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The role of sleep in forgetting in temporal lobe epilepsy: A pilot study

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ABSTRACT

The purpose of this study was to examine how sleep impacts memory function in temporal lobe epilepsy (TLE). Patients with TLE ($n=7$) and control subjects ($n=9$) underwent training and overnight testing on (1) a motor sequence task known to undergo sleep-dependent enhancement in healthy subjects, and (2) the selective reminding test, a verbal memory task on which patients with TLE have shown impaired performance 24 hours after training. Sleep data were collected by polysomnography. Results indicate that patients with TLE display greater forgetting on the selective reminding test compared with controls over 12 hours of daytime wakefulness, but not over a similar period including a night of sleep. Slow wave sleep is correlated with overnight performance change on the selective reminding test. Patients with TLE show no deficit in sleep-dependent motor sequence task improvement. The findings provide potential insight into the pattern and pathophysiology of forgetting in TLE.

1. Introduction

Subjective memory impairment and objective memory abnormalities on neuropsychological testing are common in patients with temporal lobe epilepsy (TLE) [1,2]. In addition, several types of memory dysfunction have been described in TLE that may not be apparent on standard testing [3]. Accelerated long-term forgetting (ALF) has been described in several case series and case reports of patients with TLE [3–5]. Patients who experience this phenomenon learn normally but forget information more quickly than expected, a process that can be observed over days or weeks. Although the etiology of ALF is unclear, one hypothesis that has not hitherto been explored is the role of sleep in ALF and other cognitive deficits seen in TLE. Over the past decade, an increasing amount of evidence has suggested that sleep plays an important role in consolidation of different types of declarative and nondeclarative memory [6,7]. Sleep disturbance and subjective sleep complaints are common in TLE [8,9], although they have not been explored as potential contributors to memory dysfunction in this population. The purpose of this study was to evaluate the role of sleep in cognitive performance in TLE by (1) determining whether patients with TLE demonstrate overnight improvement on a procedural motor sequence learning task on which healthy subjects show sleep-dependent improvement [10], and (2) evaluating whether patients with TLE perform differently when tested after a period of wakefulness versus a period of sleep on a verbal memory test on which such patients have previously been found to perform more poorly than controls at 24-hour retest [5].

2. Methods

2.1. Participants

Outpatients ($n=7$) with probable or definite ($n=6$) TLE were recruited from a tertiary care epilepsy referral clinic. Definite TLE was defined by documentation of temporal lobe focus on continuous EEG/video monitoring, and probable TLE was defined by seizure semiology in combination with interictal EEG, neuroimaging, and clinical history [11]. Patients were on stable antiepileptic drug (AED) regimens, with no new AEDs added in the 2 months prior to enrollment and no change in dose(s) of existing AED(s) in the 1 month prior to enrollment. Two patients with TLE did undergo medication alterations as part of a scheduled admission for continuous video/EEG monitoring within the study period. In the patients with TLE who underwent continuous video/EEG monitoring, medications were stable for approximately 1 week prior to any individual testing block. None of the patients had a history of epilepsy surgery. Healthy control subjects ($n=9$) were recruited from the community by newspaper and Internet advertisements. Both healthy subjects and those with TLE were screened to exclude known sleep or memory disorders. To estimate overall intellectual ability, subjects were administered the Wechsler Abbreviated Scale of Intelligence (WASI). None of the participants were regularly taking medication to enhance sleep. The institutional review boards of Brigham and Women's

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Hospital and Beth Israel Deaconess Medical Center approved the study, and informed written consent was obtained from each participant. See Table 1 for characteristics of patients and control subjects. See Supplementary Table 1 (see Appendix) for further details on patients with TLE.

2.2. Finger tapping motor sequence task

During training on the finger tapping motor sequence task (MST) [10], and again at retest 24 hours later, subjects were shown a numeric sequence of five numbers on a computer screen (e.g., 4–1–3–2–4). Using their left hand, subjects performed twelve 30-second trials during which they repeatedly typed the displayed sequence as quickly and accurately as possible. There were 30-second pauses between trials. Each trial was scored for the number of correct sequences typed, as well as the number of errors. Training occurred between 8 AM and 4 PM, and testing took place 24 hours later.

2.3. Selective reminding test

During the selective reminding test (SRT) [12], subjects were read a list of 12 unrelated words at the rate of one word every 2 seconds, and were immediately asked to recall verbally as many words as possible, in any order. Patients were then selectively reminded verbally of those words they omitted on the previous trial, and were again asked to recall all 12 words. Selective reminding followed by recall continued until two consecutive trials yielded recall of all 12 words, or until 12 trials were completed. After a 30-minute delay period, during which subjects completed questionnaires and watched an episode of a television sitcom during any remaining time, they again recalled as many of the studied words as possible. Approximately 12 hours later, recall was again tested. After this final recall, subjects were asked to identify the original 12 words from a list containing 20 additional new words, with all 32 words presented on a single sheet of paper.

All subjects underwent the SRT protocol twice using different word lists: once with baseline testing in the morning and retest approximately 12 hours later in the evening (wake condition), and a second time with baseline testing in the evening and retest approximately 12 hours later the following morning (sleep condition). Subjects were instructed not to nap during the day between morning baseline testing and evening retesting. Studied word lists were identical to Forms 2 and 3 of Hannay and Levin [13]. Use of the two word lists was counterbalanced across conditions.

To eliminate the possibility that poor performance at 12 hours in the TLE group was a function of inadequate learning at baseline, only patients with TLE and control subjects who recalled 11 or 12 words by the end of training were included in the final analysis (7 of 9 controls, 6 of 7 patients with TLE). However, even with all subjects included, there still were no significant differences in performance during the final trial at baseline ($P = 0.65$ for the wake condition, $P = 0.74$ for the sleep condition), and no differences at the 0-minute test, either between groups or across conditions (mixed model, condition [AM, PM, repeated] × group [control, TLE] ANOVA: main effect of condition, $P = 0.24$; main effect of group, $P = 0.72$; interaction, $P = 0.51$), suggesting that the two groups had comparable learning potential.

Table 1
Characteristics of subjects in this study.

	Patients with TLE	Control subjects	*P* value (unpaired *t* test)
Age (years)	44.0	44.7	0.90
Education (years)	15.6	16.2	0.60
Beck Depression Inventory score	9.9	1.3	0.002
Pittsburgh Sleep Quality Index	6.1	4.6	0.42
Epworth Sleepiness Score	6.4	5.0	0.44
Insomnia Severity Index	11.0	6.2	0.11
Edinburgh Handedness Scale	89.3	77.2	0.47
Verbal IQ	103.4	112.2	0.21
Performance IQ	108.4	113.1	0.59
Full Scale IQ	106.7	114.3	0.32

2.4. Overnight sleep recordings

Participants were wired for standard polysomnographic (PSG) sleep recordings the evening of the SRT sleep condition. Recordings took place in the General Clinical Research Center of Brigham and Women's Hospital, Boston. EEG (C3, C4, Cz, O1, O2, F3, F4, A1, A2), EOG, submental EMG, nasal pressure, rib cage and abdominal movements, and lower extremity EMG were recorded on an Embla A10 ambulatory monitor (Medcare Systems, Buffalo, NY, USA). Temporal leads (T3 and T4) were added for patients with TLE. EEG data were sampled at 200 Hz and bandpass filtered between 0.3 and 35 Hz for analysis. Two patients with TLE underwent the overnight portion of the study during their first night of a planned admission for continuous video/EEG monitoring already scheduled for clinical purposes. For these two patients, EOG, submental EMG, nasal pressure, rib cage and abdominal movement channels, and lower extremity EMG were added to the standard long-term monitoring (LTM) 22-lead scalp EEG leads for the first night of their LTM admission. PSG records were scored for sleep stages [14] and for arousals, respiratory events, and periodic limb movements of sleep [15].

2.5. Actigraphy

Participants wore a Mini-Mitter Actiwatch-64 actigraph (Philips Respironics, Bend, OR, USA) on their wrist from the first visit of the first study block until study completion. The actigraph monitors and records wrist movement in 1-minute epochs, and provides estimates of sleep and nap times based on periods of wrist immobility.

2.6. Experimental design

After a screening visit, subjects were scheduled for three test blocks, with a minimum of 4 days between blocks. The MST protocol was run during the first block, and the SRT protocol during blocks 2 and 3 with the order of conditions (wake, sleep) counterbalanced. All participants maintained sleep diaries for the duration of the study (blocks 1 through 3), and patients with TLE additionally maintained seizure diaries. Subjective sleepiness was assessed prior to each testing session using the Stanford Sleepiness Scale. Subjects were asked to abstain from alcohol during testing blocks from 24 hours prior to each training session until the end of testing for that block. Patients with TLE continued their normal schedules of antiepileptic drugs, taking them at approximately 12-hour intervals. Although caffeine intake was not regulated, there was no difference in average daily caffeine intake between the groups.

3. Results

3.1. Participants

Table 1 summarizes the characteristics of patients with TLE and control subjects. There were no significant differences in age, education, sleep quality indexes, or IQ scores. Patients with TLE did have significantly higher scores on the Beck Depression Inventory, although the mean score for patients with TLE was less than 10, the threshold for clinically significant mood disturbance. Supplementary Table 1 (see Appendix) provides additional details on participants with TLE.

3.2. Finger tapping motor sequence task

Patients with TLE did not differ from control subjects in performance speed on the MST (Fig. 1) either during the training session (first trial, $P=0.55$; final 3 trials, $P=0.79$) or at retest 24 hours later (initial improvement [last three training trials vs first three retest trials], $P=0.23$; plateau learning [last three training trials vs last three retest trials], $P=0.63$) (Fig. 1, inset). See Supplementary Table 2 (see Appendix) for additional details regarding MST performance.

3.3. Selective reminding test

In the sleep condition, no significant difference in recall was seen between patients with TLE and control subjects (Fig. 2A). A mixed model ANOVA of group (TLE, control) × time (0, 30 minutes, 12 hours; repeated) showed a main effect of time ($F=8.6$, $P=0.0007$), but no main effect of group ($F=0.4$, $P=0.54$) and no interaction between group and time ($F=0.6$, $P=0.50$). In addition, no difference between patients with TLE and control subjects was seen at 30-minute recall (9.8 vs 11.0, $P=0.17$) or at 12-hour recall (9.3 vs 9.1, $P=0.90$).

In contrast, significant group differences in recall were observed in the wake condition (Fig. 2B). A mixed model ANOVA of group (TLE, control) × time (0, 30 minutes, 12 hours; repeated) showed a main effect of time ($F=23.9$, $P<0.001$) as well as main effect of group ($F=11.7$, $P=0.006$) and a significant group × time interaction ($F=9.1$, $P=0.01$). Post hoc t tests revealed no significant group differences at 30-minute recall (10 vs 11.4, $P=0.07$). However, at 12 hours, the TLE group recalled 30% fewer words than controls (7.2 vs 10.3, $P=0.005$). Similar results were obtained when the percentage change in recall between the final training trial and 12-hour retest session was analyzed (group × condition interaction, $F=4.9$, $P=0.05$) (Fig. 3), with significantly greater forgetting by the TLE group in the wake condition (37% vs 12%, $P=0.009$), but not in the sleep condition (19% vs 23%, $P=0.72$). Adding Beck Depression Inventory scores, which differed between groups, as a covariate also had no impact (main effect of group: $F=10.0$, $P=0.01$; main effect of Beck score: $F=1.2$, $P=0.31$).

3.4. Selective reminding test performance and slow wave sleep

Overnight changes in performance on declarative memory tasks have often been associated with the amount of slow wave sleep (SWS) during the intervening night [16–18], and especially with the SWS in the first half of the night [19]. In the current study, for all subjects combined, deterioration in performance between zero time and the 12-hour recall sessions correlated significantly with percentage SWS in the entire night ($r=0.64$, ANCOVA—group: $F=1.1$, $P=0.31$; percentage SWS: $F=8.2$, $P=0.02$) (Fig. 4), and

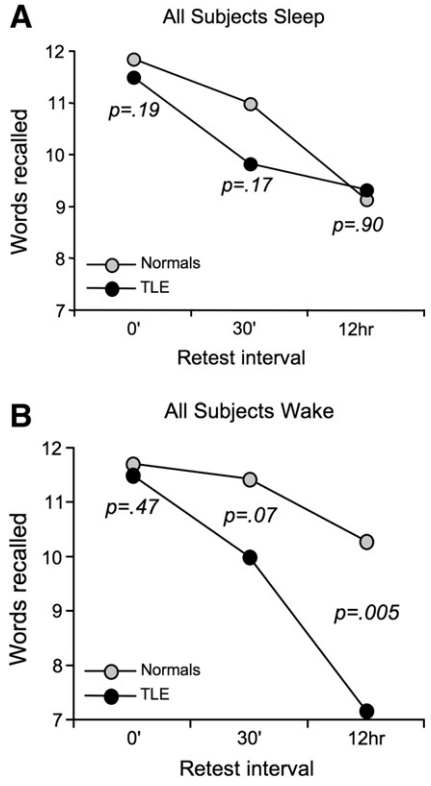

Fig. 2. Selective reminding test (SRT). Mean free recall for healthy controls (light gray circles) and patients with TLE (dark gray circles) across time. (A) Last evening trial, 30-minute delay, 12-hour (sleep) delay. (B) Last morning trial, 30-minute delay, 12-hour (wake) delay. Patients with TLE have significantly worse recall at 12 hours, but only after a period of wakefulness (B), and not after a period of sleep (A).

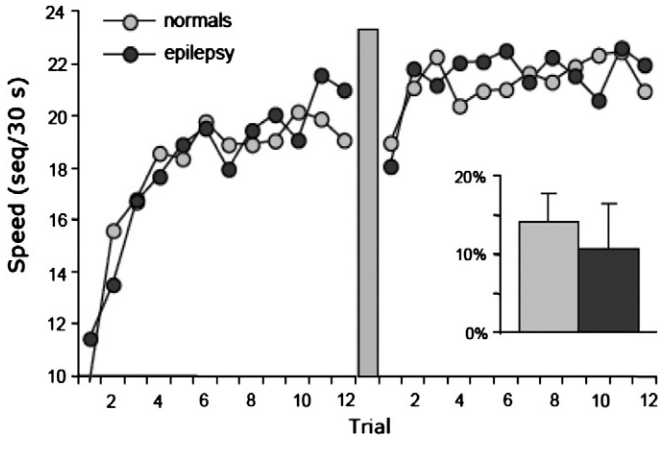

Fig. 1. Motor sequence task (MST) performance, measured as the number of correct sequences typed during a 30-second trial. Control subjects (light gray circles) and patients with TLE (dark gray circles) did not significantly differ either during baseline learning (left) or during retest after the passage of 24 hours, including a night of sleep (right). Inset: Chart displays plateau learning, that is, the percentage change in performance from the last six trials at training to the last six trials at retest in control subjects (light gray) and patients with TLE (dark gray) ($P=0.63$).

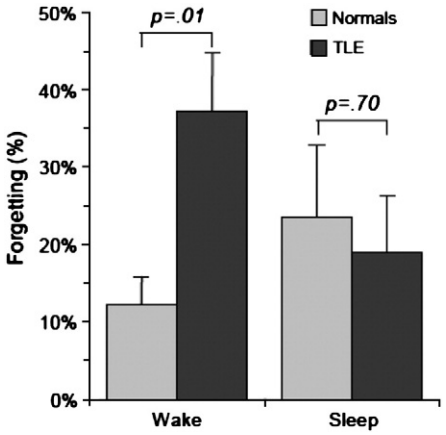

Fig. 3. Percentage change in mean free recall on the selective reminding test (SRT) between the final baseline trial and the retest 12 hours later. Results for healthy controls (light gray bars) and patients with TLE (dark gray bars) are illustrated over a period of wakefulness (left) and a period of sleep (right). Patients with TLE worsened significantly over wakefulness, but not over sleep. Group × time interaction as measured by a mixed model ANOVA ($F=4.9$, $P=0.05$).

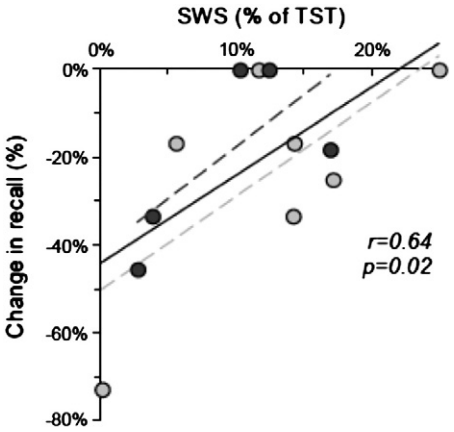

Fig. 4. Correlation of the percentage change in performance on the selective reminding test (SRT) (between the last trial at baseline and retest 12 hours later) and slow wave sleep (SWS) as a percentage of total sleep time (TST). For all subjects combined, the percentage change in SRT performance correlated significantly with the percentage of SWS during the entire night ($r=0.64$, $P=0.02$). Correlation plots for patients with TLE (dark gray) and control subjects (light gray) are also shown, although they did not reach significance.

approached significance in the first half of the night ($r=0.59$, ANCOVA—group: $F=0.6$, $P=0.46$; percentage SWS: $F=4.1$, $P=0.074$; not shown). Separate analyses of the correlation with total SWS for patients with TLE and controls yielded numerically stronger correlations, which failed to reach significance because of smaller sample sizes (controls: $r=0.69$, $P=0.088$; TLE: $r=0.70$, $P=0.190$) (Fig. 4).

3.5. Sleepiness and overnight sleep recordings

There was no significant difference between patients with TLE and control subjects in total sleep time or in the percentage of any individual stage of sleep either during the night as a whole or during any individual quartile of the night. No electrographic seizures were recorded during overnight polysomnography. Two subjects (one with TLE and one control) met criteria for mild obstructive sleep apnea (5<Apnea Hypopnea Index<15) based on polysomnographic recordings. Repetition of all of the analyses without these subjects did not change the results substantively. See Supplementary Table 3 (see Appendix) for additional details regarding sleep architecture.

Stanford Sleepiness Scale (SSS) scores did not significantly differ between the TLE and control groups either in the wake condition at baseline (unpaired *t* test: 2.7 vs 2.1, $P=0.39$) or at retest (2.8 vs 2.7, $P=0.86$) or in the sleep condition at baseline (2.0 vs 2.3, $P=0.48$) or at retest (2.8 vs 2.6, $P=0.55$).

3.6. Actigraphy

On the basis of actigraphic data collected over an average of 3 weeks, there was no significant difference between the groups in either mean nocturnal sleep time (patients with TLE: 394 minutes, controls: 392 minutes, $P=0.94$) or sleep efficiency (patients with TLE: 87%, controls: 84%, $P=0.15$). There were also no differences in the frequency or length of naps.

3.7. Seizure diaries

On the basis of subject self-report of seizure occurrence, one participant reported a simple partial seizure on the first day of the MST. Otherwise, subjects denied any clinical seizures within 5 days of initiating any of the individual testing blocks.

4. Discussion

In this study, patients with TLE, who were equivalent to controls in terms of sleep quality, sleep architecture, and total sleep time, as measured by both polysomnography and actigraphy, showed ALF on a declarative memory task across 12 hours of daytime wakefulness (words recalled: 7.2 vs 10.3, $P=0.005$), similar in magnitude to that previously reported across a 24-hour period (7.3 vs 9.8) [5]. In contrast, forgetting across 12 hours including a night of sleep was similar for both groups (words recalled: 9.1 vs 9.3, $P=0.90$). Both groups also showed similar sleep-dependent enhancement of procedural learning on a motor sequence task (10.8% vs 14.0%, $P=0.63$). Although the results must be confirmed with further studies, these data provide potential insight into the pattern of forgetting in patients with TLE and raise additional questions regarding the underlying pathophysiology. Most simply, sleep appears to protect the TLE-affected brain against accelerated forgetting.

Accelerated long-term forgetting implies a defect in memory consolidation. Previous suggestions for an underlying cause of ALF have included ongoing seizures, antiepileptic drug effects, structural lesions (hippocampal pathology), and psychiatric disorders or psychosocial factors such as self-esteem [3]. Although the patients with TLE in our study had higher Beck Depression Inventory scores compared with controls, this did not explain the group difference on a measure of long-term memory. Also, depressed patients have not shown accelerated forgetting compared with controls on a picture recognition task when retested at 24 hours [20].

The cause of the increased forgetting (compared with healthy controls) across the day is unclear. It could reflect chronic damage to the memory structures involved in TLE. Alternatively, it could be a real-time effect of interictal discharges or subclinical seizure activity during the day that either disrupts recently formed memories or impairs daytime memory consolidation. Though there is some recent evidence relating interictal discharges to cognitive disruption in animal models [21], this has not been fully explored in humans. We were not able to note such an association in our study, as most of the patients with TLE did not undergo continuous EEG monitoring during the day. Neither chronicity ($r=0.60$, $P=0.20$) nor partial seizure frequency ($r=0.39$, $P=0.45$) predicted the extent of daytime ALF seen.

An important question that cannot yet be answered is why ALF might occur differentially over a period of wakefulness versus a period of sleep in patients with TLE. One possible explanation is that patients with TLE may be quicker to fatigue (related to TLE itself or to specific AEDs), resulting in a decrement in performance over the day. However, SSS scores were similar for the morning and evening SRT tests (main effect of time: $P=0.74$, of group: $P=0.64$; interaction: $P=0.40$), as was training performance (main effect of time: $P=0.77$, of group: $P=0.92$; interaction: $P=0.47$). More interesting is the possibility that sleep provides protection against forgetting in TLE. This could result from passive protection against the impact of interference from daytime activities, active consolidation and stabilization of the memories, or a combination of both [6,7]. The finding that postsleep performance on the SRT, a declarative memory task, correlated with the percentage of slow wave sleep in our study provides supporting evidence that active sleep-dependent memory consolidation is providing protection against forgetting in TLE. Consolidation of hippocampus-dependent memory has a known association with SWS, which has been demonstrated in both animal [16] and human [17,19] subjects. Patients with TLE and control subjects in this study exhibited equal percentages of SWS, which is likely contributing to their equivalent performance on this declarative memory task after a night of sleep.

Considering the small sample size and the preliminary nature of the findings, more definitive studies should be performed with larger samples. Future studies could look at forgetting over several periods,

such as 12 hours, 24 hours, and a longer time interval of 2 to 6 weeks. This would permit a better understanding of the role of sleep as well as the role of other variables such as seizure frequency. Additionally, continuous EEG monitoring between memory tests during the day would be a means of exploring the possible role of interictal discharges or subclinical seizure activity in forgetting.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.yebeh.2011.04.061.

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