

Material-specific lateralization of working memory in the medial temporal lobe

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ABSTRACT

Mnemonic deficits in patients with medial temporal lobe (MTL) damage arising from temporal lobe epilepsy (TLE) are traditionally constrained to long-term episodic memory, sparing short-term and working memory (WM). This view of WM as being independent of MTL structures has recently been challenged by a small number of patient and neuroimaging studies, which have focused primarily on visual and visuospatial WM. In the present study we investigated material-specific lateralization of WM in 96 patients with unilateral damage to MTL stemming from TLE (56 left) and 30 control subjects using a pair of matched verbal and visuospatial supraspan tasks. Patients with unilateral TLE were impaired on both verbal and visuospatial WM tasks irrespective of the affected hemisphere. Patients with unilateral right TLE showed an additional deficit for visuospatial WM capacity when contrasted with patients with left TLE, whereas patients with unilateral left TLE showed increased intrusion errors on the verbal task when compared to patients with right TLE. These findings suggest a material-specific lateralization of WM in the MTL.

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1. Introduction

Pervasive memory impairment is a common symptom of damage to medial temporal lobe (MTL) structures arising from temporal lobe epilepsy (TLE). While patients with MTL damage frequently display profound deficits of long-term episodic memory, they seldom exhibit impairments of short-term memory or working memory (WM) (Cave & Squire, 1992; Sidman, Stoddard, & Mohr, 1968; Spiers, Maguire, & Burgess, 2001), even after extensive bilateral damage to MTL structures (Milner, Corkin, & Teuber, 1968; Scoville & Milner, 1957). This has led to the widely accepted neuroanatomic dissociation between long-term memory (LTM) and WM in humans, with LTM relying primarily on the MTL (Squire & Zola-Morgan, 1991) and WM on a network of prefrontal and parietal areas (Jonides et al., 1993; Petrides, Alivisatos, Meyer, & Evans, 1993; Smith & Jonides, 1997). Recently, this view has been challenged by a number of studies examining WM performance in patients with damage involving MTL structures (Axmacher et al., 2007; Hannula, Tranel, & Cohen, 2006; Hartley et al., 2007; Olson, Moore, Stark, & Chatterjee, 2006; Olson, Page, Moore, Chatterjee, & Verfaellie, 2006; van Asselen et al., 2006) and in healthy volunteers

performing WM tasks during functional neuroimaging with fMRI (Axmacher et al., 2007; Cabeza, Dolcos, Graham, & Nyberg, 2002; Karlsgodt, Shirinyan, van Erp, Cohen, & Cannon, 2005; Nichols, Kao, Verfaellie, & Gabrieli, 2006; Piekema, Kessels, Mars, Petersson, & Fernandez, 2006; Ranganath & D'Esposito, 2001; Ranganath, Cohen, & Brozinsky, 2005; Stern, Sherman, Kirchoff, & Hasselmo, 2001) and magnetoencephalography (Campo et al., 2005).

The critical role of MTL structures in long-term memory formation has been shown in numerous studies spanning 50 years of research (e.g. Bird, Shallice, & Cipelotti, 2007; Jones-Gotman et al., 1997; Milner, 1971; Scoville & Milner, 1957). Much of the early neuropsychological research involved patients with unilateral resections of MTL structures for the surgical treatment of intractable epilepsy. Capitalizing on the unilateral nature of these resections, such studies helped establish the material-specific hypothesis of hemispheric function for memory, with the left hemisphere specializing in verbal material (e.g. Baxendale, 1997; Frisk & Milner, 1990; Helmstaedter & Elger, 1996; Jones-Gotman et al., 1997; Lee, Yip, & Jones-Gotman, 2002; Milner, 1958; Ojemann & Dodrill, 1985) and the right being more critically involved in visuo-perceptual (e.g. Jones-Gotman, 1986; Milner et al., 1968; Pigott & Milner, 1993) and visuospatial learning (e.g. Abrahams, Pickering, Polkey, & Morris, 1997; Bohbot et al., 1998; Crane & Milner, 2005; Feigenbaum, Polkey, & Morris, 1996; Kessels, de Haan, Kappelle, & Postma, 2001; Smith & Milner, 1981, 1989). Functional neuroimaging studies have since corroborated the importance of medial temporal structures, principally hippocampus, in long-term mem-

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ory encoding and retrieval (Buckner et al., 1995; Gabrieli, Brewer, Desmond, & Glover, 1997) and have also demonstrated material-specific lateralization of medial temporal activity (Golby et al., 2001; Kelley et al., 1998; Kennepohl, Sziklas, Garver, Wagner, & Jones-Gotman, 2007; Powell et al., 2005).

Working memory is characterized as a limited-capacity store for the maintenance and manipulation of small amounts of information. The most common model of WM, put forth by Baddeley (1992), posits three subsystems: two for information maintenance – the visuospatial sketchpad and the phonological loop – and an episodic buffer responsible for binding information from the other subsystems, and from long-term memory, into a unitary multimodal representation (Baddeley, 2000, 2003). Consistent with the material-specific hypothesis of hemispheric processing, functional neuroimaging (Awh et al., 1996; Henson, Burgess, & Frith, 2000; Smith & Jonides, 1997) and neuropsychological studies (Vallar, DeBetta, & Silveri, 1997) have found that verbal WM is most often lateralized to the left hemisphere whereas visuospatial WM is often lateralized to the right (Courtney, Petit, Maisog, Ungerleider, & Haxby, 1998; Smith & Jonides, 1997), although some debate remains as to the degree of lateralization of verbal and visuospatial WM in prefrontal cortex (Nystrom et al., 2000; Owen, 2000).

Notably lacking from most neuroimaging studies of WM is activity in MTL structures (e.g. Cohen et al., 1997; Postle, Stern, Rosen, & Corkin, 2000; for a review see Wager & Smith, 2003). This is mirrored in the neuropsychological literature in which WM is typically found to be spared following MTL damage (Cave & Squire, 1992; Ryan & Cohen, 2004). Interestingly, research on nonhuman animals presents a very different picture whereby temporal and MTL involvement in visual and visuospatial working memory is crucial for successful performance (Friedman & Goldman-Rakic, 1988; Miller & Desimone, 1994; Miyashita & Chang, 1988). This has led to a nonhuman animal model of spatial working memory involving dorsolateral prefrontal cortices, parietal cortex, temporal cortex and medial temporal regions (Constantinidis & Procyk, 2004). With the exception of the MTL, there is significant overlap between this model of WM, derived from studies of rats and nonhuman primates, and the model derived from the human neuroimaging and neuropsychology research outlined above. While the human model does not include medial temporal structures, the importance of this brain region, based on findings from nonhuman animals, begs further investigation.

The recent interest in the contribution of the MTL to WM performance (Hasselmo & Stern, 2006; Ranganath & Blumenfeld, 2005) does not mean that there are no previous hints of MTL involvement in WM. In a carefully controlled patient study, Owen, Morris, Sahakian, Polkey, and Robbins (1996) examined visual, visuospatial and verbal WM performance in TLE patients with surgical resections from frontal cortex, anterior temporal lobe (often including partial resection of amygdala and hippocampus) or MTL structures (amygdala and hippocampus). While visuospatial WM impairments were largest in the group with frontal resection, significant impairments were also found in the temporal and MTL resection groups. Interestingly, verbal WM was intact in all three patient groups (Owen et al., 1996). However, the authors were unable to examine material-specific lateralization of WM deficits due to the small number of patients in their MTL group (12 with left, and 7 with right, side resections). A number of recent studies have examined the impact of MTL damage on WM performance, albeit exclusively in the visual and visuospatial domains and using patients with predominantly bilateral damage to the hippocampus and MTL region (e.g. see: Hannula et al., 2006; Hartley et al., 2007; Olson, Moore, et al., 2006; Olson, Page, et al., 2006; van Asselen et al., 2006). For instance, Olson, Moore, et al. (2006) examined visual WM in three patients with bilateral MTL damage; though

they did find deficits on all measures of visual WM, the bilateral nature of the lesions in their patient group obviously precludes implicating either hemisphere in decreased WM ability. In another recent study, van Asselen et al. (2006) administered two tests of visuospatial WM – the oft-used Corsi Block-Tapping task and a computerized task that required participants to search for a target object hidden in a set of virtual boxes – to a series of stroke patients. Using an ROI-based approach, they delineated lesions in prefrontal, parietal and hippocampal cortices based on CT or MRI scans and examined the relationship between lesion size and location and WM performance. The authors found that both left and right hippocampal lesion groups were impaired in comparison to controls on the computerized visuospatial WM task, but not on the Corsi Blocks task. Interestingly, this impairment was largest for patients with right hippocampal lesions, suggesting a critical role for the right hippocampus in visuospatial WM and lending support to the material-specific hypothesis. Interpretation of this finding is tempered, however, by the overall small number of patients with hippocampal damage (left hemisphere $n=6$; right hemisphere $n=10$) and further by the fact that over half of these patients also had lesions outside the hippocampus. Of the 16 patients with hippocampal lesions, 9 had lesions in prefrontal and/or parietal regions, areas that the authors also examined for WM related deficits.

The question of hemispheric laterality of WM remains open; with one study reporting a critical role for the right MTL in spatial WM (van Asselen et al., 2006), and others unable to address laterality as only patients with bilateral damage to MTL were studied (Hannula et al., 2006; Hartley et al., 2007; Olson, Moore, et al., 2006; Olson, Page, et al., 2006), and still others failing to find any effect of side of epilepsy (Owen, Sahakian, Semple, Polkey, & Robbins, 1995; Owen et al., 1996). As noted, recent studies investigating the role of MTL structures in WM have focused exclusively on visual and visuospatial material (Hannula et al., 2006; Hartley et al., 2007; Olson, Moore, et al., 2006; Olson, Page, et al., 2006) and are thus ill suited to investigate any material-specific interaction that might exist between WM and side of damage. Should the MTL be involved in WM in a material-specific manner, it is hypothesized that a double-dissociation between verbal and visuospatial WM performance would occur – patients with damage to left MTL would demonstrate impaired verbal WM, whereas patients with damage to right MTL would demonstrate impaired visuospatial WM. Furthermore, to the degree that either MTL participates in WM irrespective of material type, it is expected that patients with unilateral TLE damage will show reduced WM capacity on both verbal and visuospatial measures in line with previous research showing impaired WM in patients with unilateral MTL damage (Owen et al., 1996; van Asselen et al., 2006).

Here we present data from a large sample of patients with unilateral TLE, on a pair of matched verbal and visuospatial supraspan tasks, to clarify the ambiguity surrounding the MTL contribution to WM. We strongly believe that a matched task approach is better suited to examining interhemispheric differences in mnemonic function as it controls for all task characteristics save modality of interest and has been instrumental in revealing deficits where unmatched tasks have not (Jones-Gotman et al., 1997; Majdan, Sziklas, & Jones-Gotman, 1996).

2. Method

2.1. Subjects

Ninety-six patients of the Montreal Neurological Hospital with unilateral TLE participated in the present study. All patients were

investigated according to a standard protocol that included neurological examination, anatomical MRI scans, EEG video monitoring, review of symptomatology and case history, in-depth neuropsychological evaluation and, in select cases, stereotactic EEG (i.e., implanted EEG depth electrodes). For the purposes of this study, side of seizure focus was determined primarily based on seizure description, neurological evaluation, MRI pathology and EEG abnormality. Fifty-seven patients were found to have a seizure focus in the left, and 39 in the right, temporal lobe. Of these 96 patients, 24 were unoperated at the time of data collection, and 72 patients were previously operated: 28 had undergone a selective amygdalohippocampectomy (SAH) sparing the temporal neocortex (16 left and 12 right) and 41 had undergone a corticoamygdalohippocampectomy (CAH) in which the resection also encroached upon the anterior temporal neocortex (27 left and 14 right); 3 patients had a tumorectomy in the left temporal lobe including hippocampus.

The SAH procedure at our institute typically involves performing a corticectomy along the superior bank of the middle temporal gyrus, then extending this line of entry down along the superior temporal sulcus, across the temporal white matter and into the temporal horn of the lateral ventricle. From this point of entry the surgeon resects the amygdala, hippocampus, entorhinal cortex and uncus, sparing the temporal neocortex (Olivier, 2000). Typically our SAH procedure removes approximately 80% of the amygdala and 60% of the hippocampus (Abosch et al., 2002). CAH includes structures removed in SAH and in addition extends the resection from the tip of the temporal lobe to approximately 5 cm along the Sylvian fissure and 5–5.5 cm along the bottom of the middle fossa on the nondominant side and 4.5–5 cm in the dominant hemisphere. The posterior resection line is extended downwards, across

the superior temporal sulcus and lateral gyri, to the collateral fissure (Olivier, 1997). All surgeries in our institute are performed by aspiration, which prohibits collection of pathological specimens. Structural magnetic resonance images of representative patients from among our sample demonstrating SAH and CAH resections (as they are performed at the Montreal Neurological Hospital) are shown in Fig. 1.

There were 6 left-handed patients in the left, and 2 in the right, TLE group. All but one of these had undergone an intracarotid amobarbital procedure (IAP) to determine lateralization of speech dominance, and in all cases they were found to be left-hemisphere dominant. Exclusion criteria were multifocal seizures, full-scale IQ ratings of less than 75 on the Wechsler Adult Intelligence Scale (revised), atypical cerebral speech representation (as determined by IAP), and age younger than 17 or older than 65. Finally, given the deleterious effects that certain antiepileptic drugs can have on cognitive performance (Aldenkamp et al., 2000; Fritz et al., 2005; Lee et al., 2003; Ortinski & Meador, 2004; Thompson, Baxendale, Duncan, & Sander, 2000), patients taking topiramate at the time of neuropsychological testing were also excluded.

Patient groups (24 unoperated, 28 SAH, 41 CAH and 3 left temporal tumorectomies) did not differ in side of epilepsy, gender composition, age, age of onset of epilepsy, years since seizure onset, years of education or Full Scale IQ (all $p > 0.187$ except years of education: $p = 0.065$). Left and right TLE groups (including unoperated, CAH, SAH and tumorectomy) did not differ in gender composition [$\chi^2(1) = 1.68, p = 0.2$], age of onset of epilepsy [unequal variances assumed, $t(59.95) = 1.52, p = 0.14$], years since seizure onset [unequal variances assumed, $t(92) = 0.3, p = 0.76$] or Full Scale IQ [$t(88) = 1.29, p = 0.2$]. Right TLE patients were older than

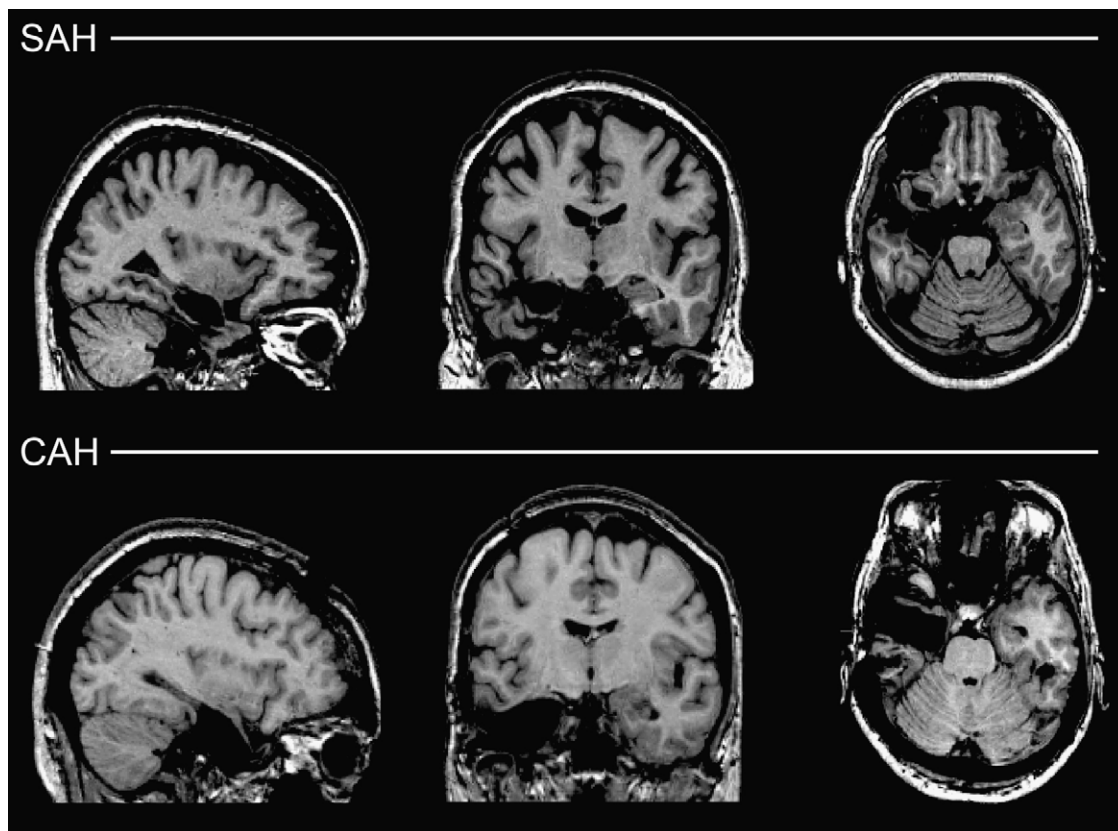


Fig. 1. T1-weighted structural magnetic resonance images showing sagittal, coronal and axial slices of representative resections in patients with unilateral temporal lobe epilepsy. *Top row:* left hemisphere selective amygdalohippocampectomy (SAH). *Bottom row:* left hemisphere corticoamygdalohippocampectomy (CAH).

Table 1
Characteristics and Wechsler Full Scale IQ of unoperated, SAH, CAH and tumorectomy patient groups

	Unoperated (n = 24)				SAH (n = 28)				CAH (n = 41)				Tumorectomy	
	Left TLE (n = 11) (6F, 5M)		Right TLE (n = 13) (8F, 5M)		Left TLE (n = 16) (10F, 6M)		Right TLE (n = 12) (10F, 2M)		Left TLE (n = 27) (13F, 14M)		Right TLE (n = 14) (9F, 5M)		Left TLE (n = 4) (4F)	
	M	S.D.	M	S.D.	M	S.D.	M	S.D.	M	S.D.	M	S.D.	M	S.D.
Age	31.0	7.9	41.9	6.1	34.8	9.2	38.2	8.6	37.7	11.1	39.5	9.7	26.0	6.1
Age of seizure onset	16.9	12.3	16.4	16.6	8.1	7.5	15.3	9.9	13.4	9.6	16.3	14.9	6.0	1.7
Years since seizure onset	16.8	14.3	25.2	12.1	26.8	7.8	22.9	14.2	23.7	11.3	23.2	11.8	16.8	14.3
Years of education	12.1	2.4	14.1	3.2	12.4	2.3	13.7	3.4	11.8	2.6	11.1	2.4	11.0	1.0
Wechsler Full Scale IQ	91.3	14.7	97.1	14.0	91.0	9.1	94.3	10.6	90.6	11.1	92.9	16.8	101.7	4.5

Note. TLE: temporal lobe epilepsy; F: female; M: male.

left TLE patients at time of testing [$t(94)=2.5$, $p=0.014$]; possible effects owing to this difference will be addressed in the analysis and discussion. The characteristics of left and right unoperated, CAH, SAH and tumorectomy patients are shown in Table 1. Within these patient groups there were missing data for age of onset ($N=2$), years of education ($N=3$) and Wechsler Full Scale IQ ($N=6$). Supraspan intrusion scores were uninterpretable or missing in six patients on the verbal supraspan task, and in four patients on the visuospatial supraspan task.

Thirty healthy control (HC) subjects (28 right-handed; 15 women) were recruited from among hospital support staff and patients' relatives. Patient groups and HC did not differ in gender composition [$\chi^2(2)=2.88$, $p=0.237$], age [$F(2,123)=2.74$, $p=0.068$] or education [$F(2,120)=2.43$, $p=0.092$]. Characteristics of HC and left and right patient groups are summarized in Table 2.

In a separate experiment, 20 right-handed participants (10 women) completed both supraspan tasks four times in four sessions over an average of 15 days (range: 10–21 days; mean number of days between sessions: 3.66, SEM: 0.14). Subjects were university students (mean age: 24.29; SEM: 0.79) recruited from the McGill University community.

2.2. Test materials and procedure

The verbal supraspan task consisted of sequences of digits pseudorandomized so as to prevent sequential (e.g. 456) and familiar (e.g. local telephone area code) sequences from appearing. For sequences of length less than 10, no digit was repeated. For sequences of length 10 or greater, the repetition of digit(s) was necessary and care was taken to keep the distance within the sequence of the first and second occurrence of the digit as large as possible. In practice, few patients reach the 10 digits set size and the repetition of items is of minor concern. There were eight trials (i.e., novel sequences of digits) per set size (i.e., sequence length), beginning with a set size of four digits and increasing until the participant could no longer perform successfully (i.e., unable to repeat any of the eight sequences at a given set size). Experimenters were trained to deliver sequences in a monotone at a steady rate of one item per second (so as not to aid participants

in “chunking” sequences in WM). Participants were instructed to repeat each sequence, in proper order, immediately after 2 hearing it.

The visuospatial supraspan task used the Corsi blocks apparatus in its original nine-block configuration (Corsi, 1972; Milner, 1971). Task instruction and administration were matched to the verbal task. The Corsi blocks apparatus consists of nine black blocks distributed in an irregular fashion on a black board. On one side of the apparatus the blocks are identified using numbers, and on the opposing side they are blank. The apparatus is positioned such that the numbered side faces the experimenter and the blank side faces the subjects. At no time were subjects allowed to see the experimenter's side of the apparatus so as to discourage them from labeling the blocks themselves and using a verbal (WM) strategy to perform the task. Sequences of blocks were tapped by the experimenter with a red pen at a steady rate of one per second. Participants were instructed to use the index finger of their dominant hand to tap back each sequence, in proper order, immediately afterwards.

As the instructions and procedure are identical for both verbal and visuospatial WM tasks, they are considered matched tests of verbal and visuospatial WM with only the type of memoranda differing between them.

Patients received the tasks during the course of their neuropsychological evaluation at the Montreal Neurological Institute. Typically, patients received the visuospatial supraspan task on the first day of their evaluation and the verbal supraspan task during the 2nd day. HC received only these tasks (administered in a counterbalanced order) along with the Crovitz-Zener handedness inventory (Crovitz & Zener, 1962).

2.3. Scoring

Participants begin with sequences of four units (digits or blocks) and complete eight trials at this set size before progressing to the next one, in which the sequence length is increased by one. In the rare instance that participants fail at sequence lengths of four, sequence lengths of three are attempted. At each successive set size, participants attempt to repeat eight different sequences accu-

Table 2
Demographics of the left and right TLE and healthy control groups

	Left TLE (n = 57) (32 women, 25 men)		Right TLE (n = 39) (27 women, 12 men)		Healthy controls (n = 30) (15 women, 15 men)	
	M	S.D.	M	S.D.	M	S.D.
Age	35.0	10.2	39.9*	8.2	38	12.6
Age of seizure onset	12.1	9.9	16.1	14.0	Not applicable	
Years since seizure onset	23.0	11.2	23.8	12.4	Not applicable	
Years of education	12.0	2.4	12.9	3.2	13.23	2.24
Wechsler Full Scale IQ	91.5	11.2	94.9	13.8	Not applicable	

Note. TLE: temporal lobe epilepsy. *Significant difference between left and right TLE groups ($p < 0.05$).

rately; the large number of trials allows for a thorough assessment of performance.

Supraspan is defined as the set size at which a subject is correct on three or fewer of the eight trials and has no correct trials at the next higher set size. For example if a subject has two of eight trials correct at a sequence length of eight but none at a sequence length of nine, the supraspan would be scored as eight. With this method, it is possible for participants to have a supraspan score two or three levels above their immediate memory span. In addition, errors of intrusion (adding numbers/tapping blocks that are not part of the original sequence) are scored for each trial at the participant's supraspan level (e.g., if a participant has a supraspan size of seven items, then intrusion errors are only calculated for the eight trials at sequence size of seven). As the frequency of intrusion errors increases with increasing sequence lengths, a correction was applied to the intrusion error measure. This correction consisted of taking the ratio between the number of intrusion errors to supraspan size. For example, if a participant achieves a supraspan size of 9 with 3 intrusion errors their intrusion error ratio will be 0.3 (i.e. 3 divided by 9). Similarly, if a participant achieves a supraspan size of 6 with 2 intrusion errors their intrusion error ratio will also be 0.3. This correction allows for direct comparisons between patients and healthy control subjects, who typically achieve a higher supraspan size and thus can make more intrusion errors.

2.4. Stability of supraspan tasks across time

Twenty university students completed both span tasks four times over four sessions. At Session 1, half of the subjects were given the digit task first and the other half were given the block task first; at subsequent testing sessions, the initial task alternated between digits and blocks. To ensure that subjects did not learn the sequences over repeated testings, a second set of sequences was generated and used on alternate sessions.

2.5. Analysis

2.5.1. Unoperated, SAH, CAH and tumorectomy patients

Two $2 \times 2 \times 4$ mixed-design analyses of variance (ANOVA) were conducted, one for supraspan size and another for intrusion errors. In both analyses the repeated measure was material type (verbal and visuospatial) and the between-subjects factors were side (left and right) and patient group (unoperated SAH, CAH and tumorectomy).

2.5.2. Patients and healthy control subjects

A 2×3 mixed-design ANOVA was performed for supraspan size with material type (verbal and visuospatial) as the repeated measure and group (left TLE, right TLE, HC) as the between-subjects factor. An identical 2×3 mixed-design ANOVA was conducted on intrusion error ratios.

2.5.3. Predictors of supraspan size and intrusion errors

In order to identify clinical and demographic variables that predict poor WM performance, separate multiple regression analyses were performed on patients' supraspan size and intrusion error ratios for each material type (verbal and visuospatial). Predictors used in the model were side of epilepsy (left and right), surgery (operated and unoperated), age, age of onset, years of education and Wechsler Full Scale IQ. All 96 patients were included in the analysis; of these, data were missing for age of onset ($n=2$), years of education ($n=3$) and Full Scale IQ ($n=6$). Missing data were replaced with the mean.

Finally, based on findings from the regression analysis, a 2×3 repeated-measures analysis of covariance (ANCOVA) was

performed for supraspan size with material type (verbal and visuospatial) as the repeated measure, group (left TLE and right TLE) and surgery (operated and unoperated) as the between-subjects factors, and participant age as covariate.

2.5.4. Temporal stability

To investigate the stability of our WM measures over time, 20 healthy college students performed the verbal and visuospatial WM tasks four times. Two-way random effects Intra-class correlation coefficients (ICCs) were calculated separately for verbal and visuospatial tasks for four pairs of test sessions (Time 1:Time 2, Time 1:Time 3, Time 1:Time 4) and for the conjunction of all test sessions (Time 1:Time 2:Time 3:Time 4). As patients are only assessed once during a typical evaluation, only single measure reliability is reported. Interpretation of the ICC scores is made according to the following convention: less than 0.40 = poor reliability; 0.40–0.75 = fair-to-good reliability; >0.75 = excellent reliability (Fleiss, 1986).

3. Results

3.1. Supraspan size

3.1.1. Supraspan size in unoperated, SAH, CAH and tumorectomy patients

Mixed-design ANOVA on the four patient groups yielded a main effect of material type [$F(1,89)=10.35, p=0.002$] indicating a greater verbal [$M=7.45$] than visuospatial [$M=6.87$] supraspan size. There was no main effect of group [$F(3,89)=1.64, p=0.19$; $M_{\text{unoperated}}=7.32$; $M_{\text{SAH}}=7.06$; $M_{\text{CAH}}=6.88$; $M_{\text{tumorectomy}}=7.67$] or of side [$F(1,89)=2.41, p=0.12$; $M_{\text{left}}=7.34$; $M_{\text{right}}=6.95$]. The interaction between material type and side of epilepsy was significant [$F(1,89)=4.46, p=0.037$]. Right TLE patients had a smaller visuospatial [$t(94)=2.69, p=0.008$; $M_{\text{left}}=6.95$; $M_{\text{right}}=6.44$] but not verbal [$t(94)=0.06, p=0.535$; $M_{\text{left}}=7.3$; $M_{\text{right}}=7.46$] supraspan size compared to left TLE patients. There was no significant interaction between side of epilepsy and patient group [$F(2,89)=2.52, p=0.09$], material type and patient group [$F(3,89)=0.24, p=0.87$] or material type, side of epilepsy and patient group [$F(2,89)=0.59, p=0.56$].

3.1.2. Supraspan size in left and right TLE and HC

As the previous analysis demonstrated no main effect of patient group, unoperated and operated patients (SAH, CAH and tumorectomy) were combined for the following analyses. Fig. 2 shows verbal and visuospatial supraspan sizes for the patients, divided into left and right TLE, and HC. Mixed-design ANOVA revealed a main effect of material type [$F(1,123)=41.9, p<0.001$], a main effect of group [$F(2,123)=22.19, p<0.001$] and a significant interaction between material type and group [$F(2,123)=4.28, p=0.016$]. Patients had a reduced supraspan size compared to healthy control subjects on both verbal [*left TLE*: $t(85)=5.1, p<0.001$; *right TLE*: $t(67)=4.64, p<0.001$] and visuospatial [*left TLE*: $t(85)=3.2, p=0.002$; *right TLE*: $t(67)=5.46, p<0.001$] supraspan tasks. As in the previous analysis, patients with right TLE had a further reduction in visuospatial supraspan size compared to patients with left TLE [$t(94)=2.69, p=0.008$ $M_{\text{left}}=6.95$; $M_{\text{right}}=6.44$]. There was no difference in performance between left and right TLE patients on the verbal supraspan task [$t(94)=0.62, p=0.535, M_{\text{left}}=7.3$; $M_{\text{right}}=7.46$].

3.2. Supraspan intrusion errors

3.2.1. Supraspan intrusion errors in unoperated, SAH, CAH and tumorectomy patients

In the mixed-design ANOVA comparing the four patient groups there was no main effect of material type [$F(1,83)=0.04, p=0.85$]

or of side of epilepsy [$F(1,83)=0.62, p=0.43$]. There was a main effect of group [$F(3,83)=3.1, p=0.03, M_{\text{unoperated}}=0.39; M_{\text{SAH}}=0.57; M_{\text{CAH}}=0.51; M_{\text{tumorectomy}}=0.23$]: patients with SAH made more intrusion errors overall than unoperated patients [$t(49)=2.53, p=0.013$]. The interaction between material type and side of epilepsy was significant [$F(1,83)=7.74, p=0.008$]. Patients with left TLE made more intrusion errors on the verbal supraspan task than patients with right TLE [unequal variances assumed $t(88)=2.81, p=0.006, M_{\text{left}}=0.58; M_{\text{right}}=0.40$]. There was no similar difference in intrusion errors on the visuospatial supraspan task [$t(90)=1.23, p=0.221, M_{\text{left}}=0.45; M_{\text{right}}=0.53$]. The interactions of patient group and side of epilepsy; material type and patient group; and material type, patient group and side of epilepsy were all *n.s.* ($p > 0.23$, all tests).

3.2.2. Supraspan intrusion errors in left and right TLE and HC

Mixed-design ANOVA revealed no main effect of material type [$F(1,117)=0.04, p=0.847$] or of side [$F(2,117)=2.3, p=0.105$]. There was a significant interaction between material type and group [$F(2,117)=5.09, p=0.008$] (Fig. 3). As in the previous analysis, this interaction indicated that patients with left TLE made more intrusion errors than did right TLE patients on the verbal supraspan task [unequal variances assumed $t(88)=2.81, p=0.006$] but not on the visuospatial task [$t(90)=1.23, p=0.221$]. Left TLE patients also made more intrusion errors than healthy control subjects on the verbal supraspan task [$t(82)=2.46, p=0.016$] but not on the visuospatial task [$t(82)=0.87, p=0.387$]. Right TLE patients, on the other hand, made more intrusion errors than did control subjects on the visuospatial supraspan task [$t(66)=2.06, p=0.043$] but not on the verbal task [$t(64)=0.16, p=0.876$]. Finally, left TLE patients made more intrusion errors on the verbal supraspan task than on the visuospatial supraspan task [$t(53)=2.56, p=0.013$], but right TLE and HC showed no differences between material types on this measure [right TLE: $t(35)=1.96, p=0.058$; HC: $t(29)=0.18, p=0.859$].

3.3. Predictors of supraspan size and intrusion errors

Results of the multiple regression analysis examining demographic and clinical variables that predicted verbal supraspan size in patients with left or right TLE resulted in a single-predictor model accounting for 12.5% of the variance in verbal supraspan

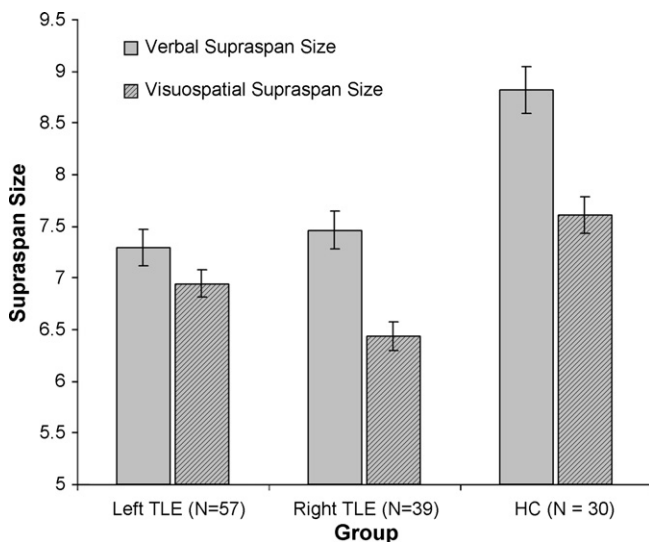


Fig. 2. Performance on verbal and visuospatial supraspan tasks as a function of group. Left and right TLE groups are comprised of both unoperated and operated patients. Error bars indicate standard error of the mean.

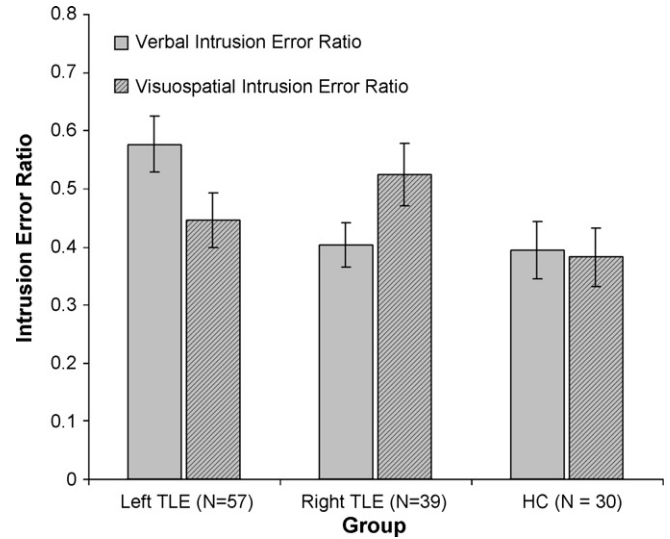


Fig. 3. Ratio of intrusion errors to supraspan set size on verbal and visuospatial supraspan tasks as a function of group. Left and right TLE groups are comprised of both unoperated and operated patients. Error bars indicate standard error of the mean.

size [$F(6,89)=3.27, p=0.006, R^2=0.181, R^2_{\text{adj}}=0.125$]. Age was a significant predictor of verbal supraspan size [$\beta=-0.25, p=0.022$], demonstrating that increasing age led to a decrease in verbal supraspan size. Multiple regression analysis of factors predicting visuospatial supraspan size yielded a three-predictor model accounting for 18% of the variance in visuospatial supraspan size [$F(6,89)=4.48, p=0.001, R^2=0.232, R^2_{\text{adj}}=0.18$]. The three variables that were significant predictors of visuospatial supraspan size were age [$\beta=-0.342, p=0.001$], Full-Scale IQ [$\beta=0.251, p=0.023$] and side of TLE [$\beta=-0.218, p=0.028$], indicating that increasing age predicts a decline in visuospatial supraspan size and that right TLE predicts a reduced visuospatial supraspan size compared to left TLE—replicating the results found in the above mixed-design ANOVAs. Finally, increasing Full-Scale IQ was predictive of a larger visuospatial supraspan size. The only common predictor across material type was age.

Identical multiple regression analyses were conducted on intrusion error ratios for both tasks. The model for verbal intrusion error ratios was significant, accounting for 11% of the variance in intrusion errors [$F(6,89)=2.86, p=0.013, R^2=0.162, R^2_{\text{adj}}=0.105$] and yielding a three-factor model with surgery [$\beta=0.229, p=0.025$], side of epilepsy [$\beta=-0.227, p=0.029$] and Full-Scale IQ [$\beta=-0.231, p=0.045$] as significant predictors. This in effect replicates the previous mixed-design ANOVA, revealing that operated patients made more intrusion errors than unoperated patients and patients with left TLE made more intrusion errors than those with right TLE on the verbal task. Furthermore, Full-Scale IQ emerged as a significant predictor of intrusion errors, indicating that patients with higher Full-Scale IQs were less likely to make intrusion errors on the verbal task. The model for visuospatial intrusion error ratios was not significant [$F(6,89)=1.83, p=0.102, R^2=0.110, R^2_{\text{adj}}=0.05$].

3.4. Supraspan size with age as covariate

Results from the regression model consistently show that age negatively predicts both verbal and visuospatial supraspan size in patients. Furthermore, as pointed out above, right TLE patients were older than left TLE patients [$t(94)=2.5, p=0.014$]. Given that our right TLE group is, on average, older than our left TLE group, it is possible that the effects seen in the mixed-design

Table 3
Performance and test–retest reliability of verbal and visuospatial WM tasks across four testing sessions

	Supraspan score			
	T1	T2	T3	T4
Verbal task (<i>M</i> and S.E.)	9.45 (0.34)	9.70 (0.31)	9.90 (0.35)	10.00 (0.39)
Visuospatial task (<i>M</i> and S.E.)	7.75 (0.24)	7.85 (0.24)	8.05 (0.23)	7.90 (0.29)
	Intraclass correlation coefficient			
	T1:T2	T1:T3	T1:T4	T1:T2:T3:T4
Verbal task (ICC and 95% CI)	0.88 (0.72–0.95)**	0.90 (0.77–0.96)**	0.91 (0.79–0.96)**	0.89 (0.79–0.95)**
Visuospatial task (ICC and 95% CI)	0.64 (0.29–0.84)*	0.67 (0.33–0.85)*	0.54 (0.14–0.79)*	0.66 (0.46–0.83)**

Note. *M*: mean; S.E.: standard error of the mean; CI: confidence interval. Significant at * $p < 0.01$; ** $p < 0.001$.

ANOVAs are attributable to the greater age of our right TLE group. In order to investigate this possibility, a mixed-design ANCOVA, using participant age as a covariate, was carried out on verbal and visuospatial supraspan size. This analysis replicates the initial mixed-design ANOVA, revealing a significant material type \times side of epilepsy interaction [$F(1,91) = 5.13, p = 0.026$]. Once again, there was no interaction between material type and surgery [$F(1,91) = 0.02, p = 0.895$] or between surgery and side of TLE [$F(1,91) = 1.21, p = 0.274$]. Critically, patients with right TLE were still reduced in visuospatial supraspan size compared to patients with left TLE, even when age was used as a covariate [$F(1,91) = 6.75, p = 0.011$; $EMM_{\text{left}} = 7.08$; $EMM_{\text{right}} = 6.52$]. Furthermore, there remained no difference in performance between left and right TLE patients on the verbal supraspan task [$F(1,91) = 0.46, p = 0.497$; $EMM_{\text{left}} = 7.38$; $EMM_{\text{right}} = 7.59$].

3.5. Stability of supraspan size over repeated testing

Overall test–retest reliability was excellent for the verbal WM task and fair to good for the visuospatial WM task (Table 3). The ICCs for the test session pairs and for the conjunction of all test sessions were highly significant (all $p < 0.01$).

4. Discussion

In the present study, we show that medial temporal lobe damage, arising from either temporal lobe epilepsy or surgical resection, results in verbal and visuospatial working memory deficits when patients are compared to age- and education-matched control subjects. Furthermore, a partial dissociation between material type and side of MTL damage was found. Patients with right TLE demonstrated decreased visuospatial WM capacity when compared with left TLE patients and increased visuospatial intrusion errors when compared to healthy control subjects. Patients with left TLE, on the other hand, demonstrated increased intrusion errors for verbal, but not visuospatial WM, when compared to patients with right TLE and healthy control subjects.

With respect to surgical resection of MTL areas, there was no effect of surgery or of type of surgery (CAH vs. SAH vs. tumorectomy) on WM size. We did find an effect of surgery type on intrusion errors, with SAH patients making more intrusion errors overall than unoperated patients. However, there was no interaction between surgery type and material (verbal or visuospatial) or between side and surgery type, suggesting that this increase in intrusion errors among SAH patients is unrelated to side of epilepsy or material type. Finally, regression analyses revealed that the best predictor of WM size across modality was age; however, when age was entered as a covariate in the original analysis, it did not account for differences between patients and healthy control subjects, nor between patient groups. Thus, the influence of age on

WM size was not responsible for the observed deficit in right TLE patients.

The finding that patients show reduced working memory capacity in both modalities in comparison with control subjects suggests that the MTL is involved generally in WM. In addition, the right MTL appears particularly important for visuospatial WM capacity, whereas damage to the left MTL increased verbal WM intrusions. Although these findings are spread across two performance measures (capacity and intrusion errors), they provide strong evidence for material-specific lateralization of WM in the MTL.

4.1. The medial temporal lobe and working memory

Medial temporal lobe structures, particularly the hippocampus, are not traditionally associated with working memory in humans. For example, a recent meta-analysis of WM in functional neuroimaging found no hippocampal involvement in any of its sample; instead, prefrontal and parietal areas were the most common findings (Wager & Smith, 2003). This human model of WM is in stark contrast to the model derived from research in nonhuman primates and rats showing a critical role for the hippocampus in spatial working memory (Friedman & Goldman-Rakic, 1988; Harley, 1979; Olton & Papas, 1979; Otto & Eichenbaum, 1992).

Recently, a number of patient (Olson, Moore, et al., 2006; van Asselen et al., 2006) and neuroimaging (e.g. Nichols et al., 2006; Piekema et al., 2006; Ranganath & D'Esposito, 2001; Stern et al., 2001) studies have emerged implicating MTL structures in WM. In two related studies, one using intracranial EEG and the other using fMRI, Axmacher et al. (2007) demonstrated converging evidence for the involvement of MTL in WM. In the first study they demonstrated sustained neural activity during the maintenance portion of a visual WM task in patients with TLE who were implanted with depth electrodes in the MTL. To ensure that this finding was not due to the disease process, healthy volunteers performed the same WM task while undergoing fMRI in a second study. This latter experiment revealed hippocampal involvement during the maintenance period of the WM task for high WM loads. A similar relationship between WM load and hippocampal activity has been reported by Rissman, Gazzaley, and D'Esposito (2007), who found increased connectivity between the hippocampus and inferior frontal gyrus as WM loads increased. At issue, however, is whether the observed hippocampal activity during the maintenance period of a WM task is related to WM performance or is simply an ongoing parallel process that does not contribute to WM. This possibility was investigated independently by Ranganath et al. (2005) and Nichols et al. (2006) who both found that hippocampal activity during the maintenance period of a novel object WM task (Ranganath et al., 2005) and a face WM task (Nichols et al., 2006) predicted subsequent recognition memory. Taken together, these findings may help explain the lack of previous neuroimaging research implicating the MTL in WM: tasks with

low WM load, or designs that collapsed across load conditions, may have failed to find hippocampal activity due to the relative ease of the task or a failure to separate out the contributions of varying WM load conditions.

In the neuropsychological literature there is a similar lack of findings of WM deficits following MTL damage (with the noted exceptions of Olson, Moore, et al., 2006; Owen et al., 1996; van Asselen et al., 2006). For example, van Asselen et al. (2006) failed to find a deficit using the Corsi blocks task in a paradigm similar to that reported here. A possible explanation for their negative findings, and those of earlier neuropsychological research, may be due to differences between simple (i.e., immediate recall) and complex (i.e., recall plus a concurrent processing requirement) span tasks. In the present study we measured performance at supraspan levels, that is, at set sizes larger than a subject's immediate memory span. The introduction of items above a subject's immediate memory span acts as interference in rehearsal. Moreover, supraspan tasks have been shown to be correlated with complex span tasks and are equally predictive of higher cognitive function (Unsworth & Engle, 2006, 2007). Neuropsychology has tended to focus on simple span tasks (e.g., digit span and block span) as proxies for WM, which may explain why the present findings differ from earlier neuropsychological investigations of MTL damage.

While the deficits in WM capacity are straightforward, data on intrusion errors paint a more complex picture. Patients with left TLE showed an increase in verbal intrusion errors compared to patients with right TLE and healthy control subjects. Patients with right TLE, however, only committed increased intrusion errors on the visuospatial task when compared to healthy control subjects. Moreover, we also found that patients with SAH made more intrusion errors overall than did unoperated patients, but this finding did not generalize to CAH patients. While many of the mistakes we observed represented ordering confusion, such as inverting items within a sequence (e.g. 478 instead of 874) or transposing items to a different part of the sequence (e.g. 4897 instead of 7489), intrusion errors are thought to reflect a more serious difficulty in inhibiting irrelevant responses. Previous reports of intrusion errors in a verbal learning paradigm found that left TLE patients made more intrusion errors than did right TLE patients and that the number of intrusion errors increased after a left temporal-lobe resection (Hermann, Wyler, Bush, & Tabatabai, 1992). Additional studies have shown that individual differences are related to the number of intrusion errors; for example elderly participants (De Beni & Palladino, 2004) and poor WM performers (Rosen & Engle, 1998) commit more intrusion errors than do healthy control subjects. With regard to our findings it would seem premature to suggest an involvement of the MTL in inhibitory control; rather, what may be occurring is that without a healthy hippocampus the maintenance of items in WM is impaired, leading to confabulation during response. In our sample this appears to be more prevalent in the left TLE patients, while right TLE patients are impaired only in comparison to healthy control subjects.

4.2. *Material specificity or novelty and familiarity?*

While the present findings are interpreted within the framework of material specificity and hemispheric specialization, there is some controversy as to the role of MTL in WM and whether it is selectively required for complex and novel material over familiar material (Piekema et al., 2006; Stern et al., 2001; Zarah, Rakitin, Abela, Flynn, & Stern, 2005), although other studies have found MTL involvement in WM even for familiar verbal material (Karlsgodt et al., 2005). Our verbal WM task uses sequences of digits, which tend to be overpracticed (i.e., memorization of phone numbers).

The visuospatial WM task, on the other hand, requires the maintenance and reproduction of spatial patterns and is thus relatively novel to most subjects. Therefore, in our study, material specificity may be confounded with familiarity.

In light of previous research, a plausible interpretation of our findings is that the MTL and, more specifically, hippocampus, is involved in the maintenance of stimuli in WM and that damage to the MTL region decreases a patient's ability to retain the items in WM. Furthermore, although the MTL is important for WM maintenance with both familiar/verbal material (Karlsgodt et al., 2005) and novel/visuospatial material (Axmacher et al., 2007; Olson, Moore, et al., 2006; Ranganath & D'Esposito, 2001; van Asselen et al., 2006), converging evidence from neuroimaging and patient studies would suggest that it is more critical for the latter (Owen et al., 1996; Stern et al., 2001). This is paralleled in episodic memory research by findings demonstrating that hippocampal activity fails to index familiarity (Davachi, Mitchell, & Wagner, 2003; Montaldi, Spencer, Roberts, & Mayes, 2006; Ranganath et al., 2004). Finally, our data and results from Piekema et al. (2006) as well as van Asselen et al. (2006) suggest that the right MTL in particular may be crucial in the maintenance of novel/visuospatial material. Nevertheless, the role of the left MTL in verbal WM cannot be ignored, owing to the increased susceptibility to intrusion errors found among left TLE patients.

4.3. *Is the role of the medial temporal lobe in working memory to form relational representations?*

Two recent studies have raised the possibility that the role of the MTL in WM processes is homologous to its proposed role in declarative forms of memory; that is, to form and maintain relationships among memoranda (Hannula et al., 2006; Olson, Page, et al., 2006). In those two studies, WM deficits were observed on tasks requiring the formation of relationships (e.g. object and location), but relative sparing was seen on simpler WM tasks without a relational requirement (Hannula et al., 2006; Olson, Page, et al., 2006). Both the verbal and visuospatial tasks used here require the storage of items (e.g. digits) or spatial positions and their relative order in time. Typically tasks that measure relational memory focus on the pairing of items with position, or items with other items. In the present case both tasks contain no such relationships (the visuospatial block task by design contains identical blocks to prevent participants from pairing items to spatial position) therefore it seems unlikely that our findings are due to deficits in relational processing.

The issue of what role the relational theory of hippocampal function plays in WM is further confounded by the number of imaging and patient studies demonstrating an MTL involvement in WM for tasks with no relational component (e.g. Axmacher et al., 2007; Cabeza et al., 2002; Campo et al., 2005; Nichols et al., 2006; Olson, Moore, et al., 2006; Ranganath & D'Esposito, 2001; Rissman et al., 2007; Stern et al., 2001). One possible explanation for these divergent findings is that WM for relations is intrinsically more difficult than WM for single features. This possibility was examined by Olson, Moore, et al. (2006) and Olson, Page, et al. (2006), who found that patients with hippocampal damage showed a selective deficit for the conjunction of item and position, but not for single feature trials that had been equated for task difficulty (WM load). Nevertheless, the number of reports demonstrating an involvement of MTL in WM for material with no relational component, including the present study, suggests that this debate is far from settled.

Recently, Baddeley extended his model of working memory to include an episodic buffer which is proposed to act as an interface between WM subsystems and long-term episodic memory and also serves as temporary storage allowing for the formation of multi-modal representations (Baddeley, 2000, 2003; Baddeley &

Wilson, 2002). Given its proposed role as a limited capacity store, dysfunction of the episodic buffer could explain the deficits seen in WM capacity in the present study, thus suggesting that the hippocampus may be a neural substrate of the episodic buffer. This possibility appears unlikely for many of the same reasons that our findings are unlikely to reflect deficits in relational processing. Moreover, our finding of material-specific lateralization of WM deficits argues against the MTL region as being a site where multimodal representations are formed, as is expected of the episodic buffer.

4.4. The possibility of extratemporal damage contributing to decreased WM performance

It has been well established that medial temporal lobe structures share reciprocal connections with a number of brain regions (Bird & Burgess, 2008), notably the prefrontal cortex (Cavada, Company, Tejedor, Cruz-Rizzolo, & Reinoso-Suarez, 2000; Goldman-Rakic, Selemon, & Schwartz, 1984), many areas of which are also found activated in functional neuroimaging studies of working memory (e.g. Petrides et al., 1993; Postle et al., 2000; Smith & Jonides, 1997). It remains a possibility that the overall WM deficit that we observe in both patient groups is related to interference with frontal lobe function via epileptogenic activity spreading along the medial temporal to prefrontal pathways (Corkin, 2001). Previous studies have shown that prefrontal comorbidities on neuropsychological tasks disappear after the diseased MTL structures are removed (Hermann & Seidenberg, 1995) and that patients with TLE occasionally demonstrate hypometabolism in prefrontal cortices, the degree of which is related to performance on tasks measuring executive function (Jokeit et al., 1997; Takaya et al., 2006). Evidence from research using voxel-based morphometry in patients with unilateral temporal lobe epilepsy has shown decreased grey matter density not only in medial temporal structures but also in the prefrontal cortices (Bernasconi et al., 2004). These results suggest that prefrontal dysfunction may be contributing to the WM deficits we observe in patients with unilateral TLE. Although there is ample neuroimaging evidence suggesting a contribution of MTL structures to the maintenance of items in WM, it is not possible in the present study to rule out prefrontal comorbidities in our patient sample. That being said, we observed no difference in WM performance between unoperated and operated patients, suggesting that putative prefrontal comorbidities in unoperated patients are not significantly influencing WM performance.

4.5. Test–retest reliability

Working memory capacity is generally conceived as a finite capacity that reflects attentional control and maintenance of information in the face of interference (Engle, 2002). Therefore, a good measure of WM capacity should be relatively resilient to short-term practice effects and changes in rehearsal strategy. Furthermore, as most of our patients are assessed both pre- and postoperatively, it is important to ensure that any changes in their postoperative test scores reflect changes in brain function owing to the surgical resection and/or to the alleviation of their epileptic symptoms. The verbal WM task used in the present study demonstrated excellent test–retest reliability across multiple sessions. The reliability for the visuospatial WM task was not as high, demonstrating only fair-to-good reliability. However, it is interesting to note that this is not due to practice effects as there was no clear improvement in test scores. Rather it appears that there is greater subject-related variability and/or increased measurement error associated with the visuospatial task, perhaps owing to its more unfamiliar nature. Nevertheless,

reliability for both tasks is more than adequate, demonstrating that the WM scores assessed by these tests are stable across time and resistant to practice effects.

5. Conclusion

Previous research in patients with unilateral damage to the MTL owing to epilepsy (Owen et al., 1996), stroke (van Asselen et al., 2006) or bilateral MTL damage due to disease, stroke or anoxia (Hannula et al., 2006; Hartley et al., 2007; Olson, Moore, et al., 2006; Olson, Page, et al., 2006) demonstrated specific impairments in visual and visuospatial WM. Only Owen et al. (1996) examined verbal WM in addition to visuospatial WM, though they found no impairments in patients with TLE. To our knowledge ours is the first study to specifically examine the issue of material specificity of WM in a large sample of patients with unilateral MTL damage. The findings in the present study add to a new and increasing body of evidence suggesting an important role of medial temporal lobe structures in human working memory for verbal and visuospatial material, particularly at high working memory loads.

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