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RESEARCH ARTICLE

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Disconnection of hippocampal networks contributes to memory dysfunction in individuals with temporal lobe epilepsy

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Abstract

A deficit in declarative memory function is common among individuals with temporal lobe epilepsy. The purpose of this study is to evaluate the relationship between the volume of the hippocampus, entorhinal cortex along with the surrounding parahippocampal white matter and memory performance in those with temporal lobe epilepsy. T1 weighted MRI scans were acquired using a 3-D pulse sequence in 50 individuals with temporal lobe epilepsy. Hippocampal and entorhinal cortex volumes were derived by manually tracing consecutive coronal slices aligned perpendicular to the long axis of the hippocampus. In addition, parahippocampal white matter volumes were determined using voxel based morphometry. Finally, declarative memory was assessed using immediate and delayed verbal and visual memory tests from the Wechsler Memory Scale third edition. Significant correlations were seen between right and left hippocampal volumes and delayed verbal memory test scores. In addition, left parahippocampal white matter showed positive correlations with immediate and delayed verbal and visual recall. Furthermore, regression models found that the right hippocampus and left parahippocampal white matter were the best predictors of immediate and delayed verbal and visual memory performance. These results show that a decrease in white matter fibers projecting to the hippocampus may cause a disruption of incoming multi-modal sensory information, contributing to the memory decline seen in individuals with temporal lobe epilepsy.

KEYWORDS
entorhinal cortex, epilepsy, hippocampus, memory, white matter

1 | INTRODUCTION

Declining memory performance for events and facts (declarative memory) is one of the most common clinical comorbidities observed in patients with temporal lobe epilepsy. The anatomical components that make up this memory system include the hippocampus, adjacent entorhinal cortex, and connecting pathways between these two structures (Squire & Zola-Morgan, 1991; Young, Otto, Fox, & Eichenbaum, 1997). Polymodal sensory information from primary and association cortices is first sent to the entorhinal cortex which then projects, via the white matter of the parahippocampal gyrus, to the hippocampus (Amaral, Insausti, & Cowan, 1995; Steward & Scoville, 1976; Suzuki & Amaral, 1994; Van Hoesen & Pandya, 1975; Van Hoesen, Pandya, & Butters, 1975; Witter & Amaral, 1991; Witter, Groenewegen, Lopes da Silva, & Lohman, 1989). Therefore, damage to any of these three components of the mesial temporal memory network may disrupt the relay of information essential to memory function.

MRI derived hippocampal atrophy in patients with temporal lobe epilepsy has been shown to be directly related to poor performance on tests assessing declarative memory function (Baxendale et al., 1998; Bonilha et al., 2007; Lencz et al., 1992; Miller, Munoz, & Finmore, 1993). In addition, white matter changes are seen in the mesial temporal region of those with temporal lobe epilepsy and poor memory performance (McDonald et al., 2008; McDonald et al., 2014; Yogarajah et al., 2008). However, little is known about the involvement of the entorhinal cortex and the volumetric changes of the white matter pathways in the parahippocampal region that connects the entorhinal cortex to the hippocampus in these patients. Atrophy or degradation of the white matter of the parahippocampal gyrus may cause a disconnection of information traveling into the hippocampus. This disconnection,

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as well as atrophy of the hippocampal formation and entorhinal cortex, may be the anatomical basis for memory dysfunction in patients with temporal lobe epilepsy.

The present study was undertaken to determine the anatomical relationship that the volumes of the hippocampus, entorhinal cortex, and parahippocampal gyrus white matter have on memory performance in those with temporal lobe epilepsy. Changes in the volume of the hippocampus and entorhinal cortex were manually measured as well as voxel-based morphometry (VBM) to assess parahippocampal white matter volume in patients with temporal lobe epilepsy.

2 | MATERIALS AND METHODS

2.1 | Subjects

The participants consisted of 50 consecutive patients with temporal lobe epilepsy who came for a presurgical evaluation at the Rush University Medical Center Epilepsy Monitoring Unit (EMU). All participants were diagnosed and localized with temporal lobe epilepsy based purely on assessment of long-term video electroencephalography (EEG) monitoring. In addition, each subject had an MRI and neuropsychological testing that included assessment of declarative memory function. Healthy control participants ($n = 24$; mean age = 29, range 24–36; 12 male and 12 female) were used to establish mean volumes of comparison for determining hippocampal atrophy. Young subjects were recruited from Rush University Medical Center students and employees, as well as their friends and family members. Control subjects 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.

Neuroimaging acquisition parameters: MRI was acquired with a 1.5 Tesla General Electric Signa scanner, using the manufacturer's 3D Fourier transform spoiled gradient recalled (SPGR) pulse sequence. The acquisition parameters were: 124 contiguous coronal images, 1.6mm thick, matrix = 256 × 192, field of view = 22 cm, TR/TE = 33.3/7 ms, flip angle = 35°, signals averaged = 1.

2.2 | Neuroimaging data processing

2.2.1 | Hippocampus

Volumes of the hippocampus were manually segmented using a personal computer-based image analysis program (Analyze, Mayo Clinic Foundation) and computed separately for the right and left hemispheres. The volume of the hippocampal formation included the fimbria, dentate gyrus, hippocampus proper, and the subiculum (Figure 1) taken from coronal slices oriented perpendicularly to the long axis of the hippocampal formation. The most rostral section began where the hippocampus could be clearly differentiated from the amygdala by the alveus. The last section traced was the one immediately rostral to the full appearance of the fornix.

To determine hippocampal atrophy, mean volumes were calculated separately for the right and left hippocampus from healthy control participants. Right hippocampal atrophy was determined if the volume difference between the right and left (left minus right) was 2 standard deviations less than the difference seen in controls (Jack et al., 1990). Similarly, left hippocampal atrophy was determined if the volume difference between the right and left (right minus left) was 2 standard deviations less than that of controls. Finally, bilateral volume differences were calculated using normalized volumes (described below) and determined to be bilaterally atrophic if each side was two standard deviations below the healthy control normalized mean.

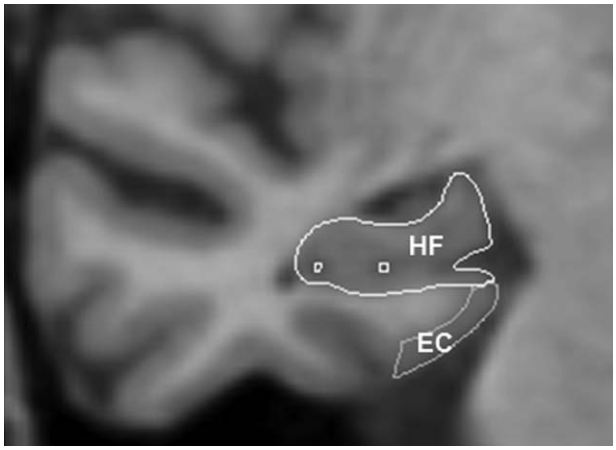

FIGURE 1 A coronal slice through the right temporal lobe illustrating the segmentation of the hippocampal formation (HF) and entorhinal cortex (EC)

2.2.2 | Entorhinal cortex

The entorhinal cortex volumes were derived from the same oblique coronal sections as the hippocampal formation so that no structure is overestimated using a previously established protocol (Goncharova, Dickerson, Stoub, & deToledo-Morrell, 2001). Manual tracings began with the most rostral slice in which the gyrus ambiens, amygdala, and white matter of the parahippocampal gyrus are first seen. The dorsomedial border in the rostral sections was the sulcus semiannularis and more caudal sections the subiculum. The most inferior point of the collateral sulcus was used at the lateral border. Sequential 1.6 mm thick slices were traced until 4.8mm (3 slices) rostral to the first appearance of the lateral geniculate nucleus.

To correct for normal individual differences in brain size, the volumes of the hippocampal formation and entorhinal cortex were divided by the intracranial volume [(normalized volumes) deToledo-Morrell et al., 2004]. The intracranial volume was computed by tracing the inner table of the cranium on consecutive 5mm thick slices reoriented in the sagittal plane and 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) × 1000000].

2.2.3 | Parahippocampal white matter

Parahippocampal white matter volume methods were taken from a previously published manuscript (Stoub et al., 2006). Briefly, whole brain optimized VBM (Good et al., 2001), within statistical parametric

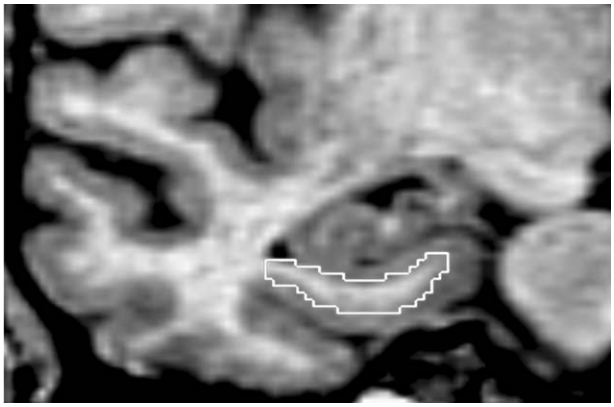

FIGURE 2 A coronal slice through the right temporal lobe illustrating the parahippocampal white matter region

mapping (SPM2), was used to assess the volume of the parahippocampal white matter. Study specific normalized probability maps, modulation and smoothing with a 6mm Gaussian kernel were included in the VBM processing protocol. To obtain volumes of the white matter for the parahippocampal gyrus, a mask was created (Figure 2) using the Wake Forest University (WFU) –Pick Atlas (Maldjian, Laurienti, Kraft, & Burdette, 2003).

2.2.4 | Neuropsychological testing

Summations of the logical memory and verbal paired associates subtests from the Weschler Memory Scale third edition (WMS-III; Wechsler, 1997) were used to assess immediate and delayed verbal memory. Visual immediate and delayed memory was evaluated using summations of the faces and family pictures test scores from the WMS-III.

2.2.5 | Statistics

To determine relationships between the hippocampus, entorhinal cortex, and parahippocampal gyrus white matter volumes and neuropsychological memory testing, Pearson product-moment correlations were derived using SigmaStat 3.5 (Systat Software Inc., Chicago, IL, USA). Multiple regression analyses with memory scores as the dependent variable were used to determine which of the three measures best predicted performance on memory testing.

3 | RESULTS

Patient demographic and seizure data are presented in Table 1. Of the 50 temporal lobe patients, 21 had a right temporal lobe, 23 had a left temporal lobe and six had bilateral temporal lobe origination of seizures, as determined solely by long-term video EEG monitoring. Table 2 displays mean volumes and ranges of all regions for each group (right, left and bilateral origination of seizures). Eleven of the 21 right temporal lobe onset participants had right hippocampal atrophy, 12 of the 23 left temporal lobe onset patients had left hippocampal atrophy, and 27 had no hippocampal atrophy determined by manual hippocampal volume measurements. None of the bilateral temporal lobe participants meet the criteria for unilateral or bilateral hippocampal atrophy.

TABLE 1 Demographic characteristics of participants

N	50
Gender	
Male	23
Female	27
Age (in years)	
Mean ± SD	36 ± 11
(Range)	(18–60)
Origination of Seizures	
Right Temporal	21
Left Temporal	23
Bilateral Temporal	6
Hippocampal Atrophy	
Right	11[a]
Left	12[b]
None	27
Number of Years Experiencing Seizures	
Mean ± SD	19 ± 14
(Range)	(2–60)

[a]All had right origination of seizures as determined by EEG.
[b]All had left origination of seizures as determined by EEG.

There were no significant correlations between age and memory performance or volume measurements. Similarly, there was no relationship between years of experiencing seizures and memory performance or volume measurements. All Pearson correlations between volumes and memory test scores are shown in Table 3. Correlations revealed a direct relationship between right and left hippocampal volumes and delayed

TABLE 2 Mean volumes and range for all regions of interest by group

	Origination of seizures		
Region of interest	**Right**	**Left**	**Bilateral**
Right Hippocampus			
Mean ± SD	2025 ± 477	2344 ± 314	2295 ± 531
(Range)	(1275–2863)	(1579–2856)	(1716–3123)
Left Hippocampus			
Mean ± SD	2254 ± 247	1801 ± 581	2267 ± 522
(Range)	(1748–2656)	(1019–2904)	(1696–3049)
Right Entorhinal Cortex			
Mean ± SD	720 ± 113	749 ± 109	656 ± 110
(Range)	(542–950)	(495–985)	(520–790)
Left Entorhinal Cortex			
Mean ± SD	680 ± 104	621 ± 185	594 ± 147
(Range)	(473–923)	(296–984)	(442–796)
Right Parahippocampal Gyrus White Matter			
Mean ± SD	1.21 ± 0.31	1.62 ± 0.25	1.52 ± 0.18
(Range)	(0.70-1.79)	(0.81-1.70)	(1.22-1.74)
Left Parahippocampal Gyrus White Matter			
Mean ± SD	1.08 ± 0.26	1.03 ± 0.29	1.11 ± 0.39
(Range)	(0.64-1.57)	(0.57-1.58)	(0.73-1.74)

TABLE 3 Correlation coefficients for regions of interest and memory test scores

Region of interest	Immediate verbal recall	Delayed verbal recall	Immediate verbal recall	Delayed verbal recall
Right hippocampus	0.263	0.323*	0.205	0.238
Left hippocampus	0.231	0.299*	0.181	0.170
Right entorhinal cortex	−0.04	0.005	0.062	−0.043
Left entorhinal cortex	0.101	0.158	0.176	0.083
Right parahippocampal gyrus white matter	−0.049	0.038	−0.103	−0.146
Left parahippocampal gyrus white matter	0.310*	0.291*	0.381**	0.310*

*$p > 0.05$.
**$p > 0.005$.

verbal memory test scores [($R = 0.32$, $p = 0.022$ and $R = 0.30$, $p = 0.035$, respectively) Figure 3]. Left parahippocampal white matter volume showed positive correlations with immediate verbal and visual memory scores [$R = 0.31$, $p = 0.029$; $R = 0.38$, $p = 0.006$, respectively) Figure 4]. In addition, delayed verbal and visual recall were also significantly associated with left parahippocampal white matter volume [($R = 0.29$, $p = 0.04$ and $R = 0.31$, $p = 0.028$, respectively) Figure 5]. There were no significant correlations with right parahippocampal white matter volume or right and left entorhinal cortex volume and memory function.

When all three bilateral volume measurements were entered simultaneously into a multiple regression model only the left parahippocampal gyrus white matter and right hippocampus accounted for the ability to predict immediate [$t(43) = 2.69$, $p = 0.010$; $t(43) = 2.36$, $p = 0.023$, respectively] and delayed [$t(43) = 2.70$, $p = 0.010$; $t(43) = 2.61$, $p = 0.012$, respectively] verbal recall. In addition, a model using visual recall revealed the right hippocampus and left parahippocampal gyrus as significant predictors of both immediate [$t(43) = 2.08$, $p = 0.043$; $t(43) = 3.44$, $p = 0.001$, respectively] and delayed [$t(43) = 2.41$, $p = 0.020$; $t(43) = 2.71$, $p = 0.010$, respectively] visual recall.

4 | DISCUSSION

This study assesses three major components of the mesial temporal lobe memory network to determine which structures relate best to memory performance in patients with temporal lobe epilepsy. Developing structural markers for declarative memory decline is imperative for understanding the in vivo pathophysiological components of the cognitive deficits patients with temporal lobe epilepsy experience.

In this sample 46% of our cohort exhibited unilateral hippocampal atrophy. While there are previous studies that have much higher incidence of hippocampal atrophy such as 86% and 80% (Arruda et al., 1996 and Van Paesschen et al., 1995, respectively), there are reports with similar rates to ours (i.e., Kuzniecky, Burgard, Faught, Morawetz, and Bartolucci, 1993 with 52% and Radhakrishnan et al., 1998 with 54%). The reason for the large discrepancy in the occurrence of hippocampal atrophy among intractable temporal lobe epilepsy patients in these studies is unclear but methodological differences including small sample sizes and the specific criteria used for determining atrophy along with population differences may confound direct comparisons among studies of this kind.

Earlier work has shown that polymodal sensory information pertaining to events and things is sent to the entorhinal cortex from association cortices and is then projected to the hippocampus (Amaral et al., 1995; Steward & Scoville, 1976; Suzuki & Amaral, 1994; Van Hoesen & Pandya, 1975; Van Hoesen et al., 1975; Witter & Amaral, 1991; Witter et al., 1989). Anatomically, two major pathways lead to the hippocampus from the entorhinal cortex, namely the perforant and direct pathways. Since these pathways traverse the anterior mesial portion of the parahippocampal gyrus, white matter in this region may be

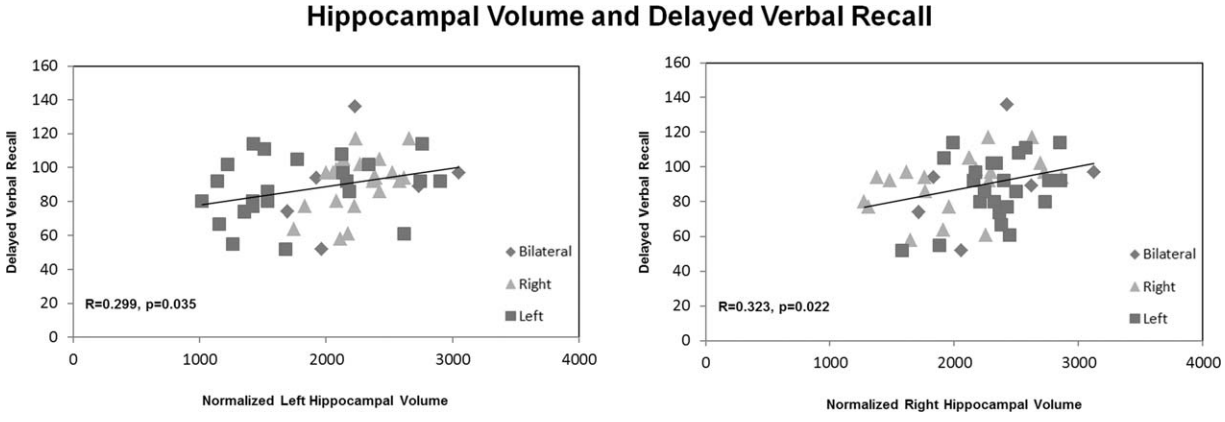

FIGURE 3 Scatterplots showing the relationship between right and left normalized hippocampal volume and delayed verbal recall

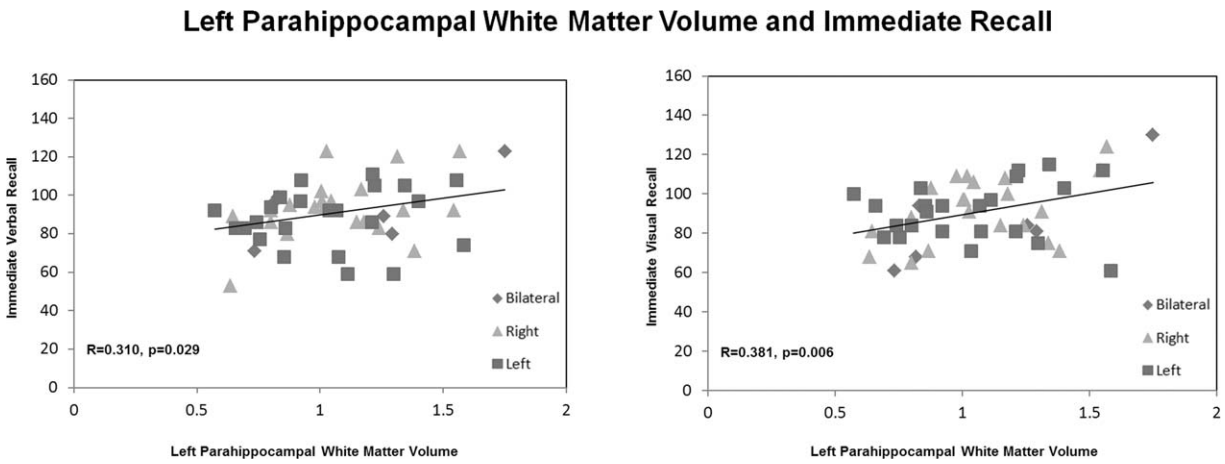

FIGURE 4 Scatterplots showing the relationship between the left parahippocampal white matter volume and immediate verbal and visual recall

an important component of the mesial temporal memory network. Therefore, degradation to either of these afferent routes into the hippocampus may compromise, or disconnect information entering the hippocampus thereby contributing to the memory dysfunction.

It has been previously shown that decreases in white matter volume in the parahippocampal white matter contribute significantly to memory dysfunction in patients with amnestic mild cognitive impairment (Stoub et al., 2006). In addition, recent findings in patients with temporal lobe epilepsy suggest a relationship between declining memory performance and white matter integrity of the parahippocampal white matter area using diffusion tensor imaging (McDonald et al., 2008; McDonald et al., 2014; Yogarajah et al., 2008). The data presented here support these findings by showing a direct structural relationship between decreases in left parahippocampal white matter volume and both immediate and delayed visual and verbal memory decline. In fact, left parahippocampal white matter was found to be the best predictor of memory performance in patients with temporal lobe epilepsy.

Neuron loss has been previously found in both the hippocampus and entorhinal cortex in patients with temporal lobe epilepsy. Specifically, preferential loss of layer III cortical neurons is seen in the entorhinal cortex in patients with chronic temporal lobe epilepsy (Du et al., 1993) and animal models of temporal lobe epilepsy (Du, Tore, Lothman, Kohler, & Scwarcz, 1995; Margerison & Corsellis, 1966) as well as loss of neurons and gliosis in CA1, CA3, and the dentate gyrus of the hippocampus (Babb & Brown, 1987; Bruton, 1988). While the exact mechanisms involved in the memory deficits in this patient population cannot be ascertained from this study, one plausible mechanism may be the degradation of the entorhinal cortex projections from layer III neurons into CA1 of the hippocampus. Although volumes of the entorhinal cortex and memory performance were not correlated in this study, there were direct correlations with hippocampal and parahippocampal white matter volume and memory performance. It may be plausible, therefore, that white matter degeneration due to demyelination or axonal degeneration from cell loss in layer III of the entorhinal cortex and CA1

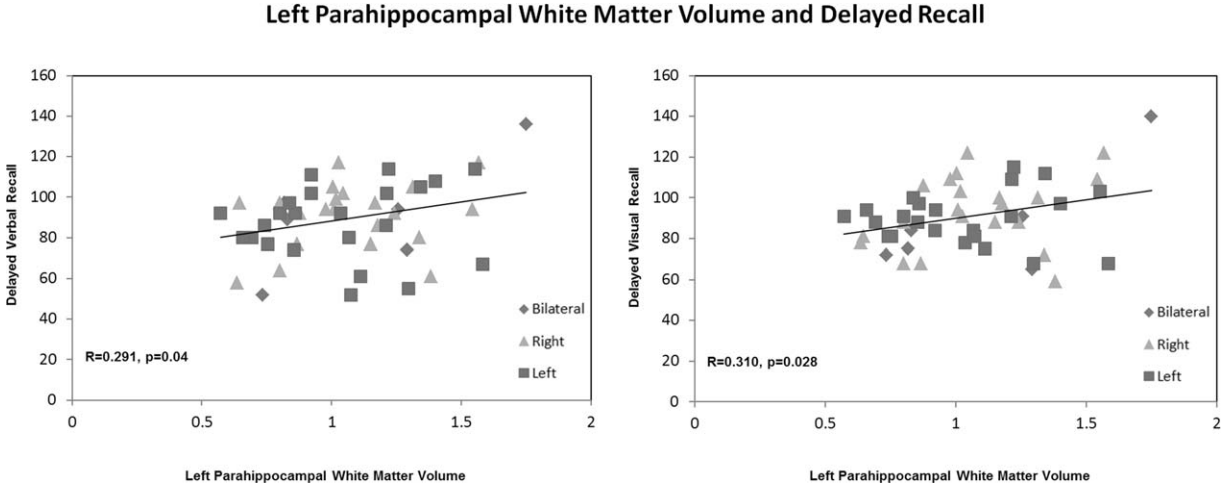

FIGURE 5 Scatterplots showing the relationship between the left parahippocampal white matter volume and delayed verbal and visual recall

hippocampal neurons could contribute to the volume and memory relationship in this area.

Previous studies have shown a relationship between poor performance in verbal memory and left but not right hippocampal volume loss in temporal lobe epilepsy patients (Bonilha et al., 2007; Lencz et al., 1992; McDonald et al., 2014). In the present study, however, we show significant correlations with delayed verbal recall and both left and right hippocampal volumes. While differences in the measurement of hippocampal volumes for these studies may help understand the different findings, future studies with increased sample size to include more patients with left and right temporal lobe epilepsy are needed that allow direct comparisons of groups to better understand laterality of memory findings. Further, multimodal studies that utilize functional and structural network approaches may help elucidate how these complex memory networks are affected bilaterally in epilepsy.

In conclusion, these results show that, in addition to reduced hippocampal volume, atrophy of white matter of the parahippocampal gyrus is a significant predictor of memory function in people with temporal lobe epilepsy. In addition, decreased left parahippocampal white matter volume is the best marker of memory decline in patients with temporal lobe epilepsy. These findings highlight the importance of white matter connections into the hippocampus that could disrupt new memory information entering into the mesial temporal lobe memory network in patients with temporal lobe epilepsy.

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