**Epilepsy is Associated with the Accelerated Aging of Brain Activity in Sleep**

Running Head: Epilepsy and Sleep-Based Brain Aging

Mike Westmeijer a,b,c\*, MSc, Peter N. Hadar a\*, MD, MSc, Haoqi Sund\*, PhD,   
Erik-Jan Meulenbrugged, MSc, Jin Jingd, PhD, Luis Paixaod, BMBCh, MSc, Ryan A. Teshd, BSc, Madalena Da Silva Cardosoe, MSc, Pierrick Arnalf, PhD, Rhoda Aug, PhD, Chol Shinh,i, MD, PhD, Soriul Kimh, PhD, Robert J. Thomasj, MD, Sydney S. Casha, MD, PhD\*\*, M. Brandon Westoverd, MD, PhD\*\*

*a.  Dept. of Neurology, Massachusetts General Hospital (MGH), Boston, MA, USA*

*b.* *Clinical Data Animation Center (CDAC), MGH, Boston, MA, USA c.* *Utrecht University, Utrecht, The Netherlands  
d. Dept. of Neurology, Beth Israel Deaconess Medical Center, Boston, MA*

*e. Dept. of Radiology, NYU-Langone Medical Center, New York, NY  
f. Dreem, Paris France*

*g. Dept. of Epidemiology, Boston University School of Medicine, Boston, MA*

*h. Institute of Human Genomic Study, College of Medicine, Korea University, Seoul, Republic of Korea*

*i. Biomedical Research Center, Korea University Ansan Hospital, Ansan, Republic of Korea   
j. Dept. of Medicine, Division of Pulmonary, Critical Care & Sleep, Beth Israel Deaconess  
 Medical Center, Boston, MA*

\* Co-first authors

\*\* Co-senior authors

Corresponding Author:

M. Brandon Westover, MD, PhD  
Department of Neurology,  
Beth Israel Deaconess Medical Center, 330 Brookline Ave, Boston, MA 02215  
[mwestover@bidmc.harvard.edu](mailto:mwestover@bidmc.harvard.edu)

Manuscript Word Count: 3795  
Number of Tables: 1

Number of Supplemental Tables: 1  
Number of Figures: 5

Number of Supplemental Figures: 4

References: 37

ABSTRACT

*Background:*

Although seizures are the cardinal problem, epilepsy is associated with other forms of brain dysfunction including impaired cognition, abnormal sleep, and increased risk of developing dementia later in life. We hypothesized that, given widespread neurologic dysfunction associated with epilepsy, accelerated brain aging would be expected in patients with epilepsy. To test this hypothesis, we set out to measure the sleep-based Brain Age Index (BAI) in a diverse group of patients with epilepsy. BAI is a machine learning-based biomarker that measures how much a person’s brain activity during overnight sleep deviates from norms based on chronological age.

*Methods:* 138 patients with epilepsy (32 exclusively focal, 106 generalizable [focal seizures with secondary generalization]) who underwent in-patient monitoring were analyzed. Age-matched controls without epilepsy were derived from a cohort of volunteers who underwent home sleep monitoring and from patients who underwent sleep lab testing. EEGs were processed and artifacts removed, and BAIs were calculated. A subset had NIH Toolbox cognitive battery testing for total, fluid, and crystallized composite cognition. Epilepsy severity metrics were defined as years with epilepsy, seizure frequency standardized by year, and seizure burden (number of seizures in life).

*Results:*

The mean BAI was higher in epilepsy patients vs. controls and differed according to epilepsy type: 0.30 years (controls) versus 5.02 years (all epilepsy, p<0.001), 5.53 years (generalizable epilepsy, p<0.001), and 3.34 years (focal epilepsy, P=0.105). Conventional sleep architecture was also disrupted in epilepsy patients relative to both control groups, most notably in generalizable epilepsy patients. A higher BAI was positively associated with increased lifetime seizure burden in focal and generalizable epilepsies; a higher BAI in patients with epilepsy was also associated with lower crystallized cognition. Lifetime seizure burden was inversely correlated with cognitive performance in fluid, crystallized, and composite cognition domains.

*Conclusion:*

Epilepsy is associated with accelerated brain aging. Higher brain age indices are associated with higher degrees of cognitive impairment and more severe epilepsy, including generalizable seizures and higher lifetime seizure burden.

Key Words: Epilepsy, Brain Age, Sleep, Cognition, EEG

## **INTRODUCTION**

Epilepsy affects more than 45 million people worldwide.1,2 Although seizures are the cardinal feature, brain dysfunction in epilepsy takes several additional forms. People with epilepsy experience increased rates of psychiatric disorders like depression and anxiety, and cognitive impairment including problems with concentration, processing speed, and memory3–7. Brain dysfunction is accompanied by abnormalities in interictal brain activity, including epileptiform discharges (spikes and sharp waves), and abnormalities during sleep such as reduced rapid eye movement (REM) and deep (stage N3) sleep, and increased sleep fragmentation8–15. People with epilepsy also have increased lifetime risk of developing dementia16,17.

The concept that a person’s “brain age” can be greater than a person’s chronological age has been proposed to account for brain dysfunction in a variety of chronic medical conditions18. The sleep EEG based Brain Age Index (BAI) is a machine learning model that quantifies how much an individual’s calculated brain age (BA), deviates from chronological age.19 Our prior work has shown that excess BAI is associated with psychiatric and neurological diseases, diabetes, hypertension, early and late-stage dementia 20, HIV infection21, and reduced life expectancy.19,22,23

Here we test the hypothesis that cognitive impairment in epilepsy is associated with accelerated sleep-based brain aging (increased BAI). We also investigate whether increased BAI in epilepsy correlates with epilepsy type, frequency of seizures, and lifetime seizure burden. 24,25

## **METHODS**

**Study Design and Ethics Approval**

This cross-sectional retrospective study was conducted on data from patients at Massachusetts General Hospital (MGH). Prospective assessment of cognitive performance using the NIH Toolbox was performed initially until enrollment had to be stopped because of the COVID-19 pandemic; for these cases verbal consent was obtained under a protocol approved by the Institutional Review Board (IRB). We further included a retrospective cohort of patients; the IRB waived the requirement for informed consent for this component of the study.

**Patients with Epilepsy**

Inclusion criteria for epilepsy patients were: Adults (≥ 18 years old) with diagnosed epilepsy who underwent continuous EEG monitoring in the Epilepsy Monitoring Unit (EMU) and had a detailed evaluation for epilepsy including an MRI brain scan and neuropsychological testing within 6 months of their EMU stay. Exclusion criteria are detailed in **Supplementary Fig. 1**. EEG recordings were obtained from Massachusetts General Brigham EEG database. Clinical data (i.e., demographics, medication, seizure semiology, and medical history) were extracted from EMU admission and clinical neurology notes. Prospective enrollment for patients admitted to the EMU who were then administered NIH toolbox took place between February 14, 2019 and March 17, 2020. Retrospective enrollment included the period from January 1, 2016 through July 21, 2022 and did not involve administration of the NIH toolbox.

**Matched Controls**

The matched controls were from two groups. The first group of non-epilepsy subjects originated from the Dreem cohort, a set of sleep-EEG recordings from volunteers who wore a portable home EEG device for 7 days on average (n=1077). The other group of non-epilepsy subjects were extracted from the Sleep Lab cohort with NIH Toolbox Cognitive Battery test results available (n = 112). Non-epilepsy subjects from both groups had to pass a set of exclusion criteria to be considered for matching (**Supplementary Figure 1**). Individuals were matched based on age and sex.26,27 28,29 We used weighted full matching to match the group of patients with epilepsy with two groups of non-epilepsy subjects who also underwent long-term EEG monitoring; this method minimizes propensity score differences between cases and controls while maintaining the highest number of control individuals30. Note that when we analyze cognition, only the Sleep Lab cohort is used as matched controls.

### **EEG Preprocessing and Artifact Removal**

EEG electrodes were placed as part of clinical care on the scalp following the international 10-20 system. EEG recordings were started on admission to the EMU and continued throughout hospitalization. For analysis, EEG signals were down sampled from 512 Hz to 200 Hz and notch filtered at 60Hz to remove line noise. We used a previously published neural network to perform automated sleep scoring; this method segments the EEG into nonoverlapping 30-second epochs, and classifies each epoch as one of 5 sleep stages: awake (A), rapid eye movement (REM) sleep, non-rapid eye movement (NREM) stage 1 (N1), NREM stage 2 (N2), or NREM stage 3 (N3).31 Artifact removal was accomplished with two complementary methods: (1) Epochs with maximum absolute amplitude > 500μV or standard deviation <1μV were removed. (2) We trained a linear discriminant analysis (LDA) classifier to classify each epoch into artifact vs clean (no artifact) based on the total power and the second order difference (for abrupt non-physiological changes) of the spectrum. (3) Epochs scored as awake with eyes open, characterized by blinking patterns and a reactive posterior dominant rhythm, were removed. (4) SpikeNet, a previously published machine learning algorithm, was used to exclude epochs with interictal epileptiform discharges (IEDs).32 (5) SPaRCNet, a recently developed deep neural network, was used to exclude epochs with seizures and seizure-like events.33 These were further reviewed manually by an epileptologist (PNH, one of the authors, below). Generalized rhythmic delta activity (GRDA) was not counted as a seizure-like pattern due to its similarity to N3-sleep.

### **Calculation of the BAI**

Brain Age (BA) was calculated using a machine learning model developed by Sun et al., which uses the sleep-EEG data from six scalp electrodes as input: two frontal electrodes (F3 and F4), two central electrodes (C3 and C4), and two occipital electrodes (O1 and O2).19 The signals were bandpass filtered between 0.5 and 20 Hz as was done in the BAI model. 510 sleep microstructure features concatenated from the 5 sleep stages were used to calculate BA, including spectral band powers and their ratios and signal complexity measures (**Supplementary Table 1**). To reduce night-to-night variability of the sleep-based BA, we averaged BA estimates across all nights of available EEG recordings during the EMU stay for each patient.34 BAI is computed as BA minus chronological age (CA; i.e., BAI = BA – CA). The top 15 sleep features ranked by *t*-test p-value in ascending order were reported.

### **EEG Spectrograms**

EEG spectrograms were computed for each night (EEGs within 11pm to 7am) for two purposes: (1) To manually ensure any seizure activity was excluded from the analysis, as BAI was designed to be used only on interictal sleep data; (2) To visualize the representative spectrograms and hypnograms. The spectrogram consisted of spectra for each 30-second epoch. The spectra were computed using multitaper spectral estimation with 0.67Hz frequency resolution using 19 tapers. To select representative spectrograms and hypnograms, sleep EEG features used by the BAI model were standardized, and mean values were calculated for the epilepsy patients and Sleep Lab controls. For each group, we selected the 10 participants with spectral features closest (i.e., based on Euclidean distance) to the group mean. Next, we manually selected three spectrograms and hypnograms for epilepsy patients that were most visually representative for the low, average, and high BAI groups (**Supplementary Figure 2**).

### **Cognitive Tests**

Cognitive performance was measured for a subset of epilepsy patients (n=49) and Sleep Lab controls (n=112, below) using the NIH Toolbox Cognitive Battery. There was no cognitive score available for the Dreem controls. The NIH Toolbox is a validated and normed assessment of behavioral and neurological function and offers reliable tools for assessing cognition.24,25 The cognitive battery consists of five subtests that measure fluid cognition and two subtests that measure crystallized cognitive abilities. Total fluid cognition and total crystallized scores were calculated based on the average standard scores of the subtests. Total composite cognition is a weighted average of total fluid cognition and total crystallized cognition.

### **Epilepsy Metrics**

Three quantitative measures of epilepsy severity were determined to capture acute and chronic phases of the disease: seizure frequency, years of epilepsy, and lifetime seizure burden. Pertinent patient information was collected from a combination of initial EMU admission note, an epilepsy surgical conference discussion note (when available), and a recent outpatient epilepsy note in the 3 months prior to EMU admission. All patients with epilepsy were first analyzed as a group and then divided into two mutually exclusive subgroups based on seizure semiology: (1) generalizable seizures (any patient who had focal seizures with secondary generalization), or (2) exclusively focal seizures. This designation was determined based on chart review of outpatient notes and of EEG and EMU reports.

Seizure frequency per year was tabulated by type of seizure. However, as this metric only provided a recent snapshot of seizure burden, chronic metrics of seizure burden were created to help quantify long-term effects of epilepsy. Years of epilepsy were determined by subtracting the age at the time of EMU admission from the age at which the first seizure occurred. Notably, this did not include the frequency of seizures, which differed significantly between patients. Lifetime seizure burden, a metric meant to more closely approximate chronic effects of epilepsy, was defined as the number of seizures a patient suffered throughout life to date. This measure was approximated by documented seizure frequency (based on chart review of notes within 6 months of EMU admission) if available or by multiplying the years of epilepsy by the previously calculated yearly seizure frequency.

### **Statistical Analyses**

Baseline patient characteristics were analyzed using Chi-Square (categorical variables) or Mann-Whitney (continuous variables) tests, comparing demographic and medical history measures between those with focal and generalizable epilepsy.

A *t*-test was used to investigate the difference in sleep stage distribution between patient groups. First, comparisons were made between all patients with epilepsy and the Sleep Lab controls, and next between epilepsy types (i.e., generalizable epilepsy and focal). Next, the difference in mean BAI between patients with epilepsy and the matched controls was investigated using a *t*-test. The pairwise comparison of mean BAI between the different epilepsy subgroups and healthy controls was conducted followed by correlating the lifetime seizure burden to BAI with a Pearson’s correlation coefficient *r.* Next, the correlation between lifetime seizure burden and cognitive performance, as well as the correlation between BAI and cognitive performance, was examined using Pearson’s *r.* Finally, the strength of the correlation between BAI and cognitive performance was compared between patients and controls using analysis of covariance (ANCOVA) using cognitive performance as the outcome variable and BAI and case/control status as covariates.

Statistical significance was defined as *p*-value < 0.05. BAI is presented as mean ± standard error (SE). Statistical analyses were performed using RStudio version 4.2.1 and Python version 3.7 (Python Software Foundation).

### **Data Availability**

The de-identified data and code to reproduce the results will be available after the time of publication. Data will be found at the Brain Data Science Platform (<https://bdsp.io/>), and code will be found at <https://github.com/PNHadar/BAI_Ep>.

## **RESULTS**

### **Baseline Characteristics**

We prospectively enrolled 41 patients to perform neuropsychological testing with the NIH toolbox. We further retrospectively identified 99 patients from the epilepsy monitoring unit who met inclusion criteria for brain age analysis; these patients did not have NIH toolbox data available. Two patients were excluded as they did not carry a diagnosis of epilepsy. The final cohort existed of 138 participants (54.3% female) with an average age of 39.6 (standard deviation 13.4 years). The baseline patient characteristics are shown in Table 1. Control subjects from the Dreem and Sleep Lab non-epilepsy groups were selected from 2,316 and 8,673 subjects respectively. After applying the exclusion criteria there were 1,077 Dreem and 112 Sleep Lab patients remaining who served as controls (**Supplementary Figure 1**).

### **Sleep EEG Macrostructural and Microstructural Features in Epilepsy**

Correlations between epilepsy vs. sleep stage distribution (sleep macrostructure) and EEG features (sleep microstructure) are shown in **Figure 1**. Overall, patients with epilepsy showed a reduced percentage of deep sleep (N3) (9.5% vs 19.1% in sleep lab controls, p<0.001); proportions for other stages were similar (8.5%, 58.8%, 23.2% for N1, N2, REM respectively, vs 9.9%, 51.6%, 19.5% for controls, p>0.05 for all).

Within the epilepsy group (**Fig 1A**), sleep stage proportions for the generalizable seizures group (n=106) for N1, N2, N3, REM sleep were 8.5%, 56.3%, 10.7%, 24.6%; whereas for the focal seizure group (n=32) these were 8.4%, 67.1%, 5.7%, and 18.8%. There was a statistically significant increase in the proportion of time spent in N3 and REM sleep in the generalizable seizures group vs. the focal epilepsy group (p=0.005 and p=.0019, respectively), and a significant decrease in the proportion of time spent in N2 sleep in the generalizable seizures group compared to the focal group (p<0.001). There was no difference seen in the proportion of N1 sleep (p=0.95).

Differences in the top 15 most significantly different sleep EEG (microstructure) features between all epilepsy patients and Sleep Lab healthy controls are shown in **Fig 1B**. These EEG features included average band powers and ratios of power in different EEG frequency bands (θ, δ, and α EEG frequencies). It is notable that the top differences involved N2 and N3 sleep features. N3 sleep features, such a frontal δ band power and frontal δ-α ratio, were highly predictive features for distinguishing sleep stages between epilepsy patients and sleep lab controls. **Supplementary Figure 2** depicts representative hypnograms and spectrograms for epilepsy patients with low, average, and high BAI; of note, patients with the highest BAI, indicating the oldest brain age, appear to have a broader delta band with increased power on all channels of the spectrogram.

### **Association between BAI and Epilepsy**

The brain age index was higher overall in patients with epilepsy compared to controls (**Fig. 2**). The BAI (SE) for controls was 0.30 [0.17] for all controls (Dreem and Sleep Lab), compared to 5.02 [0.43] in all epilepsy patients, 5.53 [0.48] for generalizable epilepsy patients (n=106), and 3.34 [0.88] for focal epilepsy patients (n=32). All patients with epilepsy had a statistically significant higher BAI compared to the Dreem (BAI 0.21 [0.18], p<0.001) and Sleep Lab (BAI 1.34 [0.52], p<0.001) control groups. Patients with generalizable seizures had a statistically significant higher BAI compared to the Dreem (p<0.001) and Sleep Lab (p<0.001) groups, and well as compared to the focal epilepsy group (p=0.0304). However, while those with focal epilepsy had a higher BAI than the Dreem and Sleep Lab control groups, this did not reach statistical significance (**Fig. 2A**). Seizure frequency did not appear to have an effect on the association between brain age and chronological age in all patients with epilepsy (**Fig. 2B**), generalizable epilepsy (**Fig. 2C**), or focal epilepsy (**Fig. 2D**). Additionally, no statistically significant difference was found between different focal seizure types (**Supplementary Figure 3**).

Higher BAI was weakly associated with an increased lifetime seizure burden overall (R2 = 0.0416, p = 0.02 (**Fig. 3A**). The association was stronger in the generalizable epilepsy group, with R2 of 0.11 (p <0.001) (**Fig. 3B**), and weaker for focal epilepsy patients (R2= 0.09, p = 0.10 (**Fig. 3C**). The average age and number of years with epilepsy were not significantly different between focal and generalizable patients (see Table 1), suggesting that the associations above are not due to age alone. **Supplementary Figure 4** demonstrates weaker but positive associations with other metrics of epilepsy severity, including years with epilepsy and seizure frequency immediately prior to EMU admission.

### **Association between Lifetime Seizure Burden and Cognitive Impairment**

There was a negative association between cognitive functioning and lifetime seizure burden. Patients with an increased lifetime seizure burden had lower scores on the NIH Toolbox Cognitive Function Battery (**Fig. 4**). Total composite cognition had the strongest negative association (R2 = 0.130, p=0.011); followed by total crystallized cognition (R2 = 0.125, p=0.012); and finally by total fluid cognition (R2 = 0.104, p=0.024). In comparison to healthy controls, there was a significant decrease in cognitive performance between epilepsy patients and controls, with mean (± standard deviation) values for total composite, fluid composite, and crystallized composite for epilepsy patients of 99.6 ± 16.6, 97.7 ± 18.9, and 102.6 ± 11.8 and for Sleep Lab controls of 109.2 ± 12.5, 105.8 ± 16.0, and 110.7 ± 9.6, with p-values of <0.001, 0.026, and <0.001 respectively.

### **Association between BAI and Cognitive Impairment in Epilepsy**

In the Sleep Lab control cohort, BAI was not significantly correlated with total composite cognition (p=0.75) or fluid cognition (p=0.15). BAI had a significant negative correlation with crystallized cognition (R2 = 0.0632, slope -0.1683, p=0.002). In the Epilepsy group, higher BAI was associated with lower total crystallized cognition (R2 = 0.102, p=0.048), but not with total composite cognition (R2 =0.0467, p=0.19) or fluid cognition (R2 = 0.0146, p=0.46) (**Fig. 5**).

When comparing the association of BAI and cognition between patients with epilepsy and controls, the explained variance was higher in epilepsy patients for composite, fluid, and crystallized cognition (0.0467, 0.0146, 0.102 in epilepsy patients vs 0.0007, 0.0142, 0.0632 in controls). The slope, or degree by which cognition worsens as brain age increases, was steeper in epilepsy patients compared to healthy controls but did not meet statistical significance. ANCOVA between the slopes of the linear regressions for total composite, fluid, and crystallized cognition in epilepsy patients compared to healthy controls (-0.66, -0.42, -0.69 compared to -0.0244, 0.1322, and -0.1683) indicated p-values of 0.12 for total composite, 0.28 for fluid composite, and 0.09 for crystallized composite cognition.

## **DISCUSSION**

Our main findings are: 1) Conventional sleep architecture differs between patients with epilepsy and controls, with increased N2 and decreased N3 across all epilepsies, and an increase in REM in the generalizable and total groups; 2) BAI is substantially elevated in patients with epilepsy, with an average excess brain age of 5.02 years; 3) BAI is higher in epilepsy patients with generalizable seizures compared to those with focal seizures that do not generalize; 4) BAI is positively associated with an increased lifetime seizure burden; 5) There is a significant negative association between lifetime seizure burden and fluid, crystallized, and composite cognition; and epilepsy patients had worse cognitive outcome measures than healthy controls; 6) In epilepsy patients, higher BAI is associated with reduced crystallized cognition.

These findings are largely consistent with existing research on sleep changes in epilepsy. In our study, we found that the underlying sleep architecture in epilepsy differed from that of controls. We find that epilepsy patients have a greater proportion of N2 sleep and a lower proportion of N3 sleep, most notably in patients with focal seizures. REM sleep constituted a larger proportion of sleep in epilepsy patients overall, and particularly within the generalizable seizure subgroup, while the focal seizure group had a similar proportion of REM sleep compared to controls. Our finding that patients with epilepsy had increased REM sleep relative to controls was unexpected and could reflect changes in drug therapy. 35–38. It is important to note that our sample is not entirely representative of epilepsy patients as a whole, specifically that patients who undergo EMU stays tend to be medication-refractory (require more medications at higher doses) and during EMU stays often have variable titrations of medications to induce seizures and undergo multiple days of interrupted sleep during close clinical monitoring; this may affect the sleep architecture of this epilepsy patient cohort. Our cohort was otherwise representative of those included in studies identifying decreased REM in those with epilepsy, so this discrepancy warrants further investigation.

BAI was higher in epilepsy patients than in controls. The control group had a BAI near 0 (-0.1 and 0.53), while epilepsy patients had higher brain age indices, ranging from 3.3 in the focal seizure group to 5.53 in the generalizable seizure group. Based on our understanding of generalizable epilepsy as disrupting large-scale brain networks, thus enabling seizure spread, it is reasonable to conclude that generalizable epilepsy is associated with more significant sleep changes due to widespread brain connectivity alterations.39,40 This could potentially explain the higher BAI of the generalizable seizure group compared to that of the healthy controls. Similarly, although there is a weak positive association, the generalizable seizure group demonstrated the strongest association between lifetime seizure burden and higher BAI, suggesting that ongoing, frequent generalizable seizures disrupt sleep networks, “aging” the sleeping brain.

Compared to healthy controls, there was an 8 to 10-point statistically significant decrease across composite cognition measures for epilepsy patients. Increasing seizure burden was noted to be associated with poorer performance on cognitive testing. Prior studies have indicated that cognitive measures, like IQ, demonstrate a significantly negative association with the number of lifetime seizures, with a close to 20-point IQ drop between those with 2-10 lifetime seizures and those with >100 lifetime seizures.41 The NIH Toolbox has been used in epilepsy to identify specify cognitive dysfunction, such as slower processing speed and multi-domain dysfunction in both focal and generalized epilepsies.42,43 The general decrease across composite, crystallized, and fluid cognition seen in our study is consistent with existing cognitive dysfunction literature in epilepsy. Higher BAI scores were associated with poorer performance on cognitive testing, for composite, fluid, and crystallized cognition. Both controls and epilepsy patients demonstrated a similar negative association between increasing BAI and poorer cognition (with the notable exception of fluid cognition in healthy controls); epilepsy patients appeared to have a slightly stronger association that did not reach statistical significance. Several sub-analyses also indicated no significant effect on the BAI-cognition association based on seizure frequency, seizure burden, or seizure type.

Overall, this study demonstrates that changes in sleep EEG in epilepsy patients that resemble the changes that occur with aging are associated with reduced cognitive performance.

Our study has several limitations. An assessment of seizure frequency and associated seizure burden was conducted via retrospective chart review, which may introduce errors based on patient recollection and physician recording; the seizure frequency used here is likely to be lower than experienced by patients. Additionally, the sleep EEG recordings used to calculate the BAI were taken from patients who were in the epilepsy monitoring unit (EMU), which may introduce biases in sampling a population with more severe epilepsy than the general epilepsy population, often requiring more medications at higher doses which can affect the BAI due to sleep disruption. During EMU hospitalization, seizure capture is the goal, so medications are weaned, and frequent seizures are often seen. Additionally, sleep is often interrupted in the hospital due to close clinical monitoring. The sleep EEG clips taken for the BAI calculation were not compared to medication levels or to a recently increased frequency of seizures. Nevertheless, prior studies of sleep and epilepsy have primarily investigated those with refractory epilepsy, which makes this sample representative of those found in the literature. Additionally, while epilepsy cases were assessed during EMU hospitalization, control patients completed sleep assessments either in a sleep lab or at home, resulting in different environmental influences between the two cohorts. Furthermore, lab-based PSG and home-based EEG can use different numbers of electrodes, therefore reducing quality of the assessment. However, our recent study suggests that even the use of two frontal electrodes (i.e., a limited number, a proxy for home-based EEG) has sufficient internal accuracy to assess brain age44. BAI, as an automated detection tool, can be biased by noise and systemic error; however, a trained EEG reader manually confirmed that we successfully excluded seizures. The trajectory of BAI over the course of life and any parallelism with change in cognition or even brain structure cannot be established from our data. Future investigations will seek to address these limitations through prospective analyses and a broader epilepsy cohort including those with less severe disease.

**CONCLUSION**

Our study demonstrates that Brain Age Index (BAI), calculated from the sleep EEG, is associated with generalizable epilepsy and increased seizure burden. Cognitive dysfunction was shown to worsen with increased lifetime seizure burden, and, in epilepsy patients, a higher BAI was associated with poorer crystalized cognitive performance. Future work will investigate the association between sleep changes and BAI with other cognitive measures, change over time, post-surgical outcomes, and structural network abnormalities in epilepsy.

**FUNDING**

This research was conducted while MBW was a Breakthroughs in Gerontology Grant recipient, supported by the Glenn Foundation for Medical Research and the American Federation for Aging Research. MBW also received funding from grants from the NIH (R01NS102190, R01NS102574, R01NS107291, RF1AG064312, R01AG062989, R01AG073410) and the American Academy of Sleep Medicine through an AASM Foundation Strategic Research Award (AASMF-SRA). RJT received funding from an AASMF-SRA and RF1AG064312.

**COMPETING INTERESTS**

Dr. Thomas is co-inventor and patent holder of the ECG-derived sleep spectrogram, which may be used to phenotype sleep quality and central/complex sleep apnea. The technology is licensed by Beth Israel Deaconess Medical Center to MyCardio, LLC. He is also co-inventor and patent holder of the Positive Airway Pressure Gas Modulator, being developed for treatment of central/complex sleep apnea. He has consulted for Jazz Pharmaceuticals and consults for Guidepoint Global and GLG Councils. He is co-inventor of a licensed auto-CPAP software to DeVilbiss-Drive.

**REFERENCES**

1. Beghi E, Giussani G, Abd-Allah F, et al. Global, regional, and national burden of epilepsy, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. 2019;18(4):357-375. doi:10.1016/S1474-4422(18)30454-X

2. Murray CJL, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2197-2223. doi:10.1016/S0140-6736(12)61689-4

3. Beghi E. Addressing the burden of epilepsy: Many unmet needs. *Pharmacol Res*. 2016;107:79-84. doi:10.1016/J.PHRS.2016.03.003

4. Keezer MR, Sisodiya SM, Sander JW. Comorbidities of epilepsy: current concepts and future perspectives. *Lancet Neurol*. 2016;15(1):106-115. doi:10.1016/S1474-4422(15)00225-2

5. Kanner AM. Management of psychiatric and neurological comorbidities in epilepsy. *Nat Rev Neurol*. 2016;12(2):106-116. doi:10.1038/NRNEUROL.2015.243

6. Rauh R, Schulze-Bonhage A, Metternich B. Assessment of Anxiety in Patients With Epilepsy: A Literature Review. *Front Neurol*. 2022;13. doi:10.3389/FNEUR.2022.836321

7. Kanner AM. Depression in epilepsy: Prevalence, clinical semiology, pathogenic mechanisms, and treatment. *Biol Psychiatry*. 2003;54(3):388-398. doi:10.1016/S0006-3223(03)00469-4

8. Louis EK St. Sleep and epilepsy: Strange bedfellows no more. *Minerva Pneumol*. 2011;50(3):159-176. Accessed March 27, 2023. https://mayoclinic.pure.elsevier.com/en/publications/sleep-and-epilepsy-strange-bedfellows-no-more

9. Gibbon FM, Maccormac E, Gringras P. Sleep and epilepsy: unfortunate bedfellows. *Arch Dis Child*. 2019;104(2):189-192. doi:10.1136/ARCHDISCHILD-2017-313421

10. Rossi KC, Joe J, Makhija M, Goldenholz DM. Insufficient Sleep, Electroencephalogram Activation, and Seizure Risk: Re-Evaluating the Evidence. *Ann Neurol*. 2020;87(6):798-806. doi:10.1002/ANA.25710

11. Halasz P, Szucs A. *Sleep, Epilepsies, and Cognitive Impairment*. Academic Press; 2017.

12. Malow BA, Selwa LM, Ross D, Aldrich MS. Lateralizing value of interictal spikes on overnight sleep-EEG studies in temporal lobe epilepsy. *Epilepsia*. 1999;40(11):1587-1592. doi:10.1111/J.1528-1157.1999.TB02044.X

13. Fountain NB, Kim JS, Lee SI. Sleep deprivation activates epileptiform discharges independent of the activating effects of sleep. *J Clin Neurophysiol*. 1998;15(1):69-75. doi:10.1097/00004691-199801000-00009

14. Nascimento FA, Nath AR. Teaching NeuroImages: Epileptiform K-complexes in genetic generalized epilepsy: Common but underappreciated. *Neurology*. 2020;94(19):E2072-E2073. doi:10.1212/WNL.0000000000009414

15. Seneviratne U, Cook M, D’Souza W. Epileptiform K-Complexes and Sleep Spindles: An Underreported Phenomenon in Genetic Generalized Epilepsy. *J Clin Neurophysiol*. 2016;33(2):156-161. doi:10.1097/WNP.0000000000000239

16. Degiorgio CM, Curtis A, Carapetian A, Hovsepian D, Krishnadasan A, Markovic D. Why are epilepsy mortality rates rising in the United States? A population-based multiple cause-of-death study. *BMJ Open*. 2020;10(8). doi:10.1136/BMJOPEN-2019-035767

17. Johnson EL, Krauss GL, Kucharska-Newton A, et al. Dementia in late-onset epilepsy: The Atherosclerosis Risk in Communities study. *Neurology*. 2020;95(24):e3248. doi:10.1212/WNL.0000000000011080

18. Cole JH, Marioni RE, Harris SE, Deary IJ. Brain age and other bodily ‘ages’: implications for neuropsychiatry. *Mol Psychiatry*. 2019;24(2):266. doi:10.1038/S41380-018-0098-1

19. Sun H, Paixao L, Oliva JT, et al. Brain age from the electroencephalogram of sleep. *Neurobiol Aging*. 2019;74:112-120. doi:10.1016/J.NEUROBIOLAGING.2018.10.016

20. Ye E, Sun H, Leone MJ, et al. Association of Sleep Electroencephalography-Based Brain Age Index With Dementia. *JAMA Netw Open*. 2020;3(9):e2017357-e2017357. doi:10.1001/JAMANETWORKOPEN.2020.17357

21. Leone MJ, Sun H, Boutros CL, et al. HIV increases sleep-based brain age despite antiretroviral therapy. *Sleep*. 2021;44(8):1-9. doi:10.1093/SLEEP/ZSAB058

22. Paixao L, Sikka P, Sun H, et al. Excess brain age in the sleep electroencephalogram predicts reduced life expectancy. *Neurobiol Aging*. 2020;88:150-155. doi:10.1016/J.NEUROBIOLAGING.2019.12.015

23. Petit D, Gagnon JF, Fantini ML, Ferini-Strambi L, Montplaisir J. Sleep and quantitative EEG in neurodegenerative disorders. *J Psychosom Res*. 2004;56(5):487-496. doi:10.1016/j.jpsychores.2004.02.001

24. National Institutes of Health. NIH Toolbox for Assessment of Neurological and Behavioral Function | Blueprint. Accessed January 9, 2023. https://neuroscienceblueprint.nih.gov/resources-tools/blueprint-resources-tools-library/nih-toolbox-assessment-neurological-and

25. Weintraub S, Dikmen SS, Heaton RK, et al. The cognition battery of the NIH toolbox for assessment of neurological and behavioral function: validation in an adult sample. *J Int Neuropsychol Soc*. 2014;20(6):567-578. doi:10.1017/S1355617714000320

26. Sen A, Jette N, Husain M, Sander JW. Epilepsy in older people. *The Lancet*. 2020;395(10225):735-748. doi:10.1016/S0140-6736(19)33064-8

27. Cole JH, Poudel RPK, Tsagkrasoulis D, et al. Predicting brain age with deep learning from raw imaging data results in a reliable and heritable biomarker. *Neuroimage*. 2017;163:115-124. doi:10.1016/J.NEUROIMAGE.2017.07.059

28. Eggert T, Dorn H, Danker-Hopfe H. Nocturnal Brain Activity Differs with Age and Sex: Comparisons of Sleep EEG Power Spectra Between Young and Elderly Men, and Between 60–80-Year-Old Men and Women. *Nat Sci Sleep*. 2021;13:1611. doi:10.2147/NSS.S327221

29. Hu Y, Shan Y, Du Q, et al. Gender and Socioeconomic Disparities in Global Burden of Epilepsy: An Analysis of Time Trends From 1990 to 2017. *Front Neurol*. 2021;12. doi:10.3389/FNEUR.2021.643450

30. Stuart EA. Matching methods for causal inference: A review and a look forward. *Stat Sci*. 2010;25(1):1. doi:10.1214/09-STS313

31. Jaoude MA, Sun H, Pellerin KR, et al. Expert-level automated sleep staging of long-term scalp electroencephalography recordings using deep learning. *Sleep*. 2020;43(11). doi:10.1093/SLEEP/ZSAA112

32. Jing J, Sun H, Kim JA, et al. Development of Expert-Level Automated Detection of Epileptiform Discharges During Electroencephalogram Interpretation. *JAMA Neurol*. 2020;77(1):103-108. doi:10.1001/JAMANEUROL.2019.3485

33. Jing J, Ge W, Hong S, Fernandes M, Lin Z YC. Development of Expert-level Classification of Seizures and Rhythmic and Periodic Patterns During EEG Interpretation. *Neurology*.

34. Hogan J, Sun H, Paixao L, et al. Night-to-night variability of sleep electroencephalography-based brain age measurements. *Clin Neurophysiol*. 2021;132(1):1-12. doi:10.1016/J.CLINPH.2020.09.029

35. Tork MA, Rashed HR, Elnabil L, et al. Sleep pattern in epilepsy patients: a polysomnographic study. *Egyptian Journal of Neurology, Psychiatry and Neurosurgery*. 2020;56(1):1-5. doi:10.1186/S41983-019-0141-4/TABLES/6

36. Yeh WC, Lai CL, Wu MN, et al. Rapid eye movement sleep disturbance in patients with refractory epilepsy: A polysomnographic study. *Sleep Med*. 2021;81:101-108. doi:10.1016/J.SLEEP.2021.02.007

37. Placidi F, Diomedi M, Scalise A, Marciani MG, Romigi A, Gigli GL. Effect of anticonvulsants on nocturnal sleep in epilepsy. *Neurology*. 2000;54(5 Suppl 1):S25-32. Accessed January 15, 2023. http://intl.neurology.org/cgi/content/full/54/5\_suppl\_1/S25

38. Bazil CW. Epilepsy and sleep disturbance. *Epilepsy and Behavior*. 2003;4(SUPPL. 2). doi:10.1016/J.YEBEH.2003.07.005

39. Focke NK, Diederich C, Helms G, Nitsche MA, Lerche H, Paulus W. Idiopathic-generalized epilepsy shows profound white matter diffusion—tensor imaging alterations. *Hum Brain Mapp*. 2014;35(7):3332-3342. doi:10.1002/HBM.22405

40. Peng SJ, Harnod T, Tsai JZ, et al. Through Diffusion Tensor Magnetic Resonance Imaging to Evaluate the Original Properties of Neural Pathways of Patients with Partial Seizures and Secondary Generalization by Individual Anatomic Reference Atlas. Published online 2014. doi:10.1155/2014/419376

41. Aldenkamp AP, Bodde N. Behaviour, cognition and epilepsy. *Acta Neurol Scand Suppl*. 2005;182(182):19-25. doi:10.1111/J.1600-0404.2005.00523.X

42. Hwang G, Dabbs K, Conant L, et al. Cognitive slowing and its underlying neurobiology in temporal lobe epilepsy. *Cortex*. 2019;117:41-52. doi:10.1016/J.CORTEX.2019.02.022

43. Garcia-Ramos C, Struck AF, Cook C, et al. Network topology of the cognitive phenotypes of temporal lobe epilepsy. *Cortex*. 2021;141:55-65. doi:10.1016/J.CORTEX.2021.03.031

44. Sun H, Paixao L, Oliva JT, et al. Brain age from the electroencephalogram of sleep. *Neurobiol Aging*. 2019;74:112-120. doi:10.1016/J.NEUROBIOLAGING.2018.10.016