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AGE-RELATED CHANGES IN THE MESIAL TEMPORAL LOBE: THE PARAHIPPOCAMPAL WHITE MATTER REGION

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Abstract

The perforant pathway originates from cells in the entorhinal cortex and relays sensory information from the neocortex to the hippocampus, a region critical for memory function. Imaging studies have demonstrated structural alterations in the parahippocampal white matter in the region of the perforant pathway in people at risk for developing Alzheimer's disease. It is not clear, however, if changes noted in this region are indicative of pathological aging or are a function of the normal aging process. We compared MRI-derived mesial temporal lobe volumes in 51 healthy older individuals and 40 young participants, with an emphasis on the parahippocampal white matter. Yearly clinical evaluations showed that 9 of the older cohort declined in cognitive function. Parahippocampal white matter, hippocampal and entorhinal cortex volumes were significantly reduced in healthy older people who remained stable over time compared to young participants. These findings suggest that volume differences in mesial temporal lobe gray and white matter structures may take place as a result of the normative aging process.

Keywords

imaging; aging; memory; hippocampus; entorhinal cortex

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Disclosure statement

The authors report no actual or potential conflicts of interest or financial gains. The data contained in the manuscript being submitted has not been previously published, has not been submitted elsewhere and will not be submitted elsewhere while under consideration at Neurobiology of Aging. All procedures were approved by the institutional review board of the participating institutions. All authors have reviewed the manuscript and approve of its contents.

1. Introduction

The entorhinal cortex and hippocampus are part of the mesial temporal lobe memory system (Squire and Zola-Morgan 1991; Young et al., 1997). Neurons of the entorhinal cortex receive multimodal sensory information from primary sensory and association cortices (Amaral et al., 1987; Van Hoesen and Pandya 1975a; Van Hoesen et al., 1975) and relay this information to the hippocampus via the axons that make up the perforant pathway (Hyman et al., 1984; Van Hoesen and Pandya 1975b).

Quantitative structural magnetic resonance imaging (MRI) techniques provide a tool for examining alterations in brain anatomy *in vivo* during healthy and pathological aging. Such changes in anatomy can be used as a proxy measure of the underlying pathology in neurodegenerative diseases. For example, using such techniques, a number of studies have now reported that atrophy of the entorhinal cortex and hippocampus, structures known to be pathologically involved very early in Alzheimer's disease (AD, Braak and Braak, 1991, 1995; Braak et al., 1998), can provide sensitive markers of risk for AD among older people with mild cognitive impairment (MCI) or subjective cognitive complaints (Cardenas et al., 2002; Chao et al., 2010; deToledo-Morrell et al., 2004; Devanand et al., 2007; Dickerson et al., 2001; Jack et al., 1999; Jessen et al., 2006; Killiany et al., 2000, 2002; Saykin et al., 2006; Stoub et al., 2005; Tapiola et al., 2008). These results are not surprising, since memory dysfunction is one of the earliest hallmarks of AD.

In addition to gray matter regions, there has recently been increased interest in assessing structural changes in white matter regions in those at risk for AD, as well as in healthy older adults (Allen et al., 2005; Bartzokis et al., 2001, 2003, 2004; Guttmann et al., 1998; Good et al., 2001; Jernigan et al., 2001; Raz et al., 2005; Resnick et al., 2003; Rogalski et al.,2009; Salat et al., 2009; Smith et al., 2007; Stoub et al., 2006). The studies that investigated the effects of aging on cerebral white matter found mostly diffuse decreases in white matter volume associated with aging (Allen et al., 2005; Guttmann et al., 1998; Jernigan et al., 2001; Raz et al., 2005; Resnick et al., 2003; Salat et al., 2009). However, age-related atrophy in the parahippocampal white matter has not received much attention.

Recent work from our laboratory has demonstrated decreased parahippocampal white matter volume in the region of the perforant pathway in people with amnestic mild cognitive impairment (aMCI), who are at risk for developing AD, compared to healthy older controls (Rogalski et al., 2009; Stoub et al., 2006). Such alterations in parahippocampal white matter could degrade information flow from the entorhinal cortex to the hippocampus and contribute to the memory deficit observed in aMCI and very mild AD. It is unclear, however, if volume changes in this region take place as a function of the aging process *per se* or are due to age-related pathological processes.

Investigations in animal models of aging have demonstrated that cell numbers remain the same in layer II of the entorhinal cortex, as well as in hippocampal CA3 and dentate gyrus regions (Rasmussen et al., 1996). However, there is a decrease in synaptophysin markers in CA3 (Smith et al., 2000) and a reduction in actual synapse numbers in the middle molecular layer of the hippocampal dentate gyrus (Geinisman et al., 1986, 1992). Additionally, electrophysiological experiments have shown a decrease in the presynaptic fiber potential in old, memory impaired rats (Barnes, 1979; Barnes and McNaughton, 1980), suggesting a pruning of axon collaterals from the perforant pathway to the dentate gyrus. If there is a cross-species correspondence in the types of brain changes that occur during aging, then the rodent data predict that humans should also show changes in the region of the perforant pathway as a function of age.

The present *in vivo* structural imaging study was undertaken to examine if healthy older individuals show volume changes, compared to younger adults, in the parahippocampal white matter region that includes the perforant pathway. In addition, we investigated the volumes of surrounding structures including the hippocampus and entorhinal cortex, regions important for episodic memory function, such as memory for events and things.

2. Subjects and Methods

2.1 Subjects

Participants included 40 young (mean age=27 years, range 22–36; 22 male and 18 female) and 51 healthy older individuals [mean age=77 years, range 65–89; 14 male and 37 female; mean Mini Mental State Examination (MMSE)=29, range 27–30]. The healthy older participants were recruited from the community for an ongoing longitudinal study (deToledo-Morrell et al., 2004), as well as from two longitudinal clinico-pathologic investigations of aging and AD in older individuals: the Religious Order Study (ROS; Mufson et al., 1999, Bennett et al., 2002) and the Rush Memory and Aging project (MAP; Bennett et al., 2005). Older subjects did not have any cognitive impairment at entry into the study based on neuropsychological tests carried out at the Rush Alzheimer's Disease Center clinic; they were followed yearly with clinical evaluations (total mean follow-up period=7.1 ± 2.5 years, with a range of 3–12 years). Selection of healthy elderly participants required a normal neurological examination, normal cognition and a MMSE (Folstein et al., 1975) score of ≥ 27 (out of a maximum of 30 points). Young subjects were recruited from Rush University Medical Center students and employees, as well as their friends and family members. Subjects in both groups were excluded from entering the study if neurologic, psychiatric and systemic conditions, or a history of temporal lobe epilepsy that could affect mesial temporal lobe structures, were identified. Informed consent was obtained from all participants according to the rules of the Institutional Review Board of Rush University Medical Center.

2.2 MRI acquisition

All subjects received an MRI scan at entry into the study. Scans were acquired with a 1.5 Tesla General Electric Signa scanner, using the manufacturer's 3D Fourier transform spoiled gradient recalled (SPGR) pulse sequence. Acquisition parameters consisted of: 124 contiguous images in the coronal plane, 1.6 mm thick, matrix=256×192, field of view=22 cm, TR/TE=34/7 msec, flip angle=35°, signals averaged=1.

2.3 Regions of Interest Volumes

The volumes of the parahippocampal white matter, entorhinal cortex and hippocampus were determined with the use of the Analyze software package (Mayo Clinic Foundation, Rochester, MN). To correct for individual differences in brain size, volumes were divided by total intracranial volume derived from sagittally formatted 5 mm slices (i.e., normalized). To compute intracranial volume, the inner table of the cranium was traced in consecutive sagittal sections spanning the entire brain. At the level of the foramen magnum, a straight line was drawn from the inner surface of the clivus to the occipital bone. Normalized volume for brain regions of interest was determined using the formula: absolute volume in mm^3/intracranial volume in $mm^3 \times 1000$.

Figure 1 depicts the segmentation of the parahippocampal white matter, entorhinal cortex and hippocampus in a single coronal MRI section for a sample participant. All three volumes were measured from the same oblique coronal sections most commonly used for hippocampal volumetry. Briefly, volumes were computed separately for the right and left hemispheres from coronal slices reformatted to be perpendicular to the long axis of the

hippocampus. The boundaries used for quantifying parahippocampal volume were published previously (Rogalski et al., 2009). Tracing of the parahippocampal white matter began with the slice in which the gyrus ambiens, amygdala and white matter of the parahippocampal gyrus were first visualized. The most caudal slice traced was one slice rostral to the first appearance of the lateral geniculate nucleus. The lateral border of the parahippocampal white matter was defined as the bend that signifies the junction between the parahippocampal white matter and the temporal stem. The medial border was defined as the point at which the white matter meets the gray matter of the entorhinal cortex.

Entorhinal cortex volume was quantified with the use of a protocol developed and validated in our laboratory, technical details of which are presented in Goncharova et al. (2001). For the entorhinal cortex, tracing began with the first section in which the gyrus ambiens, amygdala and the white matter of the parahippocampal gyrus first appeared visible. The superomedial border in rostral sections was the sulcus semiannularis and in caudal sections the subiculum. The shoulder of the collateral sulcus was used as the lateral border. The latter is a somewhat conservative criterion that allowed consistency in tracings and avoided the use of different lateral borders depending on individual differences in the depth of the collateral sulcus (see, for example, Insausti et al., 1998). The lateral border was constructed by drawing a straight line from the most inferior point of the white matter to the most inferior tip of the gray matter. The last section measured was three 1.6 mm sections rostral to the image in which the lateral geniculate nucleus first appeared visible.

The protocol and validation procedures used for quantifying hippocampal volume were published previously (deToledo-Morrell et al., 1997; Wilson et al., 1996). Tracings of the hippocampus started with the first section where it could be clearly differentiated from the amygdala by the alveus and included the fimbria, dentate gyrus, the hippocampus proper and the subiculum. Tracings continued on all consecutive 1.6 mm thick images until the slice before the full appearance of the fornix.

2.4 Memory testing

Episodic memory function was tested using the verbal version of the Buschke ‘controlled learning’ task (Buschke and Grober, 1986; Grober and Buschke, 1987). This task has been shown to distinguish between “apparent” and “genuine” memory deficits in elderly individuals (Buschke and Grober, 1986; Grober and Buschke, 1987), since it controls for attention or the use of inefficient strategies in acquiring information. Participants were asked to learn a list of 16 items presented four at a time as previously described (deToledo-Morrell et al., 2000a). Items were shown as line drawings with one picture in each quadrant of a card. When a category cue was given verbally, the subject had to search, point to and name the object from that category. After this was done for four items, immediate cued recall of the four items was tested by presenting each category cue to the subject. If the subject failed to recall an item in response to its cue, the item was shown again, and the entire process was repeated until immediate cued recall was correct for the four items. Then, the next set of four items was presented until all 16 items were correctly retrieved during immediate cued recall. The search and naming procedure ensured that all participants used the same strategy in processing information and that the items have been correctly encoded.

After the subjects learned the items, three trials of free recall were administered, with each trial being preceded by 20 seconds of interference. On each trial, subjects were allowed a maximum of 2 minutes to name as many of the learned items as possible. Next, a category cue was provided for each item missed on that trial. If the subject still failed to recall the item with the cue, he/she was reminded of the missed item which he/she then repeated. An additional trial of free recall was administered after approximately 60 min to test for delayed recall.

2.5 Statistical Analyses

To evaluate group and hemisphere differences for all measured structures separate 2-way repeated measures analyses of covariance (ANCOVA) were used with gender as the covariate. Group differences in the performance of the verbal memory task were assessed with 1-way ANCOVAs with gender as the covariate.

3. Results

Mean right and left parahippocampal white matter volumes for the healthy old and young participants are presented in Figure 2A. A repeated measures ANCOVA found significant group [$F(2,88)=10.94$, $p=0.001$], but not hemisphere effects, with no significant interaction between them.

Yearly clinical evaluations available for the healthy old cohort demonstrated that of the original 51 participants enrolled, 9 declined in cognitive function during the 7 year follow-up period, with 6 of the 9 receiving a diagnosis of AD (McKhann et al., 1984; mean age of all declining participants was 79 years, range 70–83; 5 male and 4 female; mean MMSE=28, range 27–30). The remaining 3 participants received a diagnosis of amnestic mild cognitive impairment (MCI). Those diagnosed with amnesitc MCI were found to have a deficit in memory only, but did not meet criteria for dementia (Petersen et al., 1999). When young subjects were compared to only the 42 old participants who remained stable over time, the difference in parahippocampal white matter volume between the two groups was smaller, but still significant [$F(1,79)=5.99$, $p=0.017$; see Figure 2B]. These findings suggest that volume reduction in this region is present not only as a function of pathological aging, but also, although to a lesser extent, as a result of the normal aging process.

Since the entorhinal cortex and hippocampus are essential for episodic memory function and are connected via the perforant pathway, we determined if there were age related volumetric changes in these two structures. Volumes for the entorhinal cortex and hippocampus for old participants who remained stable compared to the young are shown in Figure 3. A repeated measures ANCOVA comparing these two groups showed significant group [$F(1,79)=7.26$, $p=0.009$] and hemisphere [$F(1,79)=6.51$, $p=0.013$] differences in hippocampal volume, with no interaction between them. The hemisphere effect was due to the right hippocampus volume being larger than the left for both groups. The analysis for entorhinal cortex volume revealed only a significant group difference [$F(1,79)=6.41$, $p=0.013$].

Memory testing was carried out on 35 of the 40 young participants in the study and on all the old participants. Separate ANCOVAs comparing the stable old and the 35 young subjects revealed a significant difference between the two groups in verbal free recall following the third trial [$F(1,74)=7.80$, $p=0.001$] and in verbal delayed recall [$F(1,74)=10.32$, $p<0.0001$].

We examined the relation between memory performance and right and left hemisphere volumes for the hippocampus, entorhinal cortex and the parahippocampal white matter, in both the young and stable old participants. Each of the three measures was entered singly into a partial correlation analysis with verbal free recall for the third trial and delayed recall as separate dependant variables and gender entered first. The analyses showed a significant relationship between delayed verbal recall and left hippocampal ($r=0.285$; $p=0.013$), as well as left entorhinal cortex ($r=0.262$; $p=0.023$) volumes (Figure 4). There were no significant relationships between delayed recall and either right hippocampal or right entorhinal cortex volumes. Neither left nor right parahippocampal white matter volumes were related to delayed verbal memory performance. Finally, there was no significant relationship between any of the left or right hemisphere volumes and verbal free recall following the third trial.

4. Discussion

The purpose of this study was to determine if older healthy individuals show age-related volume changes in the mesial temporal lobe regions with age, with a specific emphasis on the parahippocampal white matter in the region that includes the perforant pathway. Based on studies in rodent models of aging (Barnes, 1979; Barnes and McNaughton, 1980; Geinisman et al., 1986, 1992) implicating the loss of axon collaterals from the perforant pathway to the dentate gyrus, we hypothesized that similar changes would exist in humans as they age.

The most important finding reported here was that alterations in parahippocampal white matter in the region that includes the perforant pathway occur in healthy older individuals. The strength of this report is that the inclusion of yearly clinical follow-up made it possible to observe cognitive decline in the old participants over time. This allowed the examination of changes in the regions of interest in stable old participants to determine “genuine” age effects. The finding that parahippocampal white matter volumes were reduced in the cognitively stable old cohort suggests that although atrophy in this region occurs as a consequence of early AD-related disease pathology (Kalus et al., 2006; Stoub et al., 2006; Rogalski et al., 2009; Salat et al., 2010; Wang et al., 2010), it is also present, to a lesser extent, during the normal aging process. In addition, Bartzokis (2004) has argued that late-myelinating regions of the brain are more susceptible to myelin breakdown. He cites the parahippocampal region as having a very long cycle of myelination, going into the fifth decade of life which may aid in explaining these findings.

Structural changes in white matter have been reported in the healthy aging population (Allen et al., 2005; Bartzokis et al., 2001, 2003, 2004; Guttmann et al., 1998; Jernigan et al., 2001; Raz et al., 2005; Resnick et al., 2003; Salat et al., 2009; Smith et al., 2007). One of the above studies (Salat et al., 2009), showed a relation between age and white matter volume reduction in multiple regions throughout the brain including the parahippocampal gyrus. However, these authors did not provide a direct comparison of older and young participants, nor did they provide longitudinal follow-up data to track what proportion of their old participants declined in cognitive status over time.

In addition to structural volumetric studies, the integrity of white matter in healthy aging has been investigated using diffusion tensor imaging (DTI) techniques (Head et al., 2004; O’Sullivan et al., 2001; Sullivan et al., 2001; Sullivan et al., 2010; Yassa et al., 2010; Ziegler et al., 2008). Only one of these studies, however, focused on the area of the parahippocampal white matter (Yassa et al., 2010). Using an ultrahigh-resolution protocol and a metric of diffusion not commonly used, these investigators found signal degradation in the perforant pathway in older adults compared to young participants. They did not, however, assess the volume of the white matter in this region.

The results reported here show a significant difference in entorhinal cortex volume between the stable old and young groups. This finding is consistent with previous imaging reports (Du et al., 2006; Fjell et al., 2009; Goncharova et al., 2001; Raz et al., 2005, 2010) that show reduced volumes in healthy aging. However, there have been other studies reporting preservation of entorhinal cortex volume (Insausti et al., 1998; Juottonen et al., 1998). The age-related change in the entorhinal cortex suggests that volume differences in the parahippocampal white matter region may be due to axonal loss in the perforant pathway, as well as other processes such as collateral pruning or demyelination.

The significant reduction in hippocampal volume in the stable old cohort is consistent with the majority of reports in the literature (Head et al., 2008; Jack et al., 2002; Jernigan et al., 2001; Raz et al., 2004, 2005; Rodrigue et al., 2004). However, there have also been human

studies (Sheline et al., 1999; Sullivan et al., 2005) and studies in nonhuman primates (Shamy et al., 2006) reporting no changes in hippocampal volume with age.

Human lesion and imaging investigations have shown that the left hippocampus is involved in verbal information processing, while the right processes non-verbal information (Abrahams et al., 1997; deToledo-Morrell et al., 2000a, 2000b; Jones-Gotman, 1986; Maguire et al., 1997; Rosen et al., 2003; Smith and Milner 1981). Consistent with these previous investigations, the present study showed significant relationships between left hippocampal and left entorhinal cortex volumes and delayed verbal recall. In addition, these findings support previous reports demonstrating a relationship between hippocampal volume and delayed memory performance in the healthy aging population (Golomb et al., 1993, 1994, 1996).

In the present study, the relation between parahippocampal white matter volume and episodic memory function was not significant. Because atrophy or degradation of information flow from the entorhinal cortex to the hippocampus would be expected to be subtle in healthy elderly people, this finding is, perhaps, not surprising. It is remarkable, however, that the change in white matter in this region resembles that found in normally-aging rodents, and suggests that this alteration may be fundamental to brain aging across mammalian species. The reduction in white matter volume reported here may reflect not only pruning of afferent and efferent fibers in the region of the parahippocampal gyrus that includes the perforant pathway, but also partial demyelination in remaining fibers, as has been observed in frontal and visual cortex of a non-human primate model of aging (Nielsen and Peters, 2001; Peters and Sethares, 2002; Makris et al., 2007).

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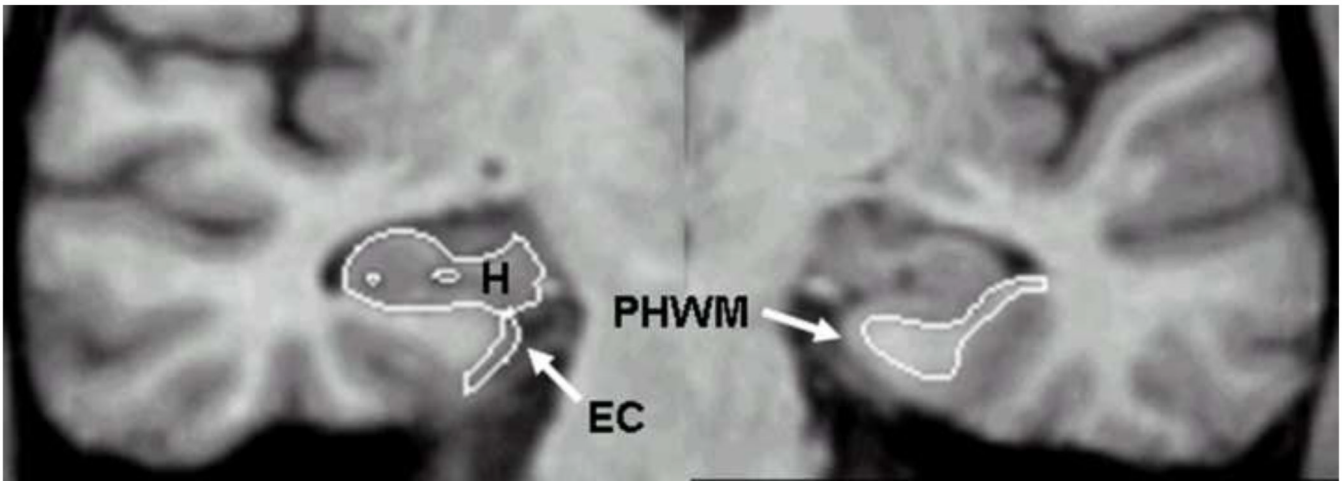

Figure 1.
A single coronal slice illustrating the segmentation of the parahippocampal white matter (PHWM), entorhinal cortex (EC) and hippocampal formation (H).

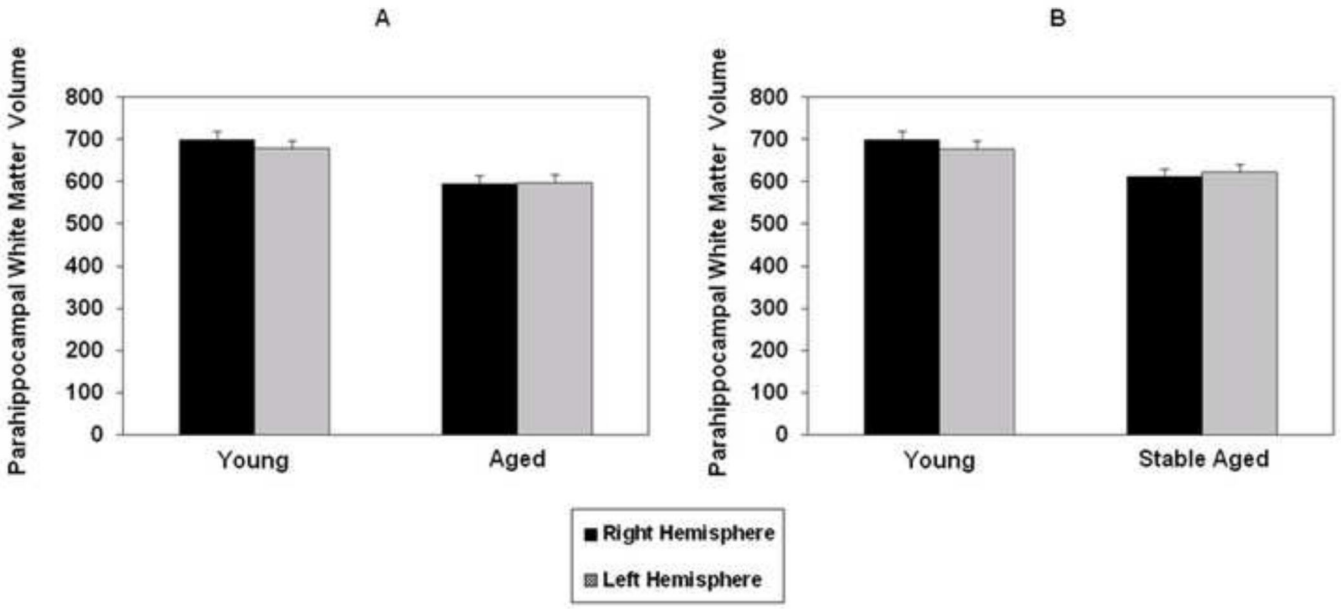

Figure 2.

Mean normalized right and left parahippocampal white matter volume in all aged subjects **(A)** and only those who remained stable during the follow-up period **(B)** compared to young participants. Vertical bars represent the standard error of the mean.

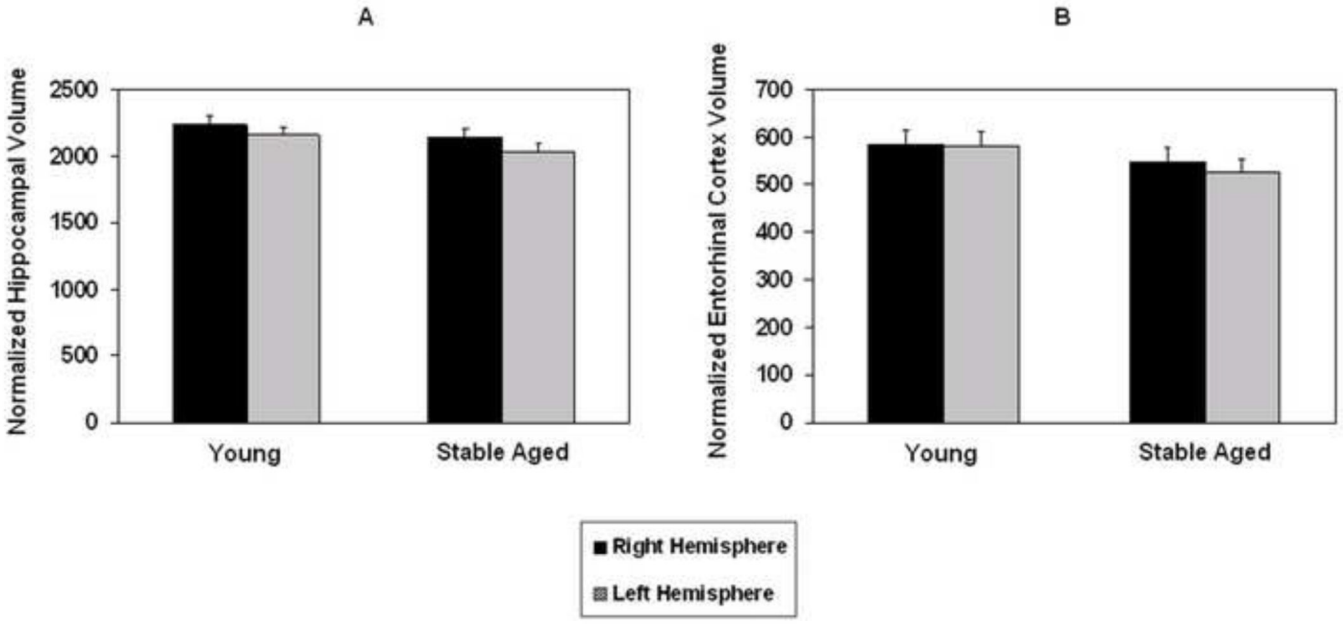

Figure 3.
Mean normalized right and left hippocampal **(A)** and entorhinal cortex **(B)** volumes in old participants who remained stable during the follow-up period compared to young subjects. Vertical bars represent the standard error of the mean.

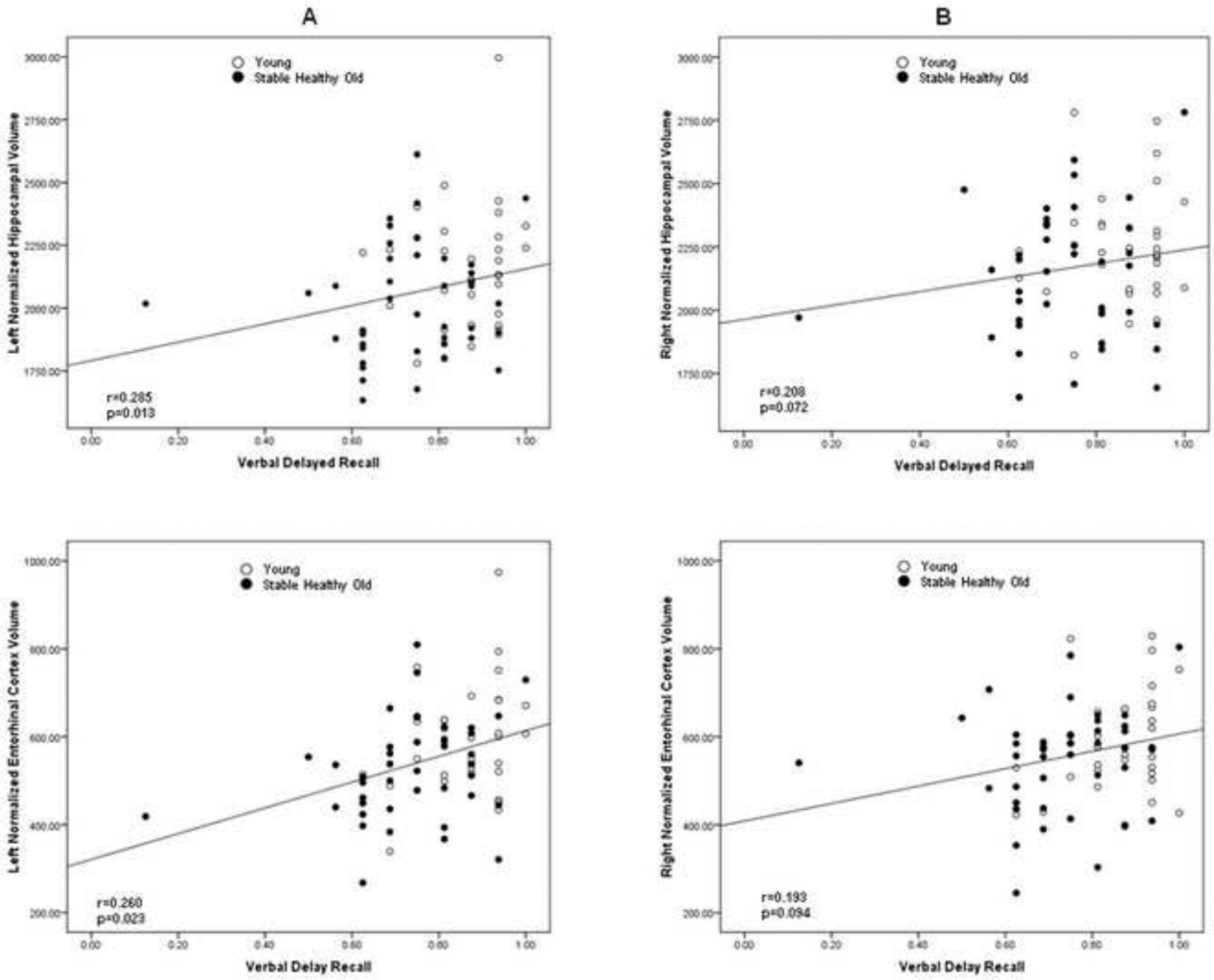

Figure 4.
Scatterplots showing the relationship between left **(A)** and right **(B)** normalized hippocampal and entorhinal cortex volume and delayed verbal recall.

Table 1

Memory recall scores of participants

	Stable Healthy Old	Declining Healthy Old	Young
N	**42**	**9**	**35**
Buschke Verbal Free (Mean Percent Correct ± SD)	**76 ± 10**	**68 ± 10**	**86 ± 10**
Buschke Verbal Delay (Mean Percent Correct ± SD)	**73 ± 15**	**76 ± 10**	**86 ± 10**