40 (R = 0.257, $R^2 = 0.066$, $F_{(1, 112)} = 7.83$, $\beta = 0.063$, $p = 0.006$, $p_{FDR} = 0.015$).

### *3.1.2 Uncal apex distance*

As a native-space alternative to the MNI y-plane coordinates representing uncal apex position, we used the distance in mm from the most anterior point of the hippocampus to the manually identified uncal apex. This measure was significantly correlated between hemispheres ($r = 0.35$, $p < 0.001$, $p_{FDR} = 0.004$), and an average bilateral measure was created (M = 19.32 mm, SD = 1.27). Furthermore, estimates of uncal apex distance (controlled for eTIV to adjust for inter-individual differences in brain size) were negatively correlated with uncal apex position ($r = -0.34$, $p < 0.001$, $p_{FDR} = 0.004$), such that a shorter distance between the hippocampus most anterior point to the uncal apex was linked to a more anterior uncal apex y-coordinate.

Uncal apex distance (estimates adjusted for eTIV) was significantly related to age across the sample (F = 18.19, edf = 1.0, $p < 0.001$, $p_{FDR} < 0.001$), such that increasing age was linked to a shorter distance between the hippocampus most anterior point and the uncal apex (Figure 1C). A linear regression estimated the annual difference in uncal apex distance to be approximately 0.026 mm (R = 0.349, $R^2 = 0.121$, $\beta = -0.026$). When estimated across segments of individuals below and above 40 years separately, uncal apex distance did not show significant age-related variation before the age of 40 years (R = 0.055, $R^2 = 0.003$, $F_{(1, 53)} = 0.16$, $\beta = -0.012$, $p = 0.694$, $p_{FDR} = 0.723$), but an average anterior displacement by 0.025 mm

after the age of 40 (R = 0.234, $R^2$ = 0.055, $F_{(1, 112)}$ = 6.44, β = -0.025, $p$ = 0.013, $p_{FDR}$ = 0.027). We also examined the association between whole hippocampal length (adjusted for eTIV) and age, observing significant shortening of the hippocampus (F = 5.03, edf = 4.12, $p$ < 0.001, $p_{FDR}$ = 0.001). A linear model estimated the decrease in length to be on average 0.045 mm per year (R = 0.367, $R^2$ = 0.135, β = -0.045).

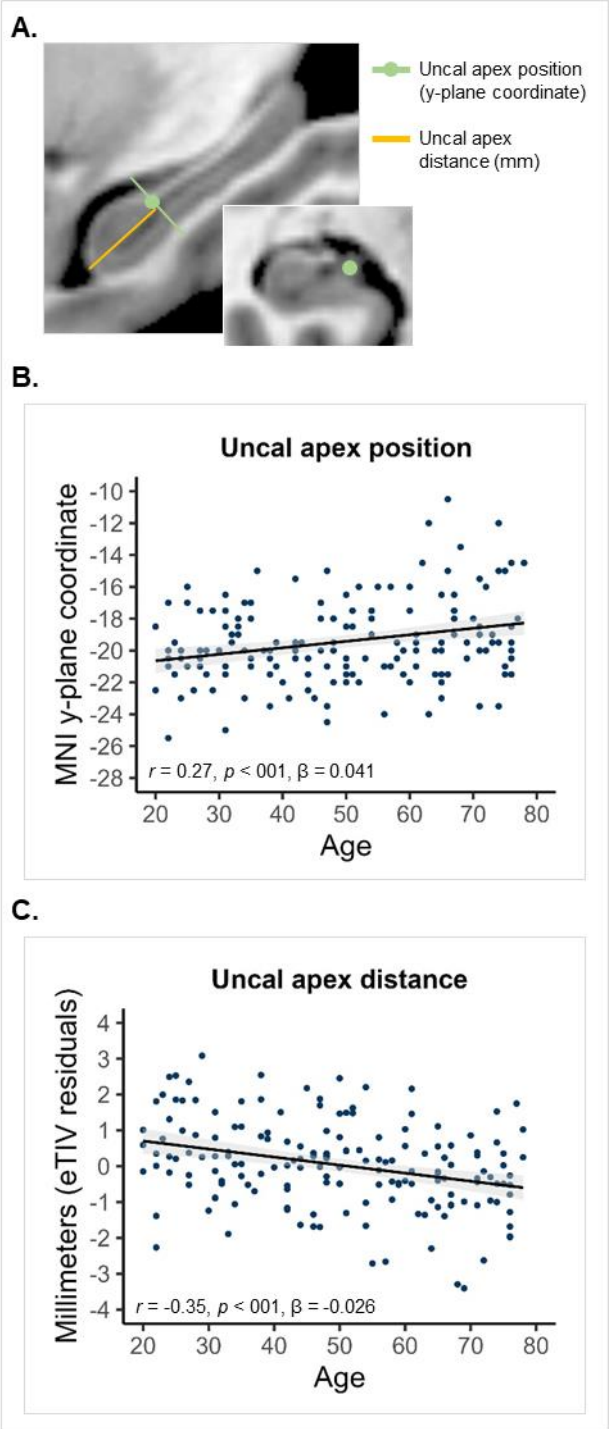


*Figure 1.* Uncal apex position- and distance estimates across the adult lifespan. A) Schematic description of the two uncal apex measures; B) Age-related differences in uncal apex position (MNI coordinates), indicating anterior displacement with increasing age; C) Age-related decrease of distance (in mm, adjusted for eTIV) between the most anterior point of the hippocampus and the manually identified uncal apex.

### 3.2 Effects of age on anterior and posterior hippocampal volume

Anterior hippocampal volume (M = 2449.46 $mm^3$, SD = 252.05) remained stable with increasing age (F = 0.4, edf = 1.0, $p$ = 0.528, $p_{FDR}$ = 0.600; R = 0.050, $R^2$ = 0.002, β = -0.741), Figure 2A. In contrast, posterior hippocampal volume (M = 1803.28 $mm^3$, SD = 255.95) significantly decreased with age across the adult lifespan (F = 13.62, edf = 1.92, $p < 0.001$, $p_{FDR} < 0.001$), with an average of 5.94 $mm^3$ per year (R = 0.395, $R^2$ = 0.156, β = -5.944), Figure 2B. This effect showed moderate signs of non-linearity, with an approximate onset of steeper decline at the age of 45 years. Given the potential underestimation of posterior hippocampal volume decline due to age-related anterior displacement of the uncal apex, we assessed effects while controlling for a) uncal apex position; and b) uncal apex distance. The negative correlation coefficient between age and posterior hippocampal volume originally observed ($r$ = -0.395) was slightly numerically amplified in both cases (uncal apex position: F = 14.21, edf = 1.95, $r$ = -0.42, $p < 0.001$, $p_{FDR} < 0.001$; uncal apex distance: F = 16.84, edf = 1.94, $r$ = -0.46, $p < 0.001$, $p_{FDR} < 0.001$), yielding an estimated yearly volume reduction of 6.57 $mm^3$ and 7.18 $mm^3$, respectively (Figure 2C).

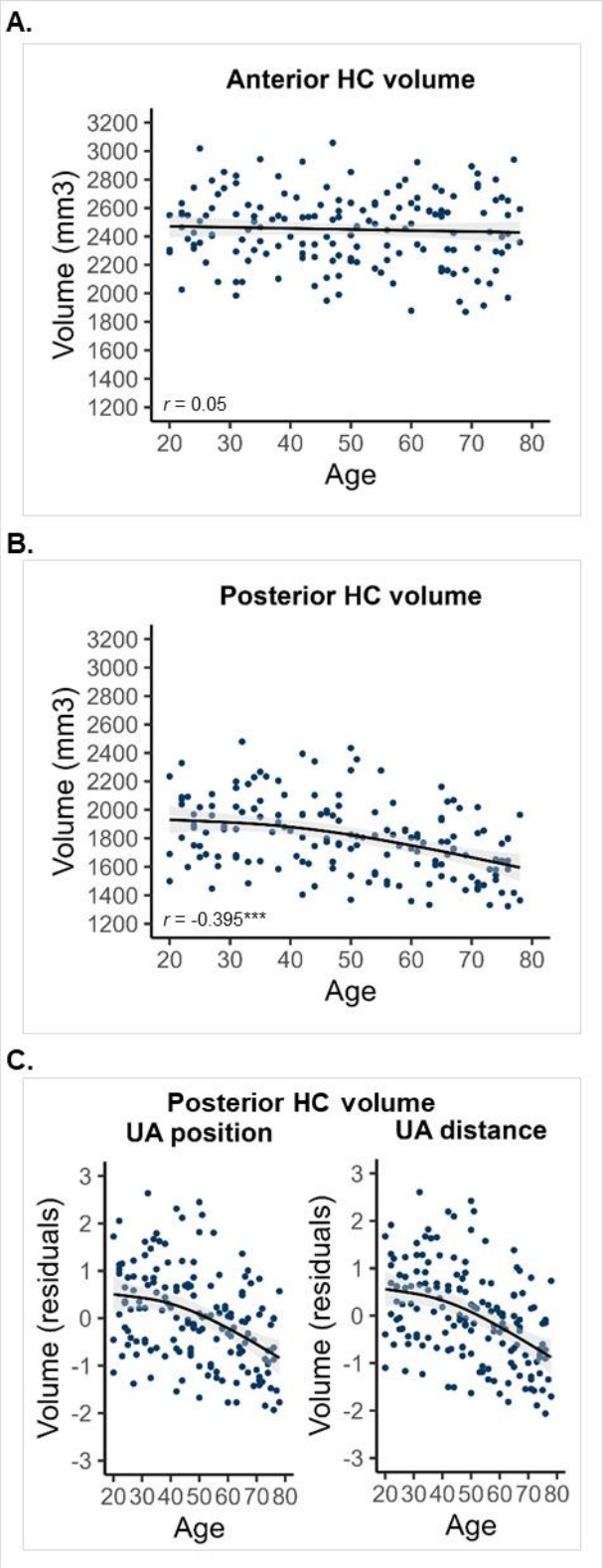


*Figure 2.* Effects of age on anterior and posterior hippocampal volume. A) Stable anterior hippocampal volumes across the adult lifespan; B) Age-related decline in posterior hippocampal volume, exacerbated from the age of approximately 45 years. C) Age-related decline in posterior hippocampal volume when controlling estimates for uncal apex position and distance, respectively.

### 3.3 Relation between uncal apex location and anterior hippocampal volume

To better understand the link between volume of the anterior hippocampus, which showed limited age-related variation, and the location of the uncal apex in aging, we tested associations between these measures across segments of participants below and above the age of 40 years. There was a trend significant age segment x uncal apex position interaction on volume of the anterior hippocampus ($F_{(1, 162)} = 4.54$, $p = 0.035$, $p_{FDR} = 0.063$), such that a more anteriorly located uncal apex position was linked to lower anterior hippocampal volume above the age of 40 years (partial $r = -0.294$, $p = 0.002$, $p_{FDR} = 0.006$), whereas uncal apex position was unrelated to anterior volume in adults below the age of 40 (partial $r = 0.114$, $p = 0.427$, $p_{FDR} = 0.534$), Figure 3A. In contrast, uncal apex distance was equally related to anterior hippocampal volume across both age segments ($F_{(1, 162)} = 0.10$, $p = 0.756$, $p_{FDR} = 0.756$), such that a shorter distance was linked to lower anterior volume (below 40: partial $r = 0.605$, $p < 0.001$, $p_{FDR} = 0.004$; above 40: partial $r = 0.591$, $p < 0.001$, $p_{FDR} = 0.004$), Figure 3B.

To characterize the link between uncal apex estimates and anterior hippocampal volume in older age, we categorized older individuals (age ≥ 60 years) into three equal-sized subgroups based on anterior volume. Main effects of group on volume and uncal apex estimates were assessed including the younger age segment (below 40 years) as reference. Post hoc analyses were conducted with Bonferroni-adjustment of p-values for multiple comparisons. The volume-based grouping yielded a significant main effect of group ($F_{(3, 107)} = 31.55$, $p < 0.001$, $p_{FDR} = 0.004$), and older adults exhibiting the lowest anterior hippocampal volume was the only subgroup with lower volume compared to young adults ($p < 0.001$), Figure 3C. Main effects of group were significant for uncal apex position ($F_{(3, 107)} = 4.87$, $p = 0.003$, $p_{FDR} = 0.008$) and distance ($F_{(3, 107)} = 13.07$, $p < 0.001$, $p_{FDR} = 0.004$). Older adults with lowest anterior volume displayed the most anterior uncal apex position (vs. young: $p = 0.002$), and the shortest uncal apex distance (vs. highest: $p < 0.001$; vs. middle: $p = 0.067$; vs. young: $p < 0.001$), Figure 3D.

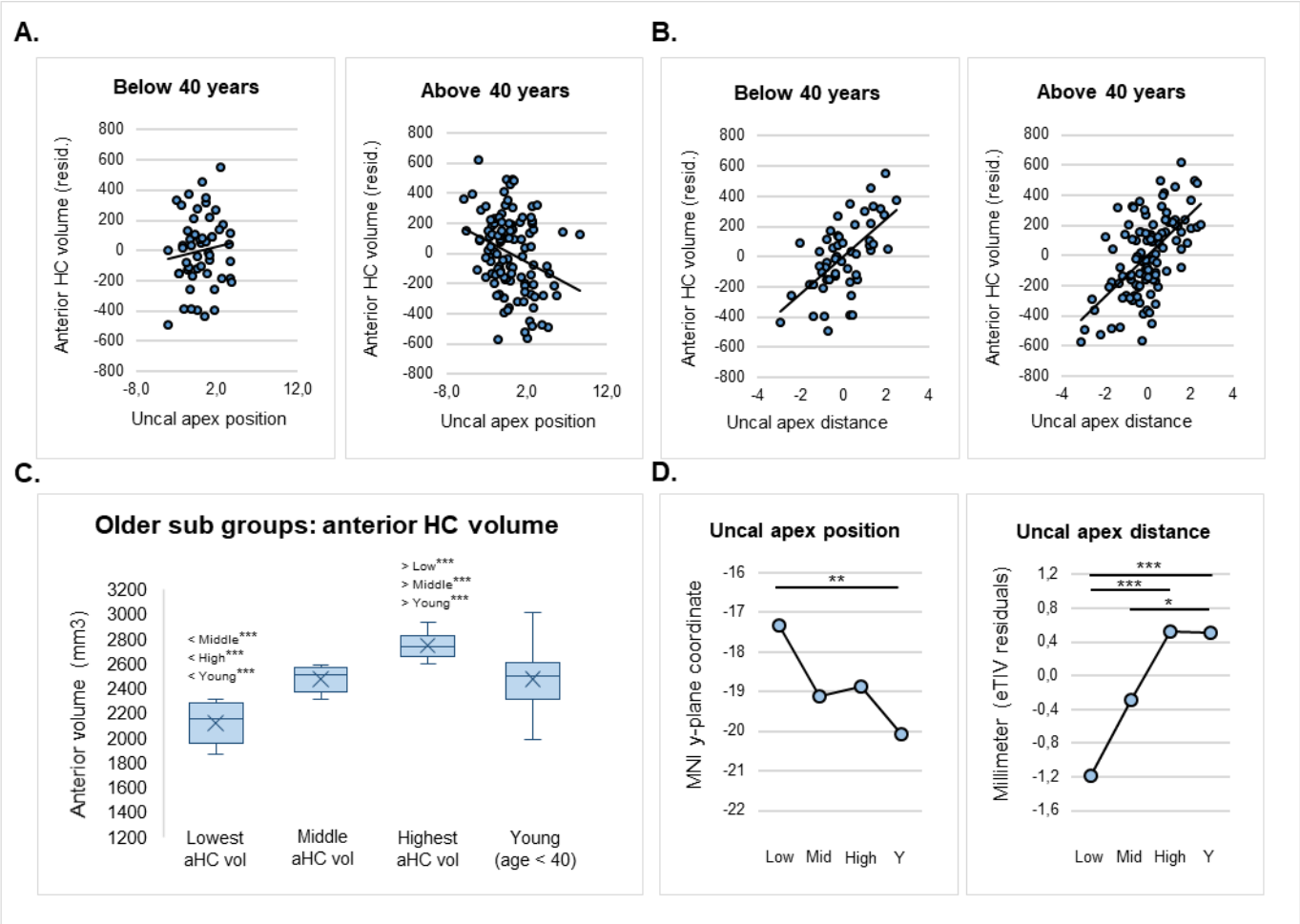


*Figure 3.* Associations between anterior hippocampal volume and uncal apex estimates. Partial correlation plots of A) Anterior hippocampal volume and uncal apex position below and above 40 years; B) Anterior hippocampal volume and uncal apex distance below and above 40 years. C) Anterior hippocampal volume across young adults (age < 40) and three older subgroups based on levels of average anterior hippocampal volume; D) Uncal apex position and distance across older subgroups and young adults (age < 40).

### 3.4 Predicting episodic memory performance

#### *3.4.1 Uncal apex position and distance*

Hierarchical regression analyses were used to evaluate the two uncal apex estimates: a) uncal apex position; b) uncal apex distance, as predictors of episodic memory over and above the covariates age and sex. Across the sample, uncal apex position significantly predicted memory performance ($\Delta R^2 = 0.029$, $F_{(1, 163)} = 7.30$, $\beta = -0.677$, partial Pearson's $r = -0.21$, $p = 0.008$, $p_{FDR} = 0.018$), indicating that a more anteriorly located uncal apex was associated with lower levels of memory performance, Figure 4A. However, uncal apex distance did not predict memory performance ($\Delta R^2 = 0.003$, $F_{(1, 163)} = 0.70$, $\beta = 0.465$, partial Pearson's $r = 0.065$, $p = 0.404$, $p_{FDR} = 0.532$), Figure 4B.

#### *3.4.2 Anterior and posterior hippocampal volume*

Neither anterior ($\Delta R^2 = 0.002$, $F_{(1, 159)} = 0.40$, partial Pearson's $r = 0.050$, $p = 0.530$, $p_{FDR} = 0.576$), posterior ($\Delta R^2 = 0.008$, $F_{(1, 159)} = 1.83$, partial Pearson's $r = 0.107$, $p = 0.178$, $p_{FDR} = 0.262$), nor total hippocampal volume ($\Delta R^2 = 0.002$, $F_{(1, 159)} = 0.553$, partial Pearson's $r = 0.059$, $p = 0.458$, $p_{FDR} = 0.545$) predicted memory performance, Figure 4C. The ratio of posterior to anterior hippocampal volume may be a relevant predictor of episodic memory (Poppenk & Moscovitch, 2011; Snytte et al., 2020). To test this in our sample, we computed a ratio value (posterior/anterior volume) for each participant. Whereas this measure, taking both anterior and posterior volumes into account, did not predict memory performance over and above age and sex ($\Delta R^2 = 0.009$, $F_{(1, 159)} = 2.18$, partial Pearson's $r = 0.117$, $p = 0.142$, $p_{FDR} = 0.222$), additionally controlling for uncal apex position ($\Delta R^2 = 0.018$, $F_{(1, 159)} = 4.42$, partial Pearson's $r = 0.165$, $p = 0.037$, $p_{FDR} = 0.061$) and uncal apex distance ($\Delta R^2 = 0.021$, $F_{(1, 159)} = 5.13$, partial Pearson's $r = 0.178$, $p = 0.025$, $p_{FDR} = 0.048$), respectively, yielded significant associations between the ratio of posterior to anterior volume and memory (Figure 4D-E).

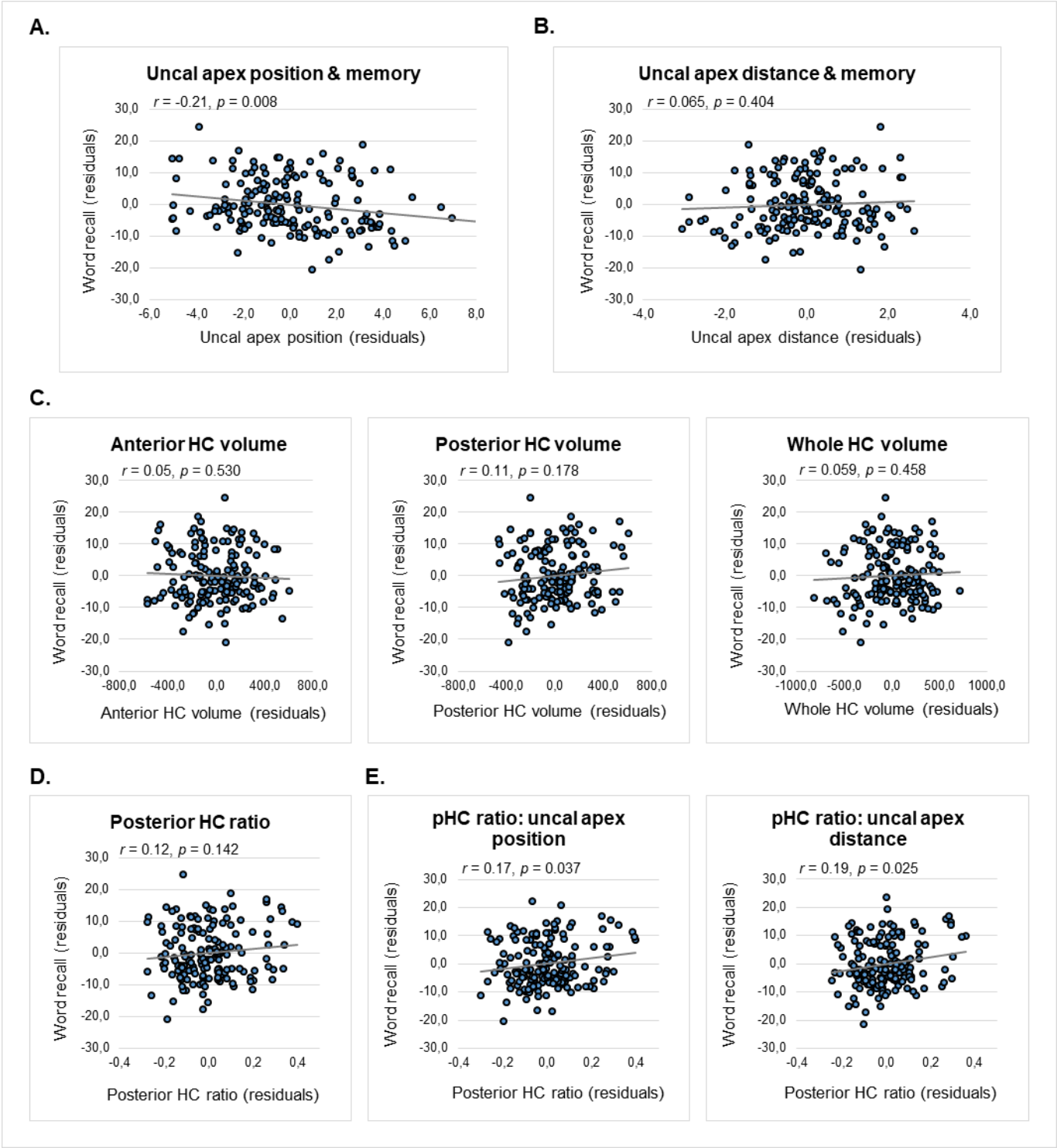


*Figure 4.* Uncal apex and hippocampal volumes as predictors of episodic memory. Partial regression plots of A) Uncal apex position; B) Uncal apex distance; C) Anterior, posterior, and whole hippocampal volume; D) Ratio of posterior to anterior hippocampal volume; E) Ratio of posterior to anterior hippocampal volume when controlling for uncal apex position (left) and uncal apex distance (right); as predictors of episodic memory performance over and above age and sex.

## 4. Discussion

The primary aim of this study was to evaluate the position of the uncal apex as a hippocampal predictor of episodic memory across the healthy adult lifespan, and to characterize the impact of inter-individual differences in uncal apex position on anterior and posterior hippocampal volume as it relates to age and episodic recollection memory.

The uncal apex is the anatomical landmark most commonly used to demarcate the border between the anterior and the posterior hippocampus (Dalton et al., 2017; Duvernoy, 2013; Malykhin et al., 2007; Olsen et al., 2013), but the discovery that it retracts anteriorly with increasing age suggests that it might be unsuitable for this purpose in contexts where the hippocampus undergoes anatomical alterations (Poppenk, 2020). Critically, this anterior displacement may lead to the misclassification of anterior hippocampal tissue as posterior tissue, in turn, over- and underestimating the effects of age on these subregions, respectively (Poppenk, 2020). Furthermore, it is possible that reduced specificity of anterior and posterior volume estimates, due to such misclassification, would impact associations between volume in these regions and aspects of memory function known to vary along the hippocampus longitudinal axis. Inter-individual differences in uncal apex position would particularly impact the ratio of posterior to anterior volume, previously highlighted as a predictor of episodic recollection in young adults (Poppenk & Moscovitch, 2011; Snytte et al., 2020).

In line with the original report (Poppenk, 2020), we observed significant age-related variation in the position of the uncal apex, with an estimated annual difference in the anterior direction across the adult lifespan (20-79 years) of approximately 0.041 mm. To circumvent potential variation being introduced by normalization, we also included an additional, native space, approximation of uncal apex location: the distance in mm from the most anterior point of the hippocampus to the uncal apex. Alternatively, the relative position of the uncal apex along the hippocampus longitudinal extent could have been used – expressed as

the difference in distance between the uncal apex and i) the most anterior point of the hippocampus, and ii) the most posterior point of the hippocampus (Snytte et al., 2022). Whereas Snytte and colleagues (2022) did not observe any age-related variation in this relative measure across the adult lifespan, this estimate should – but does not – account for age-related decreases in the total length of the hippocampus (in the present study, almost twice as large as the estimated shortening of the uncus), likely masking effects of age on uncal apex position. Here, we observed age variation in native-space uncal apex distances consistent with the MNI y-plane coordinates of uncal apex position, with an annual shortening of approximately 0.026 mm.

In support of our hypothesis, we observed that uncal apex position successfully predicted recollection performance over and above age and sex, such that a more anteriorly located uncal apex was linked to lower levels of memory. However, this was not replicated in native-space uncal apex distances. This may warrant some degree of caution when evaluating the association between uncal apex *position* and memory, and necessitates replication in additional samples to establish the source and extent of behaviorally meaningful variation in this normalization-dependent measure. Nevertheless, the two measures consistently displayed similar patterns of impact on associations of hippocampal volume with age and memory.

Whereas anterior hippocampal volume remained stable with increasing age, we observed a non-linear decline of posterior hippocampal volume across the adult lifespan, slightly steeper from the age of approximately 45 years. Controlling for uncal apex position and for uncal apex distance, as to account for potentially misclassified tissue, numerically increased the strength of the association between age and posterior volume, which – in terms of direction – is in line with misclassified anterior tissue contributing to an underestimation of age-related posterior volume decline (Poppenk, 2020). An important question relates to the underlying source of uncal apex displacement in aging. Currently, gray matter atrophy of the anterior hippocampus constitutes the main candidate (Poppenk, 2020), but it is plausible that other

factors, such as alterations in the shape of the hippocampus (Bussy et al., 2021), may contribute – especially in the context of limited anterior volume decline. However, despite limited age-related anterior hippocampal shrinkage in our sample, we did observe that older adults exhibiting the lowest levels of anterior volume also showed the most anteriorly located uncal apex. In contrast, older individuals displaying an average level of anterior volume comparable to that in young adults, showed significantly less anterior displacement of the uncal apex.

Overall, our volumetric findings mirror a general pattern of greatest posterior hippocampal decline evident across both longitudinal (Chauveau et al., 2021; Langnes et al., 2020) and cross-sectional studies covering the adult lifespan (Hoang et al., 2024; Kalpouzos et al., 2009; Malykhin et al., 2008, 2017; Nordin et al., 2018; Snytte et al., 2022) – despite variation in methods – which include native-space uncal apex landmark-based segmentation (Chauveau et al., 2021; Hoang et al., 2024; Malykhin et al., 2008, 2017; Snytte et al., 2022), segmentation based on the MNI coordinate y -21 (Langnes et al., 2020; Nordin et al., 2018), and voxel-wise analyses (Kalpouzos et al., 2009). Although the opposite pattern (i.e., greatest anterior hippocampal decline) has been reported (Ta et al., 2012), most studies that make this observation exclude younger and middle-aged adults (Chen et al., 2010; Gordon et al., 2013; Hackert et al., 2002; Nordin et al., 2017), capturing the age segment across which longitudinal data seem to suggest a steeper anterior age trajectory (Langnes et al., 2020).

Consistent with a specialization of function across the hippocampus longitudinal extent (Grady, 2019; J. Persson et al., 2018; Poppenk et al., 2013; Strange et al., 2014), is the observation that volume of anterior and posterior hippocampal subregions often constitute better predictors of memory performance than estimates of whole hippocampal volume (Hoang et al., 2024; Malykhin et al., 2024; Poppenk & Moscovitch, 2011). Specifically, previous studies in young adults emphasize a trade-off between anterior and posterior volume, such that greater posterior to anterior volume ratios benefit episodic recollection (Poppenk &

Moscovitch, 2011; Snytte et al., 2020). When accounting for the potential misclassification of anterior tissue by controlling for uncal apex position and distance, we similarly observed that recollection memory was predicted by the ratio of posterior to anterior volumes, here, across the adult lifespan. These results align well with longitudinal evidence differentially linking recognition and recollection aspects of episodic memory to anterior and posterior hippocampal volume in aging, respectively (N. Persson & Andersson, 2022), as well as to cross-sectional adult-lifespan data supporting a role of the posterior hippocampus in verbal recollection (Hoang et al., 2024; Malykhin et al., 2024), but contrasts with longitudinal evidence supporting a main role of the anterior hippocampus in verbal recollection memory (Langnes et al., 2020). Although a number of factors other than differences in segmentation methods may underlie inconsistencies in volume-memory associations in aging, our results emphasize the importance of maximizing specificity in anterior and posterior volumetric estimates for efficient prediction of recollection memory, and suggest that accounting for the location of the uncal apex contributes to this.

## 5. Conclusion

Using both normalized and native-space estimates, we demonstrate that the uncal apex shows a significant anterior displacement with increasing age across the adult lifespan, and that accounting for its position contributes to the efficacy of hippocampal volume in predicting episodic recollection performance. Importantly, our results indicate that normalized y-plane coordinates denoting uncal apex position may successfully predict memory performance on their own, however, this should be further evaluated in independent samples and across several measures of memory. Ultimately, longitudinal data is necessary to evaluate displacement of the uncal apex in aging and the underlying factors contributing to this anatomical change.

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**Data availability statement**

Data from the DyNAMiC study are not publicly available. Access to the original data may be shared upon request from the Principal investigator, Dr. Alireza Salami.

**Conflict of interest statement**

The authors declare no conflict of interest.

**Ethical approval**

The DyNAMiC study was approved by the Regional Ethical board in Umeå, Sweden (ref. no 2017/248-31).

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