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Route Learning Impairment in Temporal Lobe Epilepsy

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Abstract

Memory impairment on neuropsychological tests is relatively common in temporal lobe epilepsy (TLE) patients. But memory rarely has been evaluated in more naturalistic settings. This study assessed TLE ($n = 19$) and control ($n = 32$) groups on a real-world route learning (RL) test. Compared to the controls, the TLE group committed significantly more total errors across the three RL test trials. RL errors correlated significantly with standardized auditory and visual memory and visual-perceptual test scores in the TLE group. In the TLE subset for whom hippocampal data were available ($n = 14$), RL errors also correlated significantly with left hippocampal volume. This is one of the first studies to demonstrate real-world memory impairment in TLE patients and its association with both mesial temporal lobe integrity and standardized memory test performance. The results support the ecological validity of clinical neuropsychological assessment.

Keywords

neuropsychology; temporal lobe epilepsy; spatial memory; visual memory; route learning; hippocampus; ecological validity

INTRODUCTION

Learning and memory impairment on standardized clinical measures is common among individuals with temporal lobe epilepsy [1] and [2] and there is a relatively strong relationship between memory test results and temporal lobe pathology and resections, especially of the hippocampal and parahippocampal regions in the dominant hemisphere [3], [4], [5] and [6]. On the other hand, memory functioning in people with epilepsy rarely has been studied in real-world situations outside the clinic [7], [8], and [9], in spite of the fact that ecological validity is vital to neuropsychology [10] and [11].

Route learning (RL) is one crucial aspect of human memory and autonomy [7], [12], [13], [14], [15] and [16]. Barrash [16] provided a comprehensive historical review of neurological/neuropsychological investigations of the family of cognitive deficits comprised by the term topographical disorientation or loss of the ability to navigate within large-scale environments. He concluded that, in the post-acute injury period, anterograde topographical

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disorientation, including RL impairment, is most closely associated with medial occipitotemporal lesions in either hemisphere. This connection between RL ability and a region that includes the medial temporal lobe makes TLE a potential “natural laboratory” for examination of RL.

Spatial memory has been studied in epilepsy patients for more than half a century [17] and [18], but RL itself began to receive systematic attention in TLE less than 20 years ago. The Rivermead Behavioral Memory Test (RBMT) was designed to complement traditional assessment procedures by providing analogues of everyday memory situations, and its subtests include a basic, five-stage RL task that is conducted within a single room [19]. The RBMT occasionally has been used in the assessment of children and adults with TLE and it has compared favorably to traditional tests [20] and [21]. Limited information is available about the performance of adult TLE patients on the RL component of the RBMT, but this particular subtest proved to be a sensitive measure of learning and memory in pediatric TLE patients who had undergone a temporal lobe resection (TLR) [21] and in adolescents with very significantly reduced hippocampal volumes and developmental amnesia due to a hypoxic/ischemic episode [22]. In the pediatric study [21], the left and right TLR groups both were impaired on RBMT route recall and they did not differ significantly from each other.

The RBMT RL subtest does not closely mimic complex real-world RL, which requires recall of a sequence of places and landmarks and the turns made along a route [13]. It differs from wayfinding, which refers to flexible navigation or the ability to find novel paths between locations based on the development of a map-like representation of an environment [23], and from route following or memory for a very familiar, over-learned route. The latter tends to have different neuroanatomical associations, which include the caudate nucleus [23]. Recent studies of more complex RL in TLE patients most often have involved virtual reality [15], [24], and [25] or videotaped routes [26], with only a couple requiring real-world RL [7] and [9].

Pereira et al. [9] administered a hospital-based RL task to left and right presurgical TLE patients ($n = 20$ in each group) and 40 controls. The examiner asked each participant to remember 15 landmarks along the corridors traversed during a single learning trial and, when a participant retraced the route, memory for the landmarks was measured. Thus, it appears this was mainly a landmark recall test and not a measure of RL per se, as it did not require a participant to remember where to turn at multiple decision points. The landmark recall performance of the right TLE group was worse than that of the left TLE group, and only the former group performed worse than the controls.

Barrash et al. [7] administered a real-world RL task to controls and patients with various types of brain injury, including TLR patients. RL impairment was defined as an age-corrected error score that was < -1.5 SD below the mean of controls. Overall, patients with unilateral right hemisphere lesions did not differ significantly on RL from those with left hemisphere lesions. RL impairment was linked most consistently with mesial temporal and/or inferior mesial occipital injury: bilateral (100% impaired), right (86%), left (72%). Interestingly, there was a severe RL deficit in all three patients whose injury included a unilateral left posterior parahippocampal lesion, as was the case for all four patients with unilateral right-sided injury in that area. A minority of the brain-injured participants in the Barrash et al. [7] RL study had undergone left ($n = 4$) or right ($n = 9$) TLR for treatment of seizures, and these appear to comprise all the cases described as having unilateral hippocampal lesions (in addition to their other areas of anterior temporal lobe resection). For this subset of 13 patients, a RL deficit was quite closely associated with right hippocampal resection (100% impaired) and less so with left hippocampal resection (25% impaired).

In this study, we examined real-world, large-scale anterograde RL performance in TLE patients, who had not undergone a TLR, and healthy controls. Because real-world memory functioning, and RL in particular, has not been studied extensively in TLE and the sensitivity and generalizability of virtual reality RL tasks in non-surgical TLE patients has not yet been firmly established, we reasoned that administering a real-world RL task would make a valuable contribution to the study of memory in TLE. RL ability was assessed on a .15-mile route through part of the first floor of a hospital that is notorious for its intricate hallways. The analyses of primary interest were the RL ability of patients versus controls and the correlation between RL performance and standard clinical neuropsychological tests. In a subset of the patients and controls, the correlation between RL ability and hippocampal volumes also was examined. Finally, the association between RL errors and epilepsy variables was examined for the TLE group.

The route learning task was not designed to be a pure test of spatial cognition or an assessment of wayfinding, but a means of studying the ability of TLE patients to learn a route in an unfamiliar, indoor environment, using the cues typically found in such an environment. We expected RL performance to be significantly poorer in the TLE group and to correlate with WMS-III indices [27]. Because left and right TLE patients do not always demonstrate distinct patterns of deficits on auditory and visual memory measures and RL has resulted in bilateral activation in some functional imaging studies, we did not predict there would be an association between RL and specific WMS-III indices or one hippocampus versus the other. In light of the general literature on memory and TLE, we hypothesized that RL performance would correlate significantly with age of seizure onset [4].

METHODS

Subjects

This research was approved by the University of Wisconsin-Madison Health Sciences Institutional Review Board and written informed consent was obtained from each participant. The study included 32 controls and 19 individuals with TLE, all of whom were between the ages of 18 and 59. Patients who had a Wechsler Adult Intelligence Scale-3rd Edition [28] short form full scale IQ (FSIQ) that was less than 80 and controls who had a FSIQ greater than 115 were excluded from the study. One control who was more than 60 years old also was excluded. In determining the WAIS-III FSIQ, the Verbal IQ was prorated on the basis of five subtests and the Performance IQ was estimated on the basis of three subtests [29] and [30]. Two patients did not have current IQ data available, and so their WAIS-III research study results from four years previous were used. See Table 1 for characteristics of the TLE and control groups. T tests showed the two groups did not differ significantly on age ($p = .80$), education ($p = .37$) or WAIS-III IQ variables (all p values $> .08$). Pearson Chi-square tests indicated the groups did not differ in regard to gender distribution ($\chi^2 = 2.35$, $p = .13$) or handedness ($\chi^2 = .62$, $p = .43$).

The majority of the 32 controls were friends, relatives or spouses of individuals with TLE. They met WMS-III criteria for healthy controls [31]; see Table 2.1, p. 21. Those in the TLE group had a history of seizures of definite or probable temporal lobe origin based on consensus neurology/neuropsychology conference review.

Methodology

During the .15-mile (241-meter) RL test, the examiner led each participant at a relatively slow pace through unfamiliar sections or “modules” of the 1st floor of the University of Wisconsin Hospital (see Figure 1). The remainder of the research evaluation took place on

the 6th floor. We have no reason to suspect that any participant was familiar with the area in which the RL was conducted. Although the RL course began in the lobby just outside the hospital cafeteria, the section of the hospital that was traversed included the entrance to lecture halls, pharmacy school faculty offices, student lockers, and organ transplant department offices. There were no inpatient or outpatient rooms or clinics on the 1st floor of the hospital. The patients' epilepsy clinic visits, including those for EEG, did not take place on the 1st floor. Finally, no participant was a past or present student or employee at the hospital.

The University of Wisconsin Hospital is considered difficult to navigate, despite the presence in lobbies of overhead signs indicating the direction to different sections of the hospital. These sections most often are represented by letters and numbers (e.g., G4), in addition to the occasional department name. Similar to the University of Iowa Hospital and Clinics route [7], our route included some hallways that go off at odd angles in a maze-like building. The route ended where it began and included 12 choice points where a wrong turn could be made. Including the starting point, the route included four lobbies where there were at least three hallway choice points. Near its end, participants retraced an earlier part of the route, from the opposite direction, for about 20 meters. There were no closed doors on the route and no windows to provide visual access to outdoor landmarks. The first author tested all participants.

Each participant was 1) asked to pay close attention to the hallway path taken by the examiner so that he/she could then lead the examiner through it and 2) informed that performance would be timed, but that accuracy was more important than speed. The examiner explained in advance that conversation was discouraged so that the examinee could pay attention to the route. Following the demonstration trial by the examiner, each participant led the way through the route three times or twice if performance on the first two trials was flawless. The examiner walked a step or two behind the participant during the test trials. When an error occurred, the examiner pointed out the correct turn and the task continued. Each trial began immediately after completion of the previous trial. The number of errors and time to completion were recorded for each trial. Participants were not questioned systematically about route learning strategies they might have employed.

For the participants who committed no errors on the first two trials, the 3rd trial was not administered, a score of zero errors was assigned for that trial and their mean time to completion was based on the time for the first two trials. For all other participants, the mean number of errors and mean time to completion was based on actual performance over three trials. Correlational analyses were conducted for RL errors and the demographically-corrected scores from the neuropsychological measures that appear in Table 2. The results were analyzed with the IBM Statistical Package for the Social Sciences (SPSS) version 20 for Windows [32].

The time in minutes that it took the examiner to lead the participants through the route did not differ between groups, control $\bar{M} = 3.73$, $SD = .12$, TLE $\bar{M} = 3.73$, $SD = .14$, $t = -.14$, $p = .89$. The level of activity encountered in the hallways during RL varied mildly, but there was no difference between groups with regard to the day of the week when participants were assessed (Mann-Whitney $U = 282.0$, $p = .64$). The time of day when the test was administered, recorded for 46 of the 51 participants, also did not differ between groups (Mann-Whitney $U = 233.0$, $p = .87$).

Brain imaging

The MRI data presented here (see Table 1) were acquired at the time of the initial research neuropsychological assessment, which took place approximately four years prior to

administration of the RLT. Thus, it is possible that the MRI data underestimate the actual level of hippocampal atrophy in some patients and older controls. Images were obtained on a 1.5 T GE Signa MR scanner at the University of Wisconsin-Madison and transferred to the University of Iowa-Iowa City, where they were processed using a semi-automated software package known as BRAINS (Brain Research: Analysis of Images, Networks, and Systems) [33]. The hippocampi were manually traced there to obtain the hippocampal volumes [34]. Because some participants in the study had claustrophobia, were too large for the MRI apparatus, or moved excessively during MRI, hippocampal data were available for 75% ($n = 24$) of the controls and 74% ($n = 14$) of the TLE patients. There was no significant TLE versus control group difference in right hippocampal volume, $t = 1.11$, $p = .28$ or left hippocampal volume, $t = .69$, $p = .50$. See Table 1.

RESULTS

Mean total errors by gender

With the groups combined, males and females did not differ significantly on the RL test, $t = 1.31$, $p = .20$.

Mean total errors by group

Because the between-group difference in FSIQ approached significance, FSIQ was used as a covariate in these analyses. The groups differed significantly on number of total errors across the three trials of the RL test, control group $M = 1.7$, $SD = 1.6$; TLE group $M = 5.8$, $SD = 4.1$, $F = 15.23$, $p < .01$. See Figure 2. The groups also differed significantly on number of errors committed for each of the three trials, Trial 1: $F = 14.11$, $p < .01$; Trial 2: $F = 7.76$, $p < .01$; Trial 3: $F = 10.6$, $p < .01$. See Figure 3a-c. For the control and TLE groups combined, there was a significant correlation between the total number of errors on RL and the mean time to completion, $r = .61$, $p < .01$. Therefore, no separate statistical analyses were performed for time to completion.

Total errors at the individual level

This analysis was conducted to determine how common RL impairment was within the TLE group. Because the RL total errors score correlated significantly with age in the control group ($r = .44$, $p < .05$), the control group was divided into two subsets, those in the age range 18 to 39 ($n = 21$) and those 40 to 59 ($n = 11$). Compared to the younger controls, the older subset of the control group showed a trend toward a greater total number of RL errors (younger control group $M = 1.29$, $SD = 1.42$; older control group $M = 2.45$, $SD = 1.81$; $t = -2.01$, $p = .05$). RL impairment was defined as a total error score > 2.0 SD above the appropriate control mean. Thus, for all participants in the 18-39 age range, RL impairment was defined by a RL total error score > 4 , whereas for participants in the 40-59 age range, impairment was an error score > 6 .

The control and TLE groups differed significantly in terms of proportion of cases with a total error score greater than 2.0 SD from the age-appropriate control mean. Only one of 32 controls (3%) was impaired at RL, compared to 8 of 19 TLE patients (42%), $\chi^2 = 12.46$, $p < .01$. Within the TLE group, RL impairment status did not correlate significantly with FSIQ ($r = -.38$, $p = .11$).

Trial 3 errors at the individual level

To further explore RL in the TLE group, performance on the third and final trial was assessed. Impairment on the third trial was arbitrarily defined as > 1 error, because none of the 32 controls committed > 1 error on that final trial. The groups differed significantly in terms of proportion of impaired cases on the final RL trial. Seven of 19 TLE patients (37%)

versus none of the controls were impaired, $\chi^2 = 13.67$, $p < .01$. Within the TLE group, Trial 3 impairment status did not correlate significantly with FSIQ ($r = -.10$, $p = .69$).

TLE group by laterality

The patients with right TLE had a higher FSIQ compared to those with left TLE ($t = 2.48$, $p = .03$). With FSIQ used as a covariate, the patients with right ($n = 8$) or left ($n = 5$) TLE were compared on total number of RL errors (right $M = 5.13$ errors, $SD = 2.8$; left $M = 6.0$ errors, $SD = 5.1$). These subgroups did not differ significantly on RL total errors, $F = .18$, $p = .84$).

Correlations

RL and neuropsychological tests—For the TLE group, Table 2 presents correlations between RL errors and demographically-corrected neuropsychological test scores. Total number of RL errors correlated significantly only with WMS-III auditory and visual memory indices and Benton Facial Recognition performance. For the control group (correlations not shown in Table), there were no significant correlations between RL errors and neuropsychological test scores ($p \geq .22$).

RL and hippocampal volumes—Table 2 also presents correlations between RL errors and hippocampal volumes. Among the TLE patients who had MRI data available ($n = 14$), RL errors ($r = -.55$, $p < .05$) correlated negatively with left hippocampal volume. The left hippocampal volume correlation with cognition was specific to memory, as only RL errors and WMS-III working memory and visual memory indices correlated significantly with the left hippocampus. Left hippocampal volume and WMS-III auditory memory indices also correlated relatively highly and the absence of significance for those correlations can be attributed to the relatively small sample size.

Within the control group (data not shown in Table), RL and WMS-III variables did not correlate significantly with hippocampal volumes, although there was a weak trend for right hippocampal volume to correlate with RL total errors ($r = .30$, $p = .16$).

RL and epilepsy variables—RL errors did not correlate significantly with age of epilepsy onset, duration of epilepsy, or overall seizure frequency (all $p \geq .33$).

DISCUSSION

Memory has rarely been formally tested in a natural environment in individuals with TLE. In this study, we assessed the ability of healthy control and TLE groups to learn a relatively complex route through hospital corridors. A primary finding was that the TLE group committed significantly more errors in total and on each trial of this real-world RL test. Approximately 40% of the TLE patients were impaired, versus 3% of controls, when total number of errors or errors on trial 3 were considered on a case by case basis. Thus, although the RL performance of the TLE group did improve across trials, it remained significantly poorer than that of the controls. In addition, RLT performance in the TLE group correlated very significantly with WMS-III memory indices, which supports the ecological validity of this clinical measure. Finally, this is the first TLE study to report a statistically significant correlation between hippocampal volume and RL ability.

The fact that RLT scores correlated significantly with both auditory and visual memory subtests does not necessarily reflect a weakness in this particular RL test. RL has been described as a complex task that requires various abilities and brain regions [7] and [16]. Other investigations of RL in non-demented patients have not reported the relationship

between auditory memory and RL. It is possible that some of our study participants tended to utilize verbal cues on the RL task [16], which included some verbal hospital signs. However, the fact that there were multiple turns, few signs at decision points, and only one demonstration trial on this relatively intricate route makes this explanation unlikely to fully account for the findings. In addition, the significant correlation between RL and a facial recognition test within the TLE group suggests RL had the expected visual-perceptual demands. While, impaired performance on our RL test could reflect a deficit in development of a cognitive map, scene learning, verbal learning, and/or executive function, this is also true for everyday route learning generally.

The absence of a significant correlation between RL and hippocampal volumes in the control group is consistent with the finding of Maguire et al. [46]. In the TLE group, RL test errors correlated significantly with the left hippocampus only. It should be noted that these correlations were based on a subset of the patients (N = 14) and non-hippocampal mesial temporal regions were not measured. Thus, these results should be considered preliminary. Glikmann et al. [15] found no relationship between a virtual navigation task and hippocampal volume asymmetry in TLE patients and observed that there are no pre-surgical TLE studies that suggest selective involvement of right temporal structures in navigation. Weniger et al. [25] suggested there was a relationship between severity of unilateral hippocampal sclerosis and route learning impairment in their sample of TLE patients, but there did not appear to be any strong lateralization effect. Considering two studies described in the introduction that required right and left TLR patients to learn the layout of a virtual town [24] or videotaped routes in a real town [26] before they were tested on numerous aspects of their learning, there was only one variable (scene recognition) on which the right TLR group performed worse than the left TLR group. Moreover, in the study by Maguire et al. [26], the patients with a left TLR as well as those with right TLR were impaired versus controls on the vast majority of topographical orientation variables. Finally, many functional imaging studies have reported both left and right mesial temporal involvement in route learning tasks.

While there are certainly indications of a preferential role for the right hemisphere in topographical orientation and other spatial memory tasks, [24], [47], [48], [49], [50], [51], [52] and [53] the frequent finding of complementary contributions from the two hemispheres has been described as unsurprising, given both the complexity and evolutionary survival value of this type of learning [7], [15], and [16]. Saling [6] suggested that “verbal and non-verbal memory are not opposites in terms of their respective patterns of cerebral organization, and at complex levels of expression neither are fully lateralized.”

Thus, although we cannot explain the absence of a significant correlation between the right hippocampus and RL, the finding of a significant left hippocampus-RL relationship can be considered consistent with reports that left TLE/TLR can be associated with poor performance on conventional visual memory measures [54], [55], [56] and [57] and that the link between the right hippocampus and visual memory performance in TLE patients has been relatively elusive overall [58] and [59]. Our RL test finding also is consistent with previous TLE/TLR studies and functional imaging data that revealed the left mesial temporal lobe plays at least a supporting role in topographical orientation [7], [13], [15], [16], [26], [53], [60], [61] and [62]. Finally, studies derived from recent conceptualizations of the hippocampus as a novelty detector indicate that associative match-mismatch processing is one of its cardinal mechanisms and that the left hippocampus plays a key role in such processing, along with complementary right mesial temporal contributions [63] and [64].

In summary, while there is a well-established association between TLE and memory dysfunction, its assessment generally has relied on table-top, laboratory-based measures. In one of the first investigations assessing real-world memory in this population, a TLE group was found to be impaired compared to controls on a large-scale RL test. In addition to providing direct evidence of a real-life cognitive complication of TLE, this study supports both the ecological validity of a commonly used clinical memory test and a key role for the mesial temporal lobe in RL. Assessment of virtual and real-world RL in pre- and post-surgical TLE patients should shed additional light on its neuropsychological and neuroanatomical correlates and the potential risk of postsurgical decline in this important ability.

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Highlights

- TLE and control groups were assessed on a real-world route learning (RL) test.
- The TLE group committed significantly more RL errors.
- RL errors correlated with standardized memory tests and left hippocampal volume.
- One of the first studies to demonstrate real-world memory impairment in TLE.
- Results support the ecological validity of clinical neuropsychological assessment.

Figure 1.
Schematic representation of the hospital path used for the route learning test. The black square in the lobby outside the cafeteria shows the starting and finishing points. The lines with arrows show the direction of the .15-mi route.

Figure 2.
Total number of route learning test errors across all three trials by case and by group.

Figure 3.
Route learning test errors for individual trials 1 to 3 by case and by group.

Table 1

Means and Standard Deviations for Demographic and Epilepsy History Variables

Variable	Group		p
	Controls	TLE	
N	32	19	
WAIS-III VIQ	98.5 (8.0)	94.7 (11.6)	.18
PIQ	109 (13.0)	103 (16.3)	.15
FSIQ	103 (8.6)	98 (12.6)	.09
Education	13.6 (1.6)	14.0 (1.8)	.37
Age	35.7 (11.3)	36.5 (10.6)	.80
% female	78	58	.13
Right hipp vol z score	-.28 (.76) ^a	-.71 (1.3) ^b	.28
Left hipp vol z score	-.20 (.75) ^a	-.53 (1.7) ^b	.50
Age of onset (yrs)	--	12.3 (7.3)	
Duration of epilepsy	--	20.3 (10.9)	
Number of AED	--	1.5 (.61)	

^a
n = 24.^b
n = 14.

WRAT-3 Reading = Wide Range Achievement test-3rd edition. WAIS-III = Wechsler Adult Intelligence Scale-3rd edition (short form). Hipp vol = hippocampal volume. AED = Antiepileptic drugs.

Table 2

Correlations between RL Errors, Hippocampal Volumes, and Neuropsychological Test Scores in the TLE Group

	RL errors ^a	Left Hipp ^b	Right Hipp ^b
RL errors	--	-.55 *	.02
WMS-III Index			
Working Memory	-.35	.57 *	.12
Auditory Immediate	-.64 **	.39	-.21
Visual Immediate	-.56 *	.62 *	.14
Auditory Delayed	-.64 **	.52	-.09
Visual Delayed	-.65 **	.65 *	.16
WAIS-III Verbal IQ	-.21	.33	.03
Performance IQ	-.35	.15	.01
Full Scale	-.32	.31	.02
WRAT-3 Word Reading	-.20	.28	-.17
Boston Naming Test	-.21	-.003	-.29
Controlled Oral Word Association	-.43	-.01	-.29
Facial Recognition	-.49 *	.47	-.07
Judgment of Line Orientation	-.36	.31	.12
Trail Making Test A (time)	-.06	-.17	-.62 *
Trail Making Test B (time)	-.40	-.06	-.37
WCST-64 perseverative responses	-.29	-.37	.06
Pegboard Test (dominant hand)	-.42	.37	-.15

*
p < .05.

**
p < .01.

^a n = 17, because neuropsychological data were not available for 2 patients.

^b $\bar{n}$ = 14 for RL errors; $\bar{n}$ = 13 for other test variables.

Note: WMS-III [27]; WAIS-III [28]; WRAT-3 Word Reading [35]; Boston Naming Test [36], [37] and [38]; Controlled Oral Word Association [39]; Benton Facial Recognition and Judgment of Line Orientation [40]; Trail Making Test [41] and [42]; WCST-64 (Wisconsin Card Sorting Test 64-card version) [43] and [44]; Purdue Pegboard [42] and [45].