Thalamic atrophy and cognition in unilateral temporal lobe epilepsy

MICHAEL SEIDENBERG,[1] BRUCE HERMANN,[2] DALIN PULSIPHER,[1] JARED MORTON,[1]
JOY PARRISH,[1] ELIZABETH GEARY,[1] AND LESLIE GUIDOTTI[1]
[1]Department of Psychology, Rosalind Franklin University of Medicine and Sciences, North Chicago, Illinois
[2]Department of Neurology, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin

Abstract

This study examined quantitative magnetic resonance volumes of the thalamus and hippocampus and determined their relationship with cognitive function and clinical seizure characteristics in a sample of 46 unilateral temporal lobe epilepsy (TLE) subjects (20 left and 26 right) and 29 controls. The hippocampus and thalamus exhibited different patterns of volume abnormality, different associations with clinical seizure characteristics, and different patterns of relationship with cognitive measures. Hippocampal volume reduction was primarily ipsilateral to the seizure focus, and thalamic volume reduction was bilateral. Ipsilateral hippocampal volume was significantly correlated with both early neurodevelopmental features (age of seizure onset) and disease characteristics (duration of epilepsy), whereas thalamus integrity was related only to disease variables. Hippocampal volume showed a selective association with verbal memory performance. In contrast, both left and right thalamic volumes were significantly correlated with performance on both memory and nonmemory cognitive domains. These findings underscore the importance of thalamic atrophy in chronic TLE and its potential implications for cognition. (*JINS*, 2008, *14*, 384–393.)

Keywords: Epilepsy, Cognition, MRI, Memory, Hippocampus, Clinical seizure characteristics

INTRODUCTION

Neuropsychological research in chronic temporal lobe epilepsy (TLE) has focused on hippocampal integrity and its corresponding impact on episodic memory (Lencz et al., 1992; Lui et al., 2005; Martin et al., 1999; O'Brien et al., 2003). However, recent evidence has demonstrated that TLE is characterized by abnormalities in brain regions that extend beyond the affected hippocampus (Hermann et al., 2003; Marsh et al., 1997). Affected brain structures include temporal lobe structures adjacent and closely linked to the hippocampus such as the amygdala and entorhinal cortex (Bernasconi et al., 2005; Moran et al., 2001), as well as extratemporal lobe structures such as the thalamus and basal ganglia (Bonilha et al., 2005; Dreifuss et al., 2001; Natsume et al., 2003). Cognitive impairment in TLE has also been shown to encompass domains other than episodic mem-

ory, including intellectual functioning, language, executive functioning, visual perceptual functions, and motor abilities (Glosser et al., 1997; Hermann et al., 1997; Marques et al., 2007; Martin et al., 2000; Oyegbile et al., 2004). These findings raise the possibility that the broader pattern of cognitive impairment in TLE is associated with brain abnormalities in regions outside the temporal lobe.

From both a neuropsychological and epilepsy perspective, the potential role of the thalamus in cognition in TLE is of considerable interest. First, there is extensive interconnectivity (multisynaptic) between the hippocampus and the anterior nuclear of the thalamus by means of the fornix, mammillary bodies, and mammillothalamic tract (Herrero et al., 2002). Second, both the hippocampus and thalamus play significant roles in seizure initiation, modulation, and propagation (Bertram et al., 2001; Guye et al., 2006; Norden & Blumenfeld, 2002). Third, neuroimaging studies have confirmed that the thalamus is affected in patients with unilateral TLE (Bonilha et al., 2005; Dreifuss et al., 2001; Juhasz et al., 1999; Kimiwada et al., 2006; Natsume et al., 2003). Finally, the thalamus is posited to play an important

role in both memory and nonmemory cognitive domains (Crosson, 1992; Johnson & Ojemann, 2000).

The hippocampus has been extensively examined in unilateral TLE, and there is general agreement that the ipsilateral hippocampus (epileptogenic) is more atrophied than the contralateral hippocampus, that both early neurodevelopmental and course variables affect the ipsilateral hippocampus but not contralateral hippocampus (Bernasconi et al., 2005; Jack, 1994; Theodore et al., 1999; Van Paesschen et al., 1997), and that memory functioning is associated with hippocampal integrity (Lencz et al., 1992; Lui et al., 2005; Martin et al., 1999; O'Brien et al., 2003).

In contrast, much less is known about the structural, clinical seizure, and especially cognitive correlates of damage to the thalamus in patients with unilateral TLE. Recent neuroimaging studies have confirmed that the thalamus is affected in patients with unilateral TLE. Cerebral and metabolic hypoperfusion on positron emission tomography, abnormalities on diffusion tensor imaging and magnetic resonance (MR) spectroscopy, and quantitative MR brain volume and voxel-based morphometry (VBM) abnormalities of the thalamus have been reported (Bonilha et al., 2005; DeCarli et al., 1998; Juhasz et al., 1999; Kimiwada et al., 2006; Sperling et al., 1990). However, findings are mixed about the extent of brain volume loss in the thalamus (ipsilateral or bilateral) relative to other neural structures, and its association with clinical seizure characteristics also remains unclear (Dreifuss et al., 2001; Natsume et al., 2003). Furthermore, the relationship between thalamic integrity and cognition (outside of memory) has not been examined in patients with unilateral TLE and has rarely been studied in relation to memory functioning. This is an important issue given the frequent presence of cognitive morbidity outside the domain of memory in TLE.

The current study examined the following three questions: (1) What is the pattern and relative extent of volumetric abnormality in the hippocampus and thalamus in unilateral TLE?, (2) What is the relationship between clinical seizure characteristics (e.g., age of onset, duration, initial precipitating injuries) and brain volume of the hippocampus and thalamus?, and (3) What is the relative relationship of thalamic and hippocampal volumes to cognitive functioning in unilateral TLE? The answers to these questions may further advance the understanding of the underlying nature of brain abnormality in TLE and its implications for neuropsychological functioning.

METHODS

The data included in this manuscript were acquired in compliance with the regulations of our local institution(s) and with the review and approval of the Institutional Review Board.

Patients

The study sample consisted of a total of 75 subjects; 46 (26 right and 20 left) with unilateral chronic TLE and a group of 29 healthy controls. The majority of TLE patients were under consideration for surgical treatment (anterior temporal lobectomy) of their medication-resistant epilepsy. For this investigation, only patients with video electroencephalogram confirmed evidence of unilateral temporal lobe onset of spontaneous seizures were included. Patients with independent left and right temporal lobe onset were excluded. All TLE patients were between 14 and 60 years of age and showed no evidence of gross MRI abnormalities (e.g., arteriovenous malformation, neoplasm) other than hippocampal sclerosis or atrophy on clinical reading. Healthy controls were either friends or family members of the TLE patients. They were also between the ages of 14 and 60 years, with no current substance abuse, medical or acute psychiatric condition, no history of loss of consciousness longer than 5 minutes, and no history of developmental learning disorder.

TLE patients were typically interviewed in the presence of a family member regarding details of their epilepsy history and clinical course. Available medical records concerning previous epilepsy-related hospitalizations and records from physicians who had treated the patients' epilepsy were reviewed blinded to the MRI and neuropsychological findings (after signed release was obtained from the patient).

MRI Protocol

Images were obtained on a 1.5 Tesla GE Signa MRI scanner. Sequences acquired for each subject included: (1) T1-weighted, three-dimensional SPGR acquired with the following parameters: TE = 5, TR = 24, flip angle = 40, NEX = 2, FOV = 26, slice thickness = 1.5 mm, slice plane = coronal, matrix = 256×192; (2) Proton Density (PD), and (3) T2-weighted images acquired with the following parameters: TE = 36 ms (for PD) or 96 ms (for T2), TR = 3000 ms, NEX = 1, FOV = 26, slice thickness = 3.0 mm, slice plane = coronal, matrix = 256×192, and echo train length = 8.

MRIs were acquired at the University of Wisconsin and were processed using a semiautomated software package, that is, Brain Research: Analysis of Images, Networks, and Systems (BRAINS 2; Andreasen et al., 1996; Harris et al., 1999). For the current study, neuroimaging analyses were conducted blinded to group status and clinical/sociodemographic characteristics of the subjects.

The T1-weighted images were spatially normalized so that the anterior–posterior axis of the brain was realigned parallel to the anterior–posterior commissure (ACPC) line and the interhemispheric fissure was aligned on the other two axes. A six-point linear transformation was used to warp the standard Talairach atlas space onto the resampled image. Images from the three pulse sequences were then co-registered using a local adaptation of automated image registration software. Following alignment of the image sets, the PD and T2 images were re-sampled into 1 mm^3 voxels. Segmentation of the image set was achieved by using a tissue classification program. Sample tissue plugs were generated over a large extent of the brain and subsequently used as input for discriminant analysis functions to classify

each voxel as gray matter, white matter, cerebrospinal fluid (CSF), blood, or unclassified. The brains were then delineated from the skull using a neural network application that had been trained on a set of manual traces. Manual inspection and correction of the output of the neural network tracing was conducted. The BRAINS2 software and procedures have been shown to be of high inter-rater reliability, intra-rater reliability, and scan–rescan reproducibility (Andreasen et al., 1996; Harris et al., 1999; Magnotta et al., 1999a, 2002).

MRI regions of interest for this investigation included the hippocampus and thalamus. Automated neural networks to trace these structures are available as part of the BRAINS2 package. These neural networks were "trained" on other data sets and implemented in the current study with subsequent manual editing by a trained technician. The neural networks serve as a tool in guiding tracing and additional manual editing is conducted as specified below. Utilization of the neural nets has been shown to be more reliable than manual tracings (Magnotta et al., 1999b; Powell et al., 2007).

Hippocampus Guidelines

A neural network application was used to trace the hippocampus in the coronal view using guidelines established and psychometrically validated by the University of Iowa with manual correction of the traces by a qualified technician. These tracings included the pes or head of the hippocampus, the body and the tail. Within the hippocampus, the subiculum, Ammon's horn, and dentate gyrus were included. The white matter structures of the alveus, fimbria, and the fornix were excluded. Within the sagittal orientation, the alveus and the uncal recess marked the anterior border. Posteriorly, the tail of the hippocampus ended at the atrium of the lateral ventricle. Ventrally, the white matter of the parahippocampal gyrus defined the border. Dorsally, the temporal horn of the lateral ventricle served as the border except in the tail of the hippocampus, where the pulvinar of the thalamus was the border. Intraclass correlation (i.e., inter-rater reliability) for tracing of the hippocampus varied between .73 and .83 (Pantel et al., 2000).

Thalamus Guidelines

An automated neural network was first applied to compute thalamic volumes and was followed by manual editing based on additional guidelines established at the University of Iowa were used to guide the thalamus trace (Ooteman & Crestinger, 2005). All images were traced in the coronal plane using a color-enhanced T1 with reference to the segmented image and unenhanced T1. Identification of voxels as gray, white, or CSF was based on tissue density values. The thalamus was traced rostral to caudal with the most anterior portion of the thalamus determined by the neural net and using the presence of the anterior commissure. The genu and posterior limb of the internal capsule served as
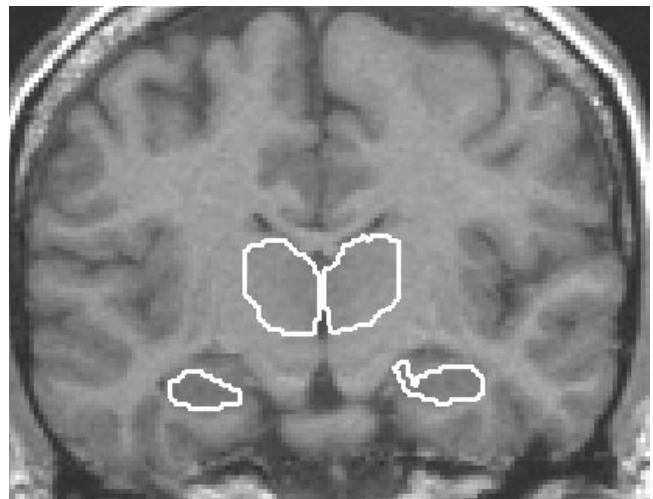

Fig. 1. Manually edited thalamic and hippocampal volumes.

the lateral border. The CSF of the third ventricle served as the medial border. Both the left and right portions of the thalamus were traced separately, excluding the massa intermedia when present. The superior border was determined by the lateral ventricles throughout, and the fornix in more posterior slices. The traces extended caudally and included both the lateral and medial geniculate bodies. The thalamus protrudes posteriorly until coming into contact with either the atrium of the lateral ventricle, the tail of the hippocampus, or both structures. In our lab, we have achieved an inter-rater reliability of .98 in tracing the thalamus. Figure 1 provides an illustration of the final tracing boundaries of the thalamus and hippocampus on a coronal slice.

Statistical Analyses

To correct for brain size, we normalized the volumes (hippocampus and thalamus) by correcting for total brain volume (total gray and white matter). Subsequent analyses to identify specific group differences were conducted with Bonferroni correction for multiple comparisons. To permit formal statistical comparison of ipsilateral and contralateral regions, controls were assigned "ipsilateral" and "contralateral" volume values by calculating an average of the relevant (thalamus or hippocampus) left and right hemisphere values. There were no significant differences between left and right hippocampi or right and left thalami in the controls group.

Clinical seizure correlates of MRI volumes included neurodevelopmental factors (e.g., age of seizure onset) and markers of chronicity/severity of epilepsy [i.e., epilepsy duration, estimated lifetime generalized seizures, and number of antiepileptic drug (AED) medications]. Pearson correlation was used to examine these relationships, and an α level of .003 was adopted to correct for multiple comparisons (a total of 16).

The relationship between cognition and MRI volumes of the thalamus and hippocampus was examined with a set of

Table 1. Subject demographic and clinical characteristics

Characteristics	Controls ($n = 29$)	Right TLE ($n = 26$)	Left TLE ($n = 20$)	p value
Chronological age (yr)	36.6 (12.4)	39.0 (12.6)	32.4 (13.0)	.23
Gender (M/F)	11/18	8/18	5/15	.63
Education	13.5 (2.2)	13.2 (2.4)	12.2 (2.2)	.14
Age of onset (yr)	NA	14.1 (9.4)	11.4 (10.1)	.36
Duration of epilepsy (yr)	NA	24.9 (14.1)	20.9 (12.5)	.33
No. of AEDs	NA	1.9 (0.6)	1.7 (0.7)	.27
Generalized seizures[a]	NA	1.8 (1.3)	1.9 (1.7)	.82
Frequency of complex partial seizures:				
None		2	1	
Daily		3	2	
Weekly		8	4	
Monthly		13	13	
Yearly		0	0	

Note. TLE = temporal lobe epilepsy; AEDs = antiepileptic drugs.
[a]An ordinal scale was developed to quantify estimated lifetime generalized seizures (1 = none, 2 = 1–10, 3 = 11–50, 4 = 50–99, 5 = 100+).

forward step-wise regression analyses. Four general domains of cognition were examined as dependent variables: verbal skills [Wechsler Adult Intelligence Scale-Revised (WAIS-R) Verbal IQ], visuospatial skills (WAIS-R Performance IQ), verbal memory (Wechsler Memory Scale III—delayed auditory memory), and nonverbal memory (Wechsler Memory Scale III—delayed visual memory). We selected the two summary IQ scores as measures of nonmemory cognition to reduce the number of specific test measure comparisons examined. The IQ indices encompass subtests of a broad range of verbal and visuospatial skills and, therefore, provide a useful composite of nonmemory functioning. Cognitive measures were transformed to Z-scores that were corrected for age, gender, and education level based on regression analyses conducted with the control group. A total of eight regression analyses (i.e., four cognitive measures for each of the two TLE groups) were conducted. In each instance, the cognitive variable was entered as the dependent variable. The four volumes (left and right for each the thalamus and hippocampus) were then entered into the first block and a step-wise analysis regression was con-

ducted. Because step-wise regression analyses overfit population estimates, adjusted R^2 values are reported to account for shrinkage estimates (Babyak, 2004).

RESULTS

Table 1 displays the mean age and education values for the three groups along with the clinical seizure characteristics for the left and right TLE groups. There were no significant group differences on age [$F(2,72) = 1.53$; $p > .05$] and years of education [$F(2,72) = 2.04$; $p > .05$]. There were also no significant group differences between the left and right TLE groups on age of onset, duration of epilepsy, number of AED medications, lifetime number of generalized seizures, and frequency of seizures (all p's $> .05$).

MRI Volumes

Table 2 displays the mean thalamic and hippocampal volumes, as well as effect sizes. One-way analysis of variance indicated significant group differences (controls, left TLE,

Table 2. Mean hippocampal and thalamic volumes, unadjusted and total brain tissue adjusted[a]

	Unadjusted volumes (cm³)			Adjusted volumes (cm³)			Effect Size (d)[b]	
	Control	Left TLE	Right TLE	Control	Left TLE	Right TLE	C *vs.* L	C *vs.* R
Ipsilateral hippocampus	1.86 (0.25)	1.52 (0.42)	1.46 (0.34)	1.85 (0.26)	1.51 (0.44)	1.50 (0.34)	0.94	1.16
Contralateral hippocampus	1.86 (0.25)	1.80 (0.31)	1.89 (0.43)	1.85 (0.26)	1.78 (0.32)	1.94 (0.41)	0.25	−0.26
Ipsilateral thalamus	6.54 (0.75)	5.84 (0.73)	5.82 (0.82)	6.44 (0.33)	5.74 (0.70)	5.98 (0.75)	1.28	0.78
Contralateral thalamus	6.54 (0.75)	6.24 (0.75)	5.78 (0.65)	6.44 (0.33)	6.15 (0.68)	5.94 (0.53)	0.54	1.13

Note. TLE = temporal lobe epilepsy; C = control; L = left; R = right.
[a]Volumes are mean (*SD*).
[b]Effect sizes calculated using adjusted volumes.

right TLE) for the ipsilateral hippocampus [$F(2,72) = 8.01$; $p < .001$], but not contralateral hippocampus [$F(2,72) = 1.06$; $p > .05$]. The controls had significantly greater ipsilateral hippocampal volume than both the right and left TLE groups (p's $< .01$). In contrast, significant group differences were observed for both the ipsilateral thalamus [$F(2,72) = 6.74$; $p = .002$] and contralateral thalamus [$F(2,72) = 4.97$; $p = .009$]. The controls had greater volume of the ipsilateral thalamus than the left TLE group ($p = .003$) and showed a similar trend in the right TLE group ($p = .03$). For the contralateral thalamus, the right TLE group had less volume than the controls ($p = .007$), but the left TLE group was not different than controls ($p > .05$).

Clinical Seizure Characteristics

Figure 2a shows the ipsilateral and contralateral hippocampal volumes for 27 TLE patients with a positive history of an initial precipitating incident (IPI+, e.g., complex febrile seizure, infectious disease) and 13 TLE patients without a history of an initial precipitating incident (IPI−). The IPI+ group showed a smaller ipsilateral hippocampus than contralateral hippocampus [$t(27) = 4.59$; $p < .001$], but the same was not true for the IPI− group [$t(12) = 1.16$; $p < .05$]. Unlike the hippocampus, there was no significant volume difference between the ipsilateral and contralateral thalamus for either the IPI+ group [$t(27) = −.59$; $p > .05$] or the IPI− group [$t(12) = −.83$; $p > .05$; Figure 2b].

Table 3 shows the correlations between ipsilateral and contralateral MRI hippocampal and thalamic volumes and clinical seizure correlates (duration of epilepsy, age of seizure onset, number of AEDs, and number of lifetime generalized seizures) for the combined right and left TLE groups. Similar findings were evident when the two TLE groups were examined separately; therefore, groups were combined to provide increased power. Duration of epilepsy and age of onset were significantly correlated with ipsilateral hippocampal volume; a smaller hippocampal volume was associated with longer duration of epilepsy and an earlier age of recurrent seizure onset. Duration of epilepsy emerged as the strongest predictor of hippocampal volume in a linear regression analysis that included chronological age, age of epilepsy onset, duration of epilepsy, and number of generalized seizures. None of the seizure correlates were significantly correlated with volume of contralateral hippocampus. Both ipsilateral and contralateral thalamus volumes were significantly correlated with duration; longer duration was associated with smaller volumes. Age of onset was not significantly correlated with either ipsilateral or contralateral thalamus volumes.

Neuropsychological Performance

The results of the step-wise regression analyses examining the relationship between the four neuropsychological indices (verbal intelligence, nonverbal intelligence, verbal memory, and nonverbal memory) and the hippocampal and
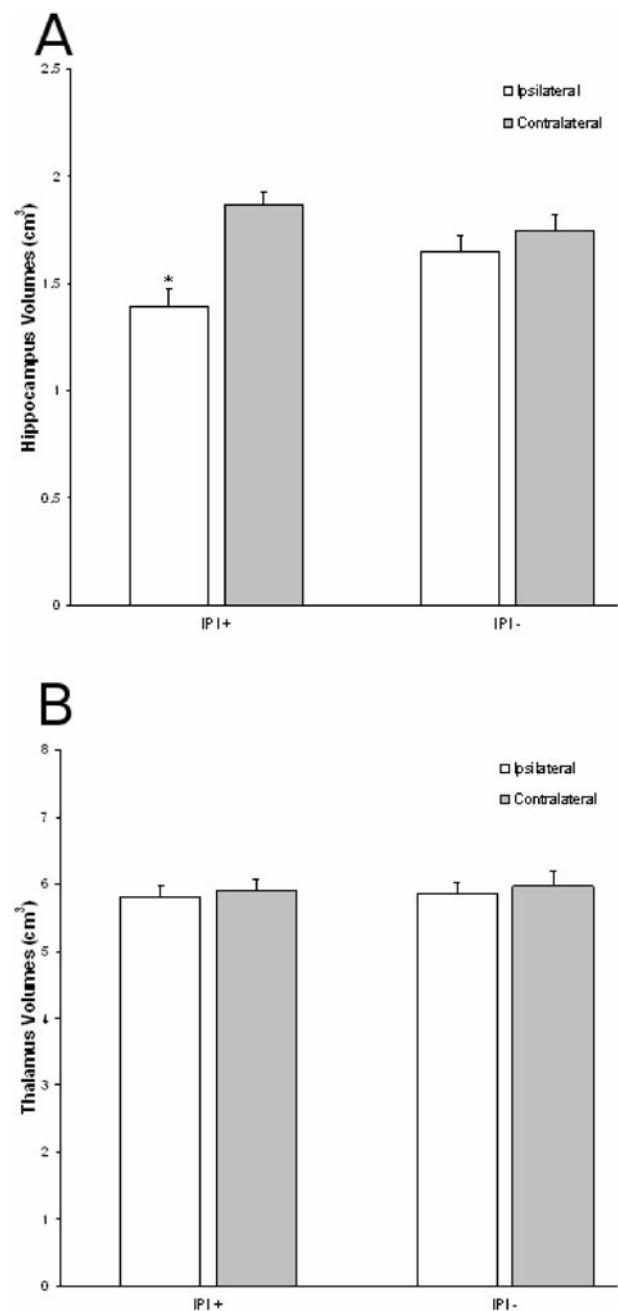

Fig. 2. Hippocampal (A) and thalamic (B) volumes for temporal lobe epilepsy (TLE) patients with a positive history of an initial precipitating incident (IPI+) and TLE patients without a history of an initial precipitating incident (IPI−) groups. The asterisk indicates a significant difference from the contralateral side.

thalamic volumes for the right and left TLE groups are shown in Table 4. We also included the adjusted R^2 value, which provides an estimate of how well the observed models might fit a new sample. Outliers (>3 SDs) were removed from analyses except for two indices [Wechsler Memory Scale (WMS) auditory delay in left TLE and WMS visual delay in right TLE]. In both instances, 20–25% of the TLE subjects scored at least 3 SDs from the mean of the control group, representing a "subgroup" at the "severe" end of the

Table 3. Clinical seizure characteristic and MR volume correlations (*n* = 46)

	Onset	Duration	Generalized seizures	No. of AEDs
Ipsilateral hippocampus	0.42[a]	−0.55[a]	−0.22	−0.34
Contralateral hippocampus	−0.10	0.39	0.04	−0.07
Ipsilateral thalamus	0.06	−0.55[a]	−0.30	−0.02
Contralateral thalamus	−0.17	−0.51[a]	−0.18	−0.18

Note. MR = magnetic resonance; AEDs = antiepileptic drugs.
[a]$p \leq .003$.

spectrum of memory impairment in unilateral TLE. Thus, on these two indices, all subjects were included in the analyses and their respective scatter plots.

Table 4 lists only those structures that entered the regression analyses as significant predictors of the cognitive indices. In all instances, no more than one structure emerged as a significant predictor. Thalamic volumes were significant predictors for both memory and nonmemory cognitive measures in both TLE groups. For the right TLE group, thalamic volumes were a significant predictor for WAIS-R verbal IQ (left thalamic volume), and performance IQ (right thalamic volume), and WMS delayed visual memory (right thalamus). For the left TLE group, thalamic volume was a significant predictor of both verbal and performance IQ scores (right thalamic volume). In contrast, the only significant relationship for hippocampus and cognition was observed for ipsilateral hippocampus volume and WMS auditory delay. Scatter plots of the six significant relationships are shown in Figures 3 and 4.

DISCUSSION

The principal findings of this study were as follows: (1) unilateral TLE patients showed significant volume reduction in both the hippocampus and thalamus compared with controls, but the extent and pattern of volume loss differed

for each structure; (2) thalamic volumes were significantly correlated with measures of both memory and nonmemory functioning, whereas the hippocampus showed a selective association with verbal delayed memory; and (3) hippocampal and thalamic volumes showed a different pattern of association with clinical seizure variables. These findings have important implications in clarifying the nature and impact of thalamic volume reduction in TLE.

MRI Volumes

As expected, ipsilateral hippocampal volume in TLE was substantially reduced compared with controls (19%), but there was no difference in contralateral hippocampus volume (1%). Significant volume reduction in the ipsilateral hippocampus with a relatively intact contralateral hippocampal volume is the MRI signature of unilateral mesial temporal lobe epilepsy (Seidenberg et al., 2005; Van Paesschen et al., 1997). The ipsilateral hippocampus showed the largest volume reduction, but thalamic volume was also significantly reduced compared with controls and was evident on both the ipsilateral (9%) and contralateral side (6%). Thalamic volume reduction in unilateral TLE has been reported, although the findings concerning the presence of ipsilateral or bilateral volume abnormality are mixed (Dlugos et al., 1999; Dreifuss et al., 2001; Keller et al., 2002; Muel-

Table 4. MRI volume and neuropsychological functioning regression values

	Predictor	R	R^2 change	Adjusted R^2	Standardized β	p value (d)
Left TLE[a]						
Verbal IQ (*n* = 20)	RTh	.49	.24	.20	.49	.03 (.31)
Performance IQ (*n* = 19)	RTh	.46	.21	.17	.46	.05 (.27)
WMS Auditory Delay (*n* = 20)	LHc	.58	.34	.30	.58	.007 (.51)
WMS Visual Delay (*n* = 20)	None	—	—	—	—	—
Right TLE[a]						
Verbal IQ (*n* = 25)	LTh	.43	.18	.15	.43	.03 (.22)
Performance IQ (*n* = 25)	RTh	.53	.29	.25	.53	.006 (.41)
WMS Auditory Delay (*n* = 21)	None	—	—	—	—	—
WMS Visual Delay (*n* = 23)	RTh	.48	.23	.19	.48	.02 (.30)

Note. MRI = magnetic resonance imaging; TLE = temporal lobe epilepsy; WMS = Wechsler Memory Scale; RTh = right thalamus; LTh = left thalamus; RHc = right hippocampus; LHc = left hippocampus.
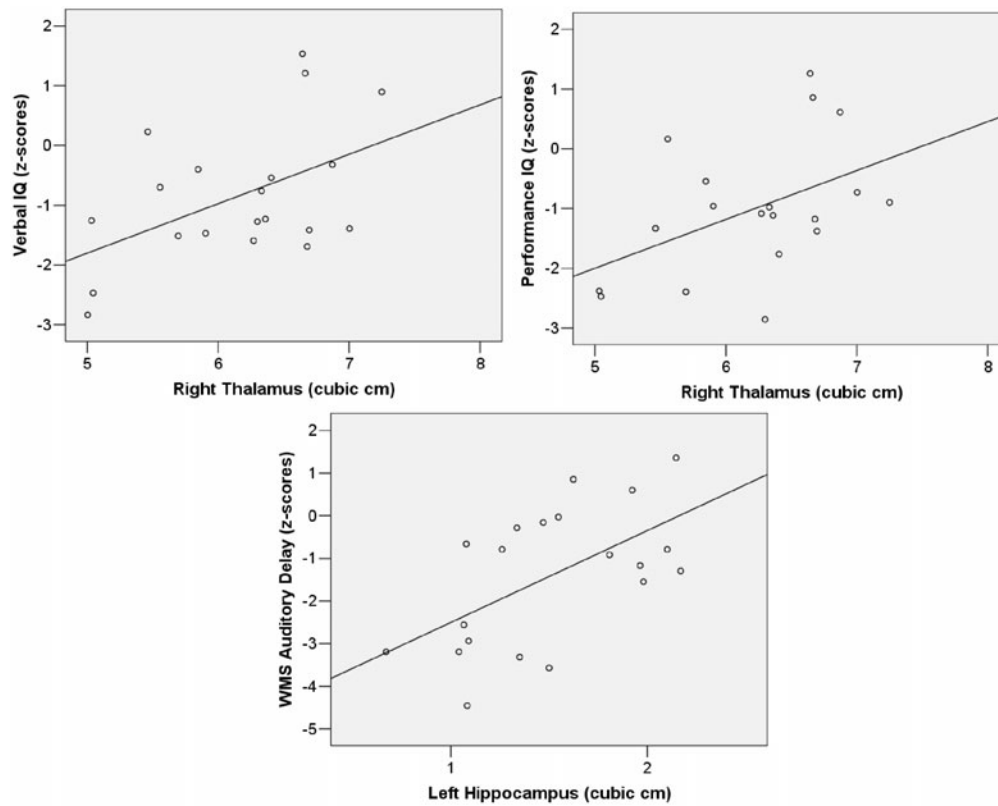[a]Outliers have been removed as indicated by *n* for each group and analysis.

Fig. 3. Left temporal lobe epilepsy cognition and magnetic resonance volume scatter plots. WMS = Wechsler Memory Scale.
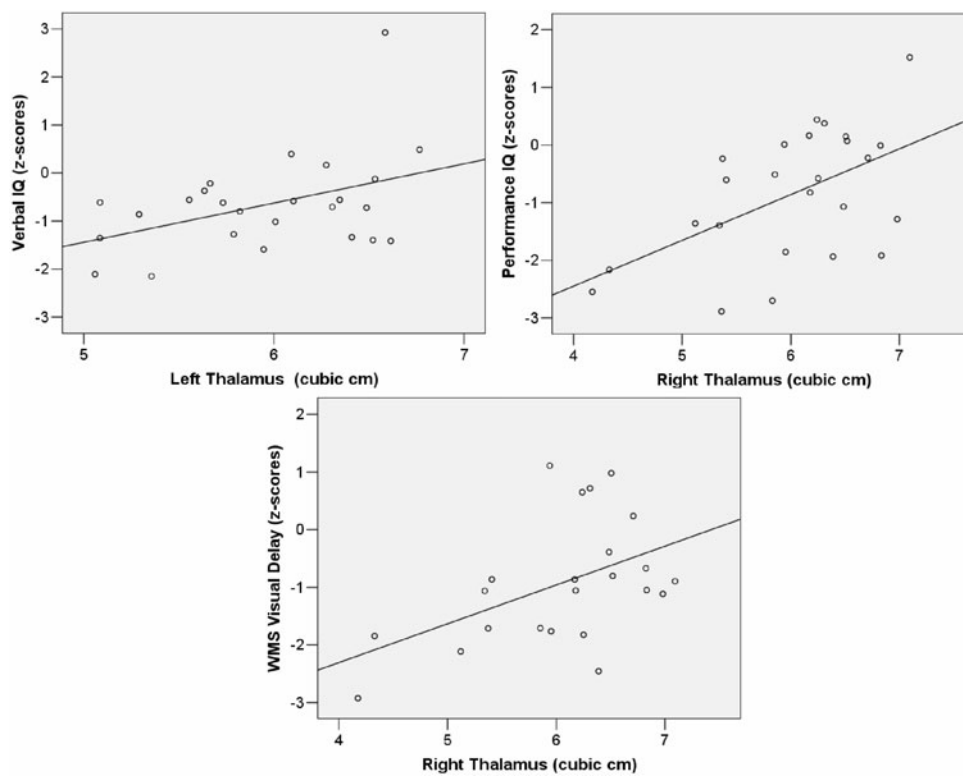

Fig. 4. Right temporal lobe epilepsy cognition and magnetic resonance volume scatter plots. WMS = Wechsler Memory Scale.

ler et al., 2006; Natsume et al., 2003; Szabo et al., 2006). Our findings implicate both the ipsilateral and contralateral thalamus.

Clinical Seizure Relationships

Thalamic and hippocampal volumes showed very distinct patterns of association with clinical seizure characteristics. These findings are consistent with the hypothesis that different mechanisms contribute to the integrity of the hippocampus and thalamus in unilateral TLE. Hippocampal volume was influenced by both early neurodevelopmental features (e.g., an early neurologic insult) and course features such as duration (Bernasconi et al., 2005; Keller et al., 2002; Seidenberg et al., 2005; Theodore et al., 1999). In contrast, thalamic volume was affected only by course variables (e.g., duration of epilepsy). The specific neuropathological mechanisms underlying thalamic volume abnormality in TLE remains unclear, although our findings indicate that it is associated with the course of the disease. A recent VBM paper reported that thalamic volume abnormality was most extensive for thalamic nuclei located in its anterior portion (e.g., anterior thalamic nucleus) due to the neurotoxic effects of recurrent seizures or from deafferentation of neurons from the affected hippocampus (Bonilha et al., 2007).

Cognitive Functioning

Cognition showed a very different pattern of association with hippocampal and thalamic volumes in unilateral TLE. Overall, thalamic volume was a stronger correlate of both memory and nonmemory cognitive functioning than hippocampal volume. Similar to several other reports, a smaller left hippocampus was significantly associated with poorer verbal memory performance and hippocampal volume in the right TLE group did not show any significant association with cognition (Bonilha et al., 2007; Griffith et al., 2004; Lencz et al., 1992; Rausch et al., 1994). However, hippocampal volume (either left or right) was not significantly correlated with the nonmemory neuropsychological indices. Thus, hippocampal volume had a very selective relationship with verbal memory performance. In contrast, both right and left thalamic volumes showed significant associations with both memory and nonmemory cognitive measures. These findings underscore the point that memory performance in unilateral TLE may be influenced by abnormalities in structures other than the hippocampus.

It is generally acknowledged that memory functioning is the primary cognitive morbidity in TLE and is related to the functional adequacy of the hippocampus. Nevertheless, it is also evident that there is a more diffuse disruption of cognition in unilateral TLE (Glosser et al., 1997; Helmstaedter et al., 2003; Hermann et al., 1997) and that there is considerable heterogeneity in cognitive dysfunction among patients with unilateral TLE (Oyegbile et al., 2004). We have previously suggested that abnormalities outside the affected hippocampus and temporal lobe may contribute to nonmemory cognitive impairment (Hermann et al., 2003). The current findings specifically implicate the thalamus as a critical neural structure in the disruption of cognitive functioning in unilateral TLE. This finding is consistent with an extensive literature implicating the importance of thalamic integrity in cognition in both normal and clinical populations (Johnson & Ojemann, 2000; O'Sullivan et al., 2004; Schwartz & Black, 2006; Sherman & Guillery, 2002). Furthermore, these findings may have relevance for pre–post surgical outcome in cognition. The focus of much of the surgical outcome literature has emphasized the integrity of the resected hippocampus for memory outcome (Chelune, 1995; Sass et al., 1992). Our findings suggest that cognitive variability in surgical outcome may also be related to thalamic integrity before and/or after surgery. It should be noted that the stepwise regression procedures that we used can sometimes generate unreliable results. For this reason, our results need to be replicated in a different population before firm conclusions can be drawn.

In summary, we report the first demonstration that thalamic integrity plays a role in characterizing the nature and extent of cognitive impairment observed in unilateral TLE. Indeed, it appears to have a more substantial association with cognition than the hippocampus, despite that the hippocampus is the primary area of neuropathology in TLE. Furthermore, the thalamus and hippocampus show different patterns of association with clinical seizure characteristics, which suggest that different underlying mechanisms play a role in their structural status. Further examination of the presence and nature of volume abnormalities to other critical adjacent brain structures (e.g., caudate, putamen) may also prove helpful in understanding the underlying neuropathology and cognitive functioning in unilateral TLE.

ACKNOWLEDGMENTS

REFERENCES

Andreasen, N.C., Rajarethianam, R., Cizadlo, T., Arndt, S., Swayze, V.W., Flashman, L.A., O'Leary, D.S., Ehrhardt, J.C., & Yuh, W.T.C. (1996). Automated atlas based volume estimation of human brain regions from MR images. *Journal of Computer Assisted Tomography*, *20*, 98–106.

Babyak, M.A. (2004). What you see may not be what you get: A brief, nontechnical introduction to overfitting in regression-type models. *Psychosomatic Medicine*, *66*, 411–421.

Bernasconi, N., Natsume, J., & Bernasconi, A. (2005). Progression in temporal lobe epilepsy: Differential atrophy in mesial temporal structures. *Neurology*, *65*, 223–228.

Bertram, E.H., Mangan, P.S., Zhang, D., Scott, C.A., & Williamson, J.M. (2001). The midline thalamus: Alterations and a potential role in limbic epilepsy. *Epilepsia*, *42*, 967–978.

Bonilha, L., Alessio, A., Rorden, C., Baylis, G., Damasceno, B.P., Min, L.L., & Cendes, F. (2007). Extrahippocampal gray matter atrophy and memory impairments in patients with medial temporal lobe epilepsy. *Human Brain Mapping*, *28*, 1376–1390.

Bonilha, L., Rorden, C., Castellano, G., Cendes, F., & Li, L.M. (2005). Voxel-based morphometry of the thalamus in patients with refractory medial temporal lobe epilepsy. *Neuroimage*, *25*, 1016–1021.

Chelune, G.J. (1995). Hippocampal atrophy versus functional reserve: Predicting memory functions following temporal lobectomy. *Archives of Clinical Neuropsychology*, *10*, 413–432.

Crosson, B. (1992). *Subcortical Functions in Language and Memory*. New York, NY: Guilford Press.

DeCarli, C., Hatta, J., Fazilat, S., Fazilat, S., Gaillard, W., & Theodore, W. (1998). Extratemporal atrophy in patients with complex partial seizures of left temporal origin. *Annals of Neurology*, *43*, 41–45.

Dlugos, D., Jaggi, J., O'Connor, W., Ding, X., Reivich, M., O'Connor, M., & Sperling, M. (1999). Hippocampal cell density and subcortical metabolism in temporal lobe epilepsy. *Epilepsia*, *40*, 408–413.

Dreifuss, S., Vingerhoets, F., Lazeyras, F., Andino, S.G., Spinelli, L., Delavelle, J., & Seeck, M. (2001). Volumetric measurements of subcortical nuclei in patients with temporal lobe epilepsy. *Neurology*, *57*, 1636–1641.

Glosser, G., Cole, L., French, J., Saykin, A., & Sperling, M. (1997). Predictors of intellectual performance in adults with intractable temporal lobe epilepsy. *Journal of the International Neuropsychologial Society*, *3*, 252–259.

Griffith, H., Pyzalski, R., Seidenberg, M., & Hermann, B. (2004). Memory relationships between MRI volumes and resting PET metabolism of medial temporal lobe structures. *Epilepsy & Behavior*, *5*, 669–676.

Guye, M., Regis, J., Tamura, M., Wendling, F., Gonigal, A.M., Chauvel, P., & Bartolomei, F. (2006). The role of corticothalamic coupling in human temporal lobe epilepsy. *Brain*, *129*, 1–12.

Harris, G., Andreasen, N.C., Cizadlo, T., Bailey, J.M., Bockholt, H.J., Magnotta, V.A., & Arndt, S. (1999). Improving tissue classification in MRI, A three-dimensional multispectral discriminant analysis method with automated training class selection. *Journal of Computer Assisted Tomography*, *23*, 144–154.

Helmstaedter, C., Kurthen, M., Lux, S., Reuber, M., & Elger, C. (2003). Chronic epilepsy and cognition, A longitudinal study in temporal lobe epilepsy. *Annals of Neurology*, *54*, 425–432.

Hermann, B., Seidenberg, M., Bell, B., Rutecki, P., Sheth, R., Wendt, G., O'Leary, D., & Magnotta, V. (2003). Extratemporal quantitative MR volumetrics and neuropsychological status in temporal lobe epilepsy. *Journal of the International Neuropsychologial Society*, *9*, 353–362.

Hermann, B., Seidenberg, M., Schoenfeld, J., & Davies, K. (1997). Neuropsychological characteristics of the syndrome of mesial temporal lobe epilepsy. *Archives of Neurology*, *54*, 369–376.

Herrero, M., Barcia, C., & Navarro, J. (2002). Functional anatomy of thalamus and basal ganglia. *Child's Nervous System*, *18*, 386–404.

Jack, C. (1994). MRI-based hippocampal volume measurements in epilepsy. *Epilepsia*, *35*, 1521–1531.

Johnson, M. & Ojemann, G. (2000). The role of human thalamus in language and memory, Evidence from electrophysiological studies. *Brain and Cognition*, *42*, 218–230.

Juhasz, C., Nagy, F., Watson, C., Silva, E., Muzik, O., Chugani, D., Shah, J., & Chugani, H.T. (1999). Glucose and [^{11}C] flumazenil positron emission tomography abnormalities of thalamic nuclei in temporal lobe epilepsy. *Neurology*, *53*, 2037–2045.

Keller, S., Wieshmann, U., Mackay, C., Denby, C., Webb, J., & Roberts, N. (2002). Voxel based morphometry of grey matter abnormalities in patients with medically intractable temporal lobe epilepsy, effects of side of seizure onset and epilepsy duration. *Journal of Neurology, Neurosurgery, and Psychiatry*, *73*, 648–656.

Kimiwada, T., Juhasz, C., Makki, M., Muzik, O., Chugani, D., Asano, E., & Chugani, H. (2006). Hippocampal and thalamic diffusion abnormalities in children with temporal lobe epilepsy. *Epilepsia*, *47*, 167–175.

Lencz, T., McCarthy, G., Bronen, R., Scott, T., Inserni, J., Sass, K., Novelly, R., Kim, J., & Spencer, D. (1992). Quantitative magnetic resonance imaging in temporal lobe epilepsy, relationship to neuropathology and neuropsychological function. *Annals of Neurology*, *31*, 629–637.

Lui, Y., Nusbaum, A., Barr, W., Johnson, G., Babb, J., Orbach, D., Kim, A., Laliotis, G., & Devinsky, O. (2005). Correlation of apparent diffusion coefficient with neuropsychological testing in temporal lobe epilepsy. *American Journal of Neuroradiology*, *26*, 1832–1839.

Magnotta, V.A., Andreasen, N.C., Schultz, S.K., Harris, G., Cizadlo, T., Heckel, D., Nopoulos, P., & Flaum, M. (1999a). Quantitative in vivo measurement of gyrification in the human brain: Changes associated with aging. *Cerebral Cortex*, *9*, 151–160.

Magnotta, V., Harris, G., Andreasen, N., O'Leary, D.S., Yuh, W.T., & Heckel, D. (2002). Structural MR image processing using the BRAINS2 toolbox. *Computerized Medical Imaging and Graphics*, *26*, 251–264.

Magnotta, V.A., Heckel, D., Andreasen, N.C., Cizadlo, T., Corson, P.W., Ehrhardt, J.C., & Yuh, W.T. (1999b). Measurement of brain structures with artificial neural networks: Two- and three-dimensional applications. *Radiology*, *211*, 781–790.

Marques, C.M., Caboclo, L.O., da Silva, T.I., Noffs, M.H., Carrete, H., Lin, K., Lin, J., Sakamoto, A.C., & Yacubian, E.M. (2007). Cognitive decline in temporal lobe epilepsy due to unilateral hippocampal sclerosis. *Episepsy & Behavior*, *10*, 477–485.

Marsh, L., Morrell, M., & Shear, P. (1997). Cortical and hippocampal volume deficits in temporal lobe epilepsy. *Epilepsia*, *38*, 576–587.

Martin, R.C., Sawrie, S.M., Edwards, R., Roth, D.L., Faught, E., Kuzniecky, R.I., Morawetz, R.B., & Gilliam, F.G. (2000). Investigation of executive function change following anterior temporal lobectomy: Selective normalization of verbal fluency. *Neuropsychology*, *12*, 501–508.

Martin, R., Sawrie, S., Hugg, J., Gilliam, F., Faught, E., & Kuzniecky, R. (1999). Cognitive correlates of 1H MRSI-detected hippocampal abnormalities in temporal lobe epilepsy. *Neurology*, *53*, 2052–2058.

Moran, N., Lemieux, L., Kitchen, N., Fish, D., & Shorvon, S. (2001). Extrahippocampal temporal lobe atrophy in temporal lobe epilepsy and mesial temporal sclerosis. *Brain*, *124*, 167–175.

Mueller, S., Laxer, K., Cashdollar, N., Buckley, S., Paul, C., & Weiner, M. (2006). Voxel-based optimized morphometry

(VBM) of gray and white matter in temporal lobe epilepsy (TLE) with and without mesial temporal sclerosis. *Epilepsia*, *47*, 900–907.

Natsume, J., Bernasconi, N., Andermann, F., & Bernasconi, A. (2003). MRI volumetry of the thalamus in temporal, extratemporal, and idiopathic generalized epilepsy. *Neurology*, *60*, 1296–1300.

Norden, A. & Blumenfeld, H. (2002). The role of subcortical structures in human epilepsy. *Epilepsy & Behavior*, *3*, 219–231.

O'Brien, C., Bowden, S., Bardenhagen, F., & Cook, M. (2003). Neuropsychological correlates of hippocampal and rhinal cortex volumes in patients with mesial temporal sclerosis. *Hippocampus*, *13*, 892–904.

Ooteman, W. & Crestinger, K. (2005). Thalamus tracing guidelines. Available at: http://www.psychiatry.uiowa.edu/mhcrc/pdf/papers/thalamus.pdf. Accessed March 1, 2006.

O'Sullivan, M., Singhal, S., Charlton, R., & Markus, H.S. (2004). Diffusion tensor imaging of thalamus correlates with cognition in CADASIL without dementia. *Neurology*, *62*, 702–707.

Oyegbile, T., Dow, C., Jones, J., Bell, B., Rutecki, P., Sheth, R., Seidenberg, M., & Hermann, B. (2004). The nature and course of neuropsychological morbidity in chronic temporal lobe epilepsy. *Neurology*, *62*, 1736–1742.

Pantel, J., O'Leary, D., & Crestinger, K. (2000). A new method for the in vivo volumetric measurement of the human hippocampus with high neuroanatomical accuracy. *Hippocampus*, *10*, 752–758.

Powell, S., Magnotta, V.A., Johnson, H., Jammalamadaka, V.K., Pierson, R., & Andreasen, N.C. (2007). Registration and machine learning-based automated segmentation of subcortical and cerebellar structures. *Neuroimage*, *39*, 238–247.

Rausch, R., Henry, T., Ary, C., Engel, J., & Mazziotta, J. (1994). Asymmetric interictal glucose hypometabolism and cognitive performance in epileptic patients. *Archives of Neurology*, *51*, 139–144.

Sass, K.J., Sass, A., Westerveld, M., Lencz, T., Novelly, R.A., Kim, J.H., & Spencer, D.D. (1992). Specificity in the correlation of verbal memory and hippocampal neuron loss: Dissociation of memory, language, and verbal intellectual ability. *Journal of Clinical and Experimental Neuropsychology*, *14*, 662–672.

Schwartz, R. & Black, S. (2006). Anterior-medial thalamic lesions in dementia, frequent, and volume dependently associated with sudden cognitive decline. *Journal of Neurology, Neurosurgery, and Psychiatry*, *77*, 1307–1312.

Seidenberg, M., Kelly, K., Parrish, J., Geary, E., Dow, C., Rutecki, P., & Hermann, B. (2005). Ipsilateral and Contralateral MRI Volumetric Abnormalities in chronic unilateral temporal lobe epilepsy and their clinical correlates. *Epilepsia*, *46*, 1–11.

Sherman, S. & Guillery, R. (2002). The role of the thalamus in the flow of information to the cortex. *Philosophical Transactions of the Royal Society of London—Series B, Biological Sciences*, *357*, 1695–1708.

Sperling, M., Gur, R., Alavi, A., Gur, R., Resnick, S., O'Connor, M., & Reivich, M. (1990). Subcortical metabolic alterations in partial epilepsy. *Epilepsia*, *31*, 145–155.

Szabo, C., Lancaster, J., Lee, S., Xiong, J., Cook, C., Mayes, B., & Fox, P. (2006). MR Imaging volumetry of subcortical structures and cerebellar Hemispheres in temporal lobe epilepsy. *American Journal of Neuroradiology*, *27*, 2155–2160.

Theodore, W., Bhatia, S., Hatta, J., Fazilat, S., DeCarli, C., Bookheimer, S., & Gaillard, W. (1999). Hippocampal atrophy, epilepsy duration, and febrile seizures in patients with partial seizures. *Neurology*, *52*, 132–136.

Van Paesschen, W., Connelly, A., King, M., Jackson, G., & Duncan, J. (1997). The spectrum hippocampal sclerosis, a quantitative magnetic resonance imaging study. *Annals of Neurology*, *41*, 41–51.