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Sleep-dependent memory consolidation in the epilepsy monitoring unit: A pilot study

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HIGHLIGHTS

- Patients with epilepsy were tested serially on a visuospatial task.
- Retention rates were higher after 12 h with sleep vs. 12 h of wakefulness.
- Overnight retention best correlated with duration of slow wave sleep.

ABSTRACT

Objective: We sought to examine whether patients with focal epilepsy exhibit sleep dependent memory consolidation, whether memory retention rates correlated with particular aspects of sleep physiology, and how the process was affected by seizures.
Methods: We prospectively recruited patients with focal epilepsy and assessed declarative memory using a task consisting of 15 pairs of colored pictures on a 5 × 6 grid. Patients were tested 12 h after training, once after 12 h of wakefulness and once after 12 h that included sleep. EMG chin electrodes were placed to enable sleep scoring. The number and density of sleep spindles were assessed using a wavelet-based algorithm.
Results: Eleven patients were analyzed age 21–56 years. The percentage memory retention over 12 h of wakefulness was 62.7% and over 12 h which included sleep 83.6% ($p = 0.04$). Performance on overnight testing correlated with the duration of slow wave sleep (SWS) ($r = +0.63$, $p < 0.05$). Three patients had seizures during the day, and 3 had nocturnal seizures. Day-time seizures did not affect retention rates, while those patients who had night time seizures had a drop in retention from an average of 92% to 60.5%.
Conclusions: There is evidence of sleep dependent memory consolidation in patients with epilepsy which mostly correlates with the amount of SWS. Our preliminary findings suggest that nocturnal seizures likely disrupt sleep dependent memory consolidation.
Significance: Findings highlight the importance of SWS in sleep dependent memory consolidation and the adverse impact of nocturnal seizures on this process.

1. Introduction

Epilepsy is one of the most common neurologic conditions with active disease present in almost 7 out of 1000 people in the U.S. (Theodore et al., 2006). The consequences of epilepsy can be quite debilitating with regard to cognitive, psychiatric, and psychosocial aspects of life (Berg, 2011; Schachter, 2006). Memory complaints are especially prevalent in individuals with epilepsy and can be more debilitating than the seizures themselves (Aldenkamp and Arends, 2004). Traditionally; memory testing for epilepsy patients has consisted of neuropsychological assessments within a single session over several hours. However, new forms of memory deficits were uncovered with serial testing over days to weeks; a phenomenon termed "accelerated long term forgetting" which has been shown to have a strong association with epilepsy (Fitzgerald et al., 2013).

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The role of sleep in memory processing and consolidation has been highlighted in a number of studies (Stickgold, 2005). Memories, once encoded, are subsequently stabilized, enhanced, elaborated and integrated into existing memory networks. The hippocampus plays a central role in the acquisition of new memories which over time become encoded in neocortical regions (Hasselmo and McClelland, 1999). Memory enhancement, at least for motor and visual discrimination, has been shown to be a sleep-dependent process (Stickgold and Walker, 2005). The important components of sleep that seem to be involved in the processing of memories include sleep spindles and the duration slow wave sleep (SWS) (Stickgold, 2005). Studies assessing memory consolidation in epilepsy patients have been limited. In one of the few studies in adult patients, verbal memory consolidation was been shown to correlate with SWS (Deak et al., 2011). Studies analyzing children with focal epilepsy have highlighted an impairment in sleep dependent memory consolidation and the adverse impact of interictal epileptiform discharges (Sud et al., 2014; Galer et al., 2015). Given the limited data available in adults and some conflicting data in children, it would be especially useful to determine whether there is evidence of memory consolidation in the epilepsy monitoring unit to understand the phenomenon better and evaluate factors which may have an influence on this process.

In the current study, we investigated whether there was evidence of sleep dependent memory consolidation in adults with focal epilepsy admitted to the epilepsy monitoring unit (EMU). We tested whether their overnight memory performance correlated with the number of spindles as well as sleep stage duration (N2 and SWS); with repeated testing. We also investigated potential effects of seizures on memory performance.

2. Methods

2.1. Cohort selection

Consecutive patients with focal epilepsy were recruited prospectively over a period of 2 years from the EMU at Brigham and Women's Hospital. Inclusion criteria were: (1) adults 18–60 years old, and (2) diagnosis of focal epilepsy by history and EEG. Exclusion criteria were: (1) EMU stays of less than 3 days, (2) history of obstructive sleep apnea or other known primary sleep disorder, (3) daily use of barbiturates or benzodiazepines, (4) prior cranial surgery, (5) inability to exhibit a greater than 40% retention rate on the memory task, (6) known active alcohol or drug use, or (7) diagnosis of a neurodegenerative condition. Data collected included patient demographics, seizure medications at the time of testing, and epilepsy characteristics. The study was approved by the Brigham and Women's Hospital institutional review board.

2.2. EEG and sleep scoring

Subjects recruited for this study underwent inpatient continuous video-EEG monitoring for clinical indications with the aim of capturing their habitual seizures. The conventional 10–20 system electrode placement was used with the addition of anterior temporal (T1,T2) leads to localize the area of ictal onset. EEG data were sampled at 256 Hz. In order to score sleep, additional submental electrodes were added. The T1, T2 electrodes were used for electrooculography. The overnight EEG recording was scored for sleep stages and for arousals using standard guidelines (Iber, 2007).

2.3. Nonverbal memory task

The memory task was a 2-D object-location memory task similar to the children's game "Concentration." It consisted of 15 pairs of colored pictures showing different animals and every-day objects. Each pair contained identical pictures of one item. All 30 possible spatial locations were shown and used as gray squares ("the back of the cards") on a 15 inch laptop screen. The locations were geometrically ordered in a checkerboard-like 5×6 matrix. At learning, the first card of each card-pair was presented alone for one second followed by the presentation of both cards for three seconds. After an interstimulus interval of three seconds, the next card-pair was presented in the same way. The entire set of card pairs was presented twice in different orders. Immediately after these two exposures, recall of the spatial locations was tested using a cued recall procedure, i.e., the first card of each pair was presented and the subject was asked to indicate the location of the second card with a computer mouse. Visual feedback was given in each case by presenting the second card at the correct location for two seconds independent of whether the response was correct or not, to enable re-encoding of the correct location of the card-pair. After presenting a card-pair, both cards were replaced by gray squares again, so that the probability of being correct if guessing remains the same throughout each run. The cued recall procedure was repeated until the subject reached a criterion of 40% correct responses. Once subjects achieved the criterion of at least 40% correct, they were tested one last time without any feedback, and the number of card pairs recalled was considered their baseline. Retention rates were calculated as number of correct card pairs recalled after 12 h/ baseline correct card pairs.

Subjects were tested on the recall procedure a maximum of 8 times, after which, if criterion was not reached, the subject's participation in the study was terminated.

2.4. Study protocol

Subjects were recruited upon admission and testing was started the following day to avoid any 'first night effect' (transient sleep structure changes provoked by sleeping in an unfamiliar environment). For each subject, there was a daytime session (7:00–9:00) and an evening session (19:00–21:00).

During the first session, subjects were 'trained' on a single set of cards. With subsequent sessions, they were first tested on the set on which they trained 10–14 h prior, and then trained on a new set (Fig. 1). Subjects were advised to refrain from caffeine, and avoid daytime naps, and they were provided with earplugs to attenuate surrounding noise during sleep. Testing was stopped if the subject was sleep deprived, experienced a focal dyscognitive seizure (with or without secondary generalization), or after 4 days of testing. Prior to each session, the subject filled out the Stanford Sleepiness Score (Hoddes et al., 1973), a measure of subjective sleepiness, to monitor the effect of sleepiness on the memory task.

2.5. Sleep spindle detection

To calculate sleep spindle measures, overnight N2 and SWS data was preprocessed and analyzed using MatLab R2013b (The MathWorks, Natick, Massachusetts) software. Manual rejection of artifact was performed visually. To detect discrete spindle events, a wavelet based algorithm (Wamsley et al., 2012) was used. The raw EEG signal was subjected to a time–frequency transformation using an 8-parameter complex Morlet wavelet. Spindles were detected at each EEG channel by applying a thresholding algorithm to the extracted wavelet scale corresponding approximately to the 10–16 Hz frequency range. For thresholding, the rectified moving average of the signal was first calculated, using a 100-ms sliding window. A spindle event was identified whenever this wavelet signal exceeded threshold (defined as 4.5 times the mean signal amplitude of all artifact-free epochs) for a minimum of 400 ms; this method has been validated in prior studies (Wamsley et al.,