Effects of Aging and Alzheimer's Disease Along the Longitudinal Axis of the Hippocampus

Brian A. Gordon[a,*], **Tyler Blazey**[b], **Tammie L. S. Benzinger**[b], and **Denise Head**[a,b]

[a]Department of Psychology, Washington University in St. Louis, St. Louis, MO, USA

[b]Department of Radiology, Washington University in St. Louis, St. Louis, MO, USA

Abstract

The hippocampus is often treated as a uniform structure, but possesses differential projections to surrounding cortex along its longitudinal axis. This heterogeneity could create varied susceptibility to pathological influences, potentially leading to non-uniform volumetric associations with advancing age and Alzheimer's disease (AD). Previous examinations of aging and AD effects on hippocampal subdivisions have produced highly discrepant findings. To clarify these inconsistencies, we examined the hippocampal head, body, and tail in a large sample of 292 cognitively normal, 37 very mildly demented, and 18 mildly demented individuals, divided into two independent samples. As often done in the literature, we characterized qualitative patterns across these regions, but extended these results by explicitly testing for quantitative differences. In each sample of cognitively normal individuals, the head and body demonstrated greater age effects than the tail. In each sample contrasting AD and cognitively normal individuals, all three regions showed significant volume reductions, with the greatest effect on the head. When examining increasing severity of dementia, the hippocampal head showed progressive volume loss, while the body and tail did not. The patterns of results examining both aging and AD were relatively consistent across the independent samples. These results indicate that there is an anterior-to-posterior gradient of loss within the hippocampus with both advancing age and AD.

Keywords

Brain aging; dorsal hippocampus; long-axis; ventral hippocampus

INTRODUCTION

The hippocampus is highly studied in examinations of healthy aging and Alzheimer's disease (AD). Total hippocampal volume declines across the adult lifespan [1, 2], and this pattern accelerates with advancing age [1–5]. Similarly, total hippocampal volume is reduced in cross-sectional examinations of AD [6–10], and progressively declines with increasing cognitive impairment [11]. Total hippocampal volume is a sensitive predictor for future impairment [12–16], and for the progression from mild to more severe stages of AD [17–19].

*Correspondence to: Brian A. Gordon, Department of Psychology, One Brookings Drive, Box 1125, St. Louis, MO 63130-4899, USA. Tel.: +1 314 935 7596; Fax: +1 314 935 4711; bagordon@wustl.edu.

The hippocampus is not a uniform structure, but has subdivisions differentially connected with surrounding cortices. Visual, auditory, and somatosensory association cortices are preferentially connected with the dorsal (posterior in humans) hippocampus [20, 21], while the ventral (anterior in humans) hippocampus has preferential indirect and direct connections with the amygdala, rostral hypothalamus, and subcortical nuclei involved in neuroendocrine and autonomic regulation [20–22]. Lesion studies have further elucidated the potential functional roles of these anatomical divisions of the hippocampus. Double dissociations are found in rodent work such that lesions to the dorsal hippocampus differentially impair spatial learning [23, 24], but spare fear conditioning and anxiety-related behaviors, whereas lesions to the ventral hippocampus have the opposite pattern of effects [22, 23, 25–27]. These structural and functional differences are mirrored at the molecular level, where gene expression significantly varies across the hippocampus [20, 28, 29]. The combination of these structural, functional, and molecular differences is thought to create unique vulnerabilities to pathological influences across the extent of the hippocampus (see [30]).

Subdivisions along the longitudinal axis of the hippocampus have been examined to determine if detrimental influences affect hippocampal volume uniformly or in a graded manner. For aging, the results have been inconsistent, with several researchers finding the greatest age-related associations with anterior regions [10, 31, 32], or effects in both anterior and posterior regions [33]. Other researchers have found greater posterior atrophy [34–37], or no significant differences along the longitudinal axis [38]. Similarly for AD, there is some evidence of greater volumetric differences between healthy controls and AD individuals in anterior portions of the hippocampus [10, 36, 39], but this is not always observed [40, 41].

These disparate findings may be driven by a number of factors. Many of the studies of both aging and dementia have been conducted on relatively small samples of the population, which limits their power as well as the reliability of the findings. The current literature is further complicated by the utilization of various methodologies to assess subregions along the longitudinal axis, including manual tracing [10, 31, 39–41] and voxel-based morphometry (VBM) [33–35]. Many of the studies using a form of manual volumetry only report numeric differences in percent change, beta weights, or correlation values [10, 31, 39, 40], but do not test statistical differences between subdivisions. Similarly, VBM analyses indicate where an effect is located, but provide no quantitative comparisons of differential strengths of associations across the hippocampus, and may exaggerate age-related volumetric differences compared to manual tracing [42]. Thus, much of the existing literature provides only qualitative or descriptive information rather than quantitative results on aging and AD effects along the longitudinal axis. These methodological issues limit the validity and utility of prior claims in the literature about selective or differential effects of aging or AD within the hippocampus.

Using high-resolution magnetic resonance imaging (MRI) scans, we investigate the effects of aging and AD in a well-characterized sample of middle-aged and older adults. The size of the total sample provided the opportunity to utilize two independent samples matched for demographic characteristics. The use of these two samples makes it possible to assess the consistency of any observed age and AD effects to a degree that is impossible utilizing previous work. In addition, *each* independent sample in the current investigation consists of a larger sample than the *total* sample in all but one study in the existing literature examining aging [37] and two of the four studies on AD [40, 41]. Further, we specifically test the relative strength of associations across the three subdivisions. In this way, observed numeric differences are explicitly tested to move beyond purely qualitative interpretations.

METHODS

Participants

Structural data were obtained from participants recruited from the Knight Alzheimer's Disease Research Center (ADRC) at Washington University. A subsample ($n = 155$) of the cognitively normal middle-aged and older adults were recruited as part of an ongoing study at the ADRC on adult children whose parents were or were not diagnosed with AD [43]. A potential pool of 465 participants was screened for health conditions as well as for the quality of the MRI segmentations (see MRI analysis section below for details). Individuals were screened for major medical conditions (i.e., Parkinson's disease, Huntington's disease, seizures, major head injury, heart attack, stroke, transient ischemic attack), and non-AD dementia (i.e., frontotemporal dementia, Lewy body dementia, or family history of early onset dementia). Clinical diagnoses were made in accordance with standard criteria [44–46]. Based on the Clinical Dementia Rating scale (CDR) [45, 46], participants were classified as cognitively normal (CDR = 0), very mildly demented (CDR = 0.5), or mildly demented (CDR = 1). The final sample consisted of 347 individuals aged 45 to 95 (CDR 0 = 292, CDR 0.5 = 37, CDR 1 = 18).

Cognitively normal participants were randomized into one of two samples matched on gender and age. A similar procedure was done for the AD group, but additionally matching for dementia severity so that an equal number of CDR = 0.5 and CDR = 1 participants were assigned to each AD sample (see Table 1 for characterizations of each sample). When examining the effects of AD, one cognitively normal sample and AD sample were paired together.

Cognitively Normal Samples 1 and 2 did not significantly differ on demographic characteristics based on χ^2 statistics or t-tests. AD Samples 1 and 2 did not significantly differ on demographic characteristics. When comparing Cognitively Normal and AD Samples 1, the AD individuals had significantly higher Geriatric Depression Scale (GDS) scores ($t_{1,171} = -3.14$, $p < 0.005$), had fewer years of education ($t_{1,171} = 1.41$, $p < 0.01$), were older ($t_{1,171} = -3.63$, $p < 0.001$), had a greater frequency of the apolipoprotein E (ApoE) $\varepsilon 4$ allele ($\chi^2 = 4.11$ $p < 0.05$), and had a greater incidence of heart problems ($\chi^2 = 8.25$, $p < 0.005$). A similar pattern was seen in the comparison of Cognitively Normal and AD Samples 2 such that AD individuals were significantly higher on GDS scores ($t_{1,172} = -4.59$, $p < 0.001$), older ($t_{1,172} = -3.67$ $p < 0.001$), and had a greater frequency of the ApoE $\varepsilon 4$ allele ($\chi^2 = 5.23$, $p < 0.05$).

APOE genotyping

TaqMan assays (Applied Biosystems, Foster City, USA) for both rs429358 (ABI#C 3084793 20) and rs7412 (ABI#C 904973 10) were used for *APOE* genotyping. Allele calling was performed using the allelic discrimination analysis module of ABI Sequence Detection Software. Positive controls for each of six possible *APOE* genotypes were included on the genotyping plate.

MRI imaging protocol

Up to two T1-weighted MPRAGE scans (TR = 2400 ms, TE = 3.16 ms, flip angle = 8°, TI = 1000 ms, 1 mm × 1 mm × 1 mm resolution, 256 mm FOV) were acquired in the sagittal direction on a Siemens 3T Trio scanner. Multiple scans for an individual were aligned using a rigid body transform and averaged together. There were on average 2.9 (SD = 7.2) months between scan acquisition and clinical assessment.

MRI analysis

Delineation of the total hippocampus—Automatic anatomic parcellations of the T1 images were obtained using the Freesurfer 5.1 [47] (http://surfer.nmr.mgh.harvard.edu/) image analysis suite. Each voxel in an MR image is assigned a neuroanatomical label based on probabilistic information from a manually labeled training set. This procedure is highly robust and generates anatomical labeling and regional volume estimates with a high correspondence to manually generated labels [48, 49], and its delineation of the hippocampus has been validated in normal aging, mild cognitive impairment, and AD [50]. Furthermore, the application of an automated procedure to outline the hippocampus facilitates expanding analyses to a much larger sample than previously examined. MRI data were examined to exclude individuals with improper hippocampal segmentations. From the initial sample of 465 individuals, two participants were excluded due to errors in the segmentation process. The structural scans were checked for gross anatomical issues (e.g., enlarged ventricles), and radiological reads were consulted to eliminate individuals with signs of pathology. One additional individual was excluded due to an abnormally large ventricle attributed to a congenital defect.

Delineation of subdivisions along the longitudinal axis—First, images were placed into Talairach stereotaxic space for manual division along the longitudinal axis using an atlas containing both younger and older adults. This was done to assure that all of the hippocampi were aligned to the same orientation before division. Second, boundary slices between hippocampal subdivisions were identified. The protocol for selecting boundary slices was based on Malykhin and colleagues [36]. This protocol is based on anatomical boundaries that are consistent with the differential patterns of connectivity across the longitudinal axis [36]. Moving anterior to posterior, while viewing coronal images, the boundary between hippocampal head and body was determined as the last slice on which the uncus was visible. The boundary between body and tail was determined as the first slice that the fornix was clearly separated from the pulvinar (see Fig. 1). The boundaries were manually determined by one of two raters, and the y-coordinate of this slice was recorded. Boundary slices were determined independently for each hemisphere. A locally generated algorithm used this boundary information to parse the Freesurfer-delineated hippocampus into regions representing the head, body, and tail by automatically assigning a unique categorical value to voxels in each region (e.g., voxels anterior to the boundary slice for the head were designated "10," those from the first to second boundary as "20," and those posterior to the boundary separating the body and the tail a "30"). This hippocampal mask was placed back into native space providing subdivision labeling. As the voxels were 1 mm isotropic, summing the number of voxels with each label provided volumetric estimates for that hippocampal subdivision. Volumes were adjusted for total intracranial volume using a covariance approach [51] and summed across hemispheres, as there were no *a priori* hypotheses regarding laterality.

Inter-rater reliability

The anatomical boundaries were manually determined by one of two raters, blind to any information about the individual. Both raters segmented ten randomly selected brains to compute inter-rater reliability using intraclass correlations (ICC) [2] [52]. Reliability was above 0.90 for all subdivisions.

Analytic approach

Covariates—Health variables (mild heart problems, hypertension, diabetes, brief head trauma) were coded for absence (0) or history (1). Depressive symptomatology was measured using the GDS [53]. Depression information was not available for one AD and

two cognitively normal participants. Their values were imputed with the mean score for their respective group.

Using the entire sample, demographic and health variables with a significant bivariate correlation with any of the volumes were considered as covariates. Gender, years of education, delay between MRI and clinical assessment, history of heart problems, history of hypertension, and GDS scores were covariates for all analyses. When examining AD effects, age and age-squared were also treated as covariates.

The cognitively normal older adult sample draws partially upon a population of individuals with a parental history of AD [43]. ApoE ε4 allele genotype information was available to code participants for the absence (0) or presence (1) of the ApoE ε4 allele to represent this genetic risk within our cognitively normal individuals. Using the entire cognitively normal sample, hierarchical regressions were used to examine the main effect of ApoE genotype as well as the ApoE genotype by age interaction after modeling the effects of all covariates as well as age and age squared. These analyses were conducted to alleviate any concerns that our sample of cognitively normal older adults contained effects that could be due to individuals particularly at-risk for developing AD. There were no main effects of ApoE genotype on the head ($F_{1,282} = 0.04$, $p = 0.83$), body ($F_{1,282} = 0.10$, $p = 0.83$), or tail ($F_{1,282} = 0.62$, $p = 0.43$), nor a genotype by age interaction for the head ($F_{1,281} = 0.32$, $p = 0.58$), body ($F_{1,281} = 0.08$, $p = 0.78$), or tail ($F_{1,282} = 0.10$, $p = 0.75$). As these effects were all nonsignificant, the influence of ApoE was not considered further.

Statistical analyses—To quantify the strength of relationships across the three hippocampal subdivisions, partial correlations were calculated between the factors of interest (i.e., age or AD status) and each region controlling for all covariates. The differential strengths of these relationships were compared using a test of correlated correlations [54, 55] that uses a standard normal z-distribution to assess statistical significance. This test compares the strength of the correlations while taking into account shared variance. This provided a quantitative test that is impossible to gather simply by presenting beta weights, percent change, or correlation values [10, 31, 39]. Additionally, it is not influenced by disparities in volume between the three hippocampal subdivisions.

Sets of hierarchical regressions were fit for each hippocampal subdivision to specifically assess the consistency of age and AD effects across samples. For the hierarchical model examining age, all covariates were entered in the first step, age was entered in the second step, age-squared in the third, a main effect of sample entered in the fourth step, and a sample by age interaction term was entered into the fifth step. Similarly the entire sample was used to compare AD effects across the two samples. In the hierarchical model examining AD effects, all covariates, including age and age-squared, were entered in the first step, AD status was entered in the second step, the main effect of sample was entered into the third step, and an interaction term between sample and AD status entered in the fourth step of the regression. These models served to measure the consistency of the observed aging and AD effects across the two samples.

RESULTS

Age effects

Relationships between age and hippocampal volumes controlling for all covariates are illustrated in Fig. 2. This relationship without controlling for covariates is presented in Supplementary Figure 1 and zero-order correlations are in Supplementary Table 1. In Cognitively Normal Sample 1, age was significantly negatively correlated with the head ($r_{partial} = -0.442$, $p < 0.001$), body ($r_{partial} = -0.447$, $p < 0.001$), and tail ($r_{partial} = -0.273$, p

< 0.01). The effect of age did not differ significantly between the head and body (Z = 0.06, p = 0.48). However, both the head and body evidenced greater effects of age than the tail (Z = −1.89 and Z = −1.86, ps < 0.05, respectively). There was a significant non-linear effect of age in the body ($r_{partial}$ = −0.204, p < 0.05), but not the head ($r_{partial}$ = −0.073, p = 0.39), or the tail ($r_{partial}$ = 0.063, p = 0.36). When comparing the non-linear effects of age across the three subdivisions, the strength of the correlations did not differ between the head and body (Z = 1.30, p = 0.10) nor the body and tail (Z = −1.34, p = 0.09), but did between the body and the tail (Z = 2.60, p < 0.05).

In Cognitively Normal Sample 2, age was significantly negatively correlated with volume in the head ($r_{partial}$ = −0.561, p < 0.001) and body ($r_{partial}$ = −0.241, p < 0.005), but not the tail ($r_{partial}$ = −0.039, p = 0.65). The age effect was greater for the head than the body (Z = −4.11, p < 0.001) or the tail (Z = −6.21, p < 0.001), and greater for the body than the tail (Z = −2.14, p < 0.05). There was a significant non-linear effect of age in the body ($r_{partial}$ = −0.186, p < 0.05) with neither the head ($r_{partial}$ = −0.086 p = 0.31) nor the tail ($r_{partial}$ = −0.019, p = 0.83) showing a significant non-linear association. When comparing the nonlinear effects of age across the three subdivisions, the correlations did not significantly differ between the head and body (Z = 1.08, p = 0.14), nor the head and the tail (Z = −0.70, p = 0.24), but the non-linear effect of age was greater for the body than the tail (Z = −1.76, p < 0.05).

In the analysis specifically examining the effects of sample (see Supplementary Table 2 for full results), there was a main effect of sample on the hippocampal head ($F_{1,282}$ = 13.73, p < 0.001) with a larger volume in Cognitively Normal Sample 1. There were no main effects of sample on the body ($F_{1,282}$ = 1.19, p = 0.28) or tail ($F_{1,282}$ = 2.17, p = 0.14). There was a significant sample by age interaction in the body ($F_{1,281}$ = 4.48, p < 0.05) with Cognitively Normal Sample 1 demonstrating a larger age effect. There were no significant interactions for the head ($F_{1,281}$ = 1.51 p = 0.22) or tail ($F_{1,281}$ = 2.03, p = 0.16).

AD effects

Associations between hippocampal volumes and AD were first examined in two independent samples collapsed across dementia severity (CDR = 0.5 and 1). Unadjusted means and standard deviations for hippocampal volumes for the four samples are presented in Table 1, and estimated marginal means controlling for all covariates are depicted in Fig. 3. In AD Sample 1, AD status was negatively associated with volume for the head ($r_{partial}$ = −0.466, p < 0.001), body ($r_{partial}$ = −0.304, p < 0.001), and tail ($r_{partial}$ = −0.267, p < 0.001). AD effects were stronger for the head compared to the body (Z = −1.95, p < 0.05) and tail (Z = −2.59, p < 0.01), but the effects did not differ between the body and the tail (Z = −0.40, p = 0.34).

In the second sample, AD was significantly negatively associated with volume for the head ($r_{partial}$ = −0.286, p < 0.001) and the body ($r_{partial}$ = −0.176, p < 0.05), but not the tail ($r_{partial}$ = −0.107, p = 0.17). The AD effect was stronger for the head compared to the tail (Z = −2.13, p < 0.05), but did not differ between the head and body (Z = −1.32, p = 0.10) nor between the body and the tail (Z = −0.79, p = 0.21).

In the analysis specifically examining the effects of sample (see Supplementary Table 3 for full results), there was a main effect of sample on the hippocampal head ($F_{1,336}$ = 10.78, p < 0.001) with Sample 1 having a slightly larger head, but no main effects in the body ($F_{1,336}$ = 0.28, p = 0.60) or tail ($F_{1,336}$ = 0.664, p = 0.42). There were no significant sample by AD interactions in the head ($F_{1,35}$ = 2.02, p = 0.16), body ($F_{1,335}$ = 2.79, p = 0.10), or tail ($F_{1,335}$ = 3.36, p = 0.07).

An additional analysis was done in the full sample (n = 347) now separating cognitively normal (CDR = 0), very mild (CDR = 0.5), and mild (CDR = 1) AD groups. Estimated marginal means are depicted in Fig. 3. Increasing dementia severity was associated with reduced volumes for the head ($r_{partial}$ = −0.403, $p < 0.001$), body ($r_{partial}$ = −0.244, $p < 0.001$), and tail ($r_{partial}$ = −0.185, $p < 0.001$). There was a greater effect of dementia severity on the head than the body (Z = −2.73, $p < 0.01$) and the tail (Z = −3.87, $p < 0.001$) but the body and tail did not significantly differ (Z = −0.94, p = 0.17). Pairwise comparisons indicated that all three subdivisions differed between cognitively normal participants and each of the AD groups (p's < 0.05), but only the head was significantly different between CDR = 0.5 and CDR = 1 ($t_{(45)}$ = 2.7, $p < 0.01$).

DISCUSSION

Previous examinations of the differential effects of advancing age or AD on hippocampal subdivisions have yielded mixed findings, and are limited by a number of methodological concerns. To address the discrepancies found across prior work, we examined age and AD effects on hippocampal subdivisions in two large independent samples of middle-aged and older adults. The two samples provided a way to assess the reliability of our observed results. Additionally, we statistically compared the strength of associations across hippocampal subdivisions. In this way, our observed results go beyond the purely qualitative analyses often put forward in the existing literature.

Across the two samples, both the head and body demonstrated significantly greater linear age effects than the tail. Further, the magnitude of the age effects on the head and tail did not significantly differ across samples. The magnitude of the influence of age on the body varied across the two samples, although the direction of the effects was consistent. Thus, in Cognitively Normal Sample 1, there was a stronger effect of age on the head than the body, but in Cognitively Normal Sample 2, the age effects on the head and body were similar in magnitude. It is beyond the scope of the current work to fully address the underlying mechanisms of the discrepancy in age effects in the body across samples. One issue is that the body may have a greater mixture of anatomical connections than the head and tail [22]. Future work is needed to clarify how variance in underlying anatomical connections may give rise to the variability observed.

Taken together, the analyses of these two samples affirm a general anterior-to-posterior gradient in the effects of advancing age. An awareness of such variability is particularly important when trying to understand relationships between structural and behavioral measures. For example, mixed findings associating hippocampal volume with memory performance in aging samples [56] may be clarified by examining subdivisions along the longitudinal axis.

In general, the entirety of the hippocampus demonstrated atrophy in individuals with AD compared to cognitively normal individuals. When comparing cognitively normal individuals to those with early-stage AD, regardless of severity (collapsed CDR = 0.5 and 1), the head of the hippocampus evidenced greater volumetric differences than the tail in both samples. In addition, the magnitude of the AD effects did not differ across samples. Furthermore, in the combined sample, the head declined in a graded fashion between CDR = 0 to 0.5 to 1, whereas the body and tail did not. This selectivity is consistent with work indicating the sensitivity of anterior regions to an increasing severity of cognitive impairment [10, 19, 37, 39]. Correlating commonly used biomarkers of AD (e.g., cerebrospinal fluid and PET measures of amyloid and tau) and cognitive measures with volume estimates of specific hippocampal subdivisions may provide a fuller characterization

of disease progression as well as provide an additional marker to examine cognitively normal individuals at risk for developing AD.

Greater anterior atrophy with both advancing age and AD may be associated with dysregulation of the hypothalamic-pituitary-adrenocortical (HPA). The hippocampus is a target of stress hormones released by the HPA axis, which is integral to the regulation of the stress response. The ventral (anterior) hippocampus has preferential connections with subcortical and hypothalamic nuclei involved in neuroendocrine function [20–22] and provides negative feedback to the HPA [57, 58]. This may predispose the anterior hippocampus to exhibit the most volume loss when HPA function is disrupted. Dysregulation of such neuroendocrine function has long been linked with advancing age [57–59], and has also been implicated in other disorders such as AD [60, 61], clinical depression [62], and chronic stress [63]. Coupled with knowledge about hippocampal projections to surrounding tissue, examining the subdivisions of the hippocampus may provide a richer understanding of these conditions.

The extant literature has varied in terms of the methods used to delineate hippocampal subdivisions, the age ranges studied, and the size of the sample populations. Protocols for delineation of the hippocampal subdivisions have included VBM [33, 35, 37], percentages of total hippocampal length on manually outlined hippocampi [31, 41], as well as manual identification of anatomical boundaries on manually outlined hippocampi [10, 32, 33, 36, 39]. The anatomical boundaries used for delineation are generally similar across studies, although some manual delineations leave out large parts of the hippocampal tail [10, 31, 34, 40]. Research that has reported greater posterior effects of aging utilized voxel-based methodologies [35, 37]. The differences between this approach and region of interest volumetric measurements may partially account for the contradictory findings in the literature examining aging, as systematic discrepancies between the two have been observed before [42]. In terms of age range, studies including younger adults have found both the greatest [32] and least [34, 36] declines in anterior regions. Thus, differences in age range do not explain the discrepancies in the literature. The current study included individuals from middle age through older adulthood. The extension of these analyses to include younger adults would provide a fuller characterization of differences throughout the lifespan. Prior work examining aging that has reported an anterior-to-posterior gradient has utilized sample sizes comparable to each of the independent samples examined here [10, 31]. In contrast, studies reporting greater posterior declines have had a small sample size (n's < 45) [34–36]. Similarly, failure to detect significantly greater AD effects in anterior regions in past literature [40, 41] is likely related to small sample sizes (<20).

There are a number of important issues to take into account in considering the current work. The cognitively normal participants include a subset of individuals with a parental history of AD, which potentially limits the generalizability of the current findings. In addition, the results presented here do not represent change with age or AD status over time, but are derived from cross-sectional data. Future work comparing longitudinal and cross-sectional data is needed to expand upon the current results. Furthermore, the sample sizes for the cognitively normal groups were much larger than the sample sizes for the AD groups, thus the estimates of aging effects may be more robust than those for AD effects. However, the magnitudes of the aging and AD effects observed here were generally consistent with those reported in previous literature (e.g., [31–33, 37–39, 41]). Finally, underlying effects on hippocampal subfields may contribute to the effects of age and AD observed across the three subdivisions. Analyses indicate an unequal distribution of hippocampal subfields across the head, body, and tail [64], such that the head contains the bulk of the subiculum and cornu ammonis 1–3, while the largest portion of the dentate gyrus is located in the body. Understanding these relationships provides a potential connection between research

examining subdivisions along the longitudinal axis in aging and AD to investigations assessing hippocampal subfields.

The work presented here expands upon previous investigations examining the effects of healthy and pathological aging across the longitudinal axis of the hippocampus. Along with careful screening criteria, the use of identical methodologies across two samples allowed for more robust determination of the effects of age and AD. We clarify previous work by examining the consistency across the two samples, as well as specifically testing the differential strength across the head, body, and tail rather than relying on qualitative approaches. We demonstrated an anterior-to-posterior gradient in the effects of both aging and AD in two cross-sectional examinations. This pattern supports the idea that the differing patterns of anatomical connectivity across the hippocampus may predispose subdivisions to specific types of vulnerability and illustrates the utility of parcellating the hippocampus.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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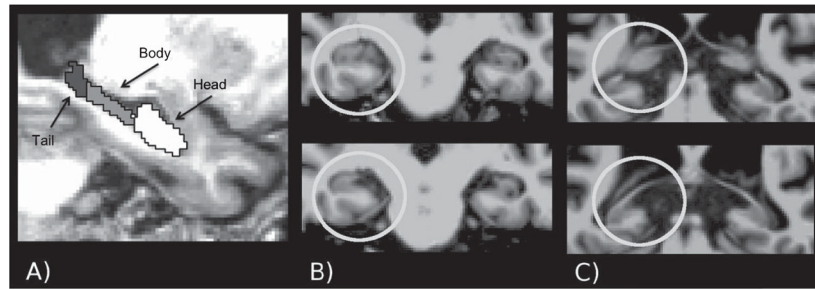
Fig. 1.
Example illustration of the subdivisions of the hippocampus: A) segmented hippocampus;
B) top panel: the last slice with the uncus present, bottom panel: the first slice with the uncus
absent; C) top panel: illustrates the fornix still immersed in the pulvinar, bottom panel: the
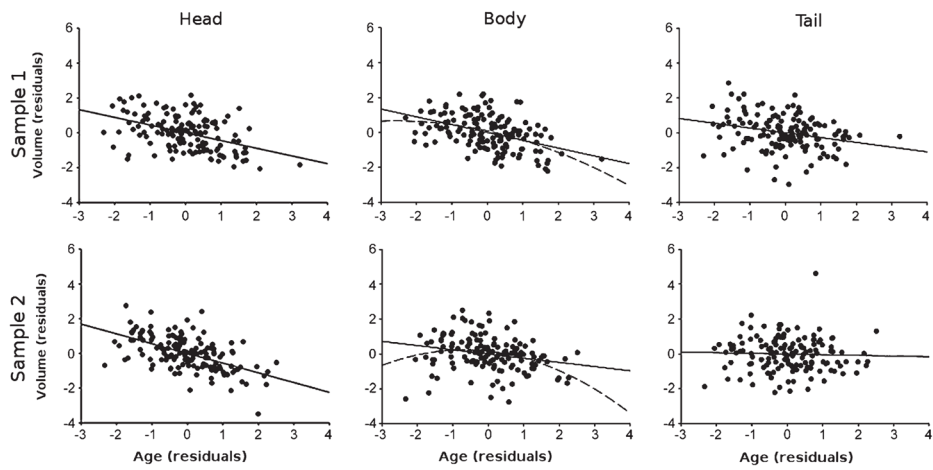fornix clearly separated from the pulvinar.

Fig. 2.
Age effects on hippocampal volumes. Top row: Cognitively Normal Sample 1; Bottom row: Cognitively Normal Sample 2. Values represent residuals controlling for covariates (see text for details). The solid line represents the linear effect while the dashed lined is the quadratic effect.
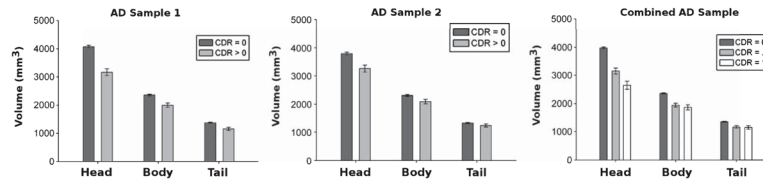
Fig. 3.
AD effects on hippocampal volumes. Left) Sample 1; Middle) Sample 2; and Right) Full Sample. Bars represents estimated marginal means (controlling for covariates; see text for details) and error bars are standard error of the mean.

Table 1

Means and standard deviations for sample characteristics

	CN Sample 1	CN Sample 2	AD Sample 1	AD Sample 2
Subjects (n)	146	146	27	28
Age	68.7 (9.9)	68.7 (9.7)	76.1 (10.9)	75.8 (7.3)
Gender (f/m)	102/34	102/34	14/13	16/12
Education	16.1 (2.7)	15.7 (2.6)	14.6 (2.4)	14.6 (3.3)
GDS	1.1 (1.5)	1.2 (1.6)	2.2 (2.0)	3.0 (3.1)
Lag	3.6 (8.2)	2.8 (7.1)	1.3 (4.4)	1.3 (3.3)
ApoE ε4 status	35%	34%	56%	57%
Head	4095.4 (677.1)	3848.9 (751.2)	3040.8 (665.7)	2965.1 (718.0)
Body	2369.4 (423.3)	2316.8 (442.7)	1890.0 (338.6)	1999.0 (353.9)
Tail	1383.4 (279.9)	1334.5 (283.2)	1098.4 (227.4)	1177.7 (229.3)

CN, Cognitively Normal; AD, Alzheimer's disease, f, female; m, male; GDS, Geriatric Depression Scale; Lag, interval (months) between MRI and clinical assessment, ApoE ε4 status, percent of the sample with at least one ε4 allele. Volumetric measures for the head, body, and tail are mm^3.