Sleep Architecture Associations with Brain Age: A Multi-Site Model Validation

Thomas J. Vanasse, PhD1, Sam Rusk, BS1, Yoav N. Nygate, MS1, Chris R. Fernandez, MS1, Jiaxiao M. Shi, PhD2, Jessica Arguelles, BS2, Matthew T. Klimper, BS2, Emerson M. Wickwire, PhD3, Nathaniel F. Watson, MD, MS4, Dennis Hwang, MD2

1 EnsoData Research, Ensodata, Madison, WI, USA
2 Kaiser Permanente, Southern California, USA
3 Department of Psychology, University of Maryland, Baltimore, MD
4 Department of Neurology, University of Washington School of Medicine, Seattle, WA

Introduction

Electroencephalogram (EEG) provides clinically relevant information for patient health evaluation and comprehensive assessment of sleep [1]. EEG-based indices have been associated with various health conditions and diseases, and hold promise as biomarkers for brain health [2]. Increase in age has been associated with a range of characteristics that exist within EEG signals recorded during sleep, such as: fragmented sleep with higher N1 sleep, reduced slow-wave sleep, reduced REM sleep, and decreased amount of sleep spindles and vertex waves [3]. Thus, EEG signals show potential for encoding the physiological information that, with the correct analysis, allows for the accurate assessment of age. Our previous research [4] demonstrated strong performance of applying deep learning to predict the brain-age index (BAI) in an internal testing dataset of 1,172 PSG studies. Furthermore, the BAI correlated with multiple disease statuses including diabetes, hypertension, and depression. In this work, we aimed to extend these findings by validating our model on larger (20x), multi-site datasets, and to explore the sleep architecture associations with BAI using ordinary least squares (OLS) regression.

Polysomnography (PSG) Datasets

Training

Training/Validation Enso Historical Dataset:
54,195 Subjects ; 10 Devices

Testing

Kaiser Permanente (KP) Historical Test Dataset:
10,694 Subjects; 1 Device; 18-100 Chronological Age (CA)

Enso Historical Test Dataset:
15,158 Subjects : 10 Devices : 18-100 CA

Methodology

- In order to predict the age of a patient from the PSG signals, a deep convolutional neural network (DCNN) was trained.
  - The input to the model was the full night raw 9-channel EEG, electrooculogram (EOG), and electromyography (EMG) montage (6 EEG leads, 2 EOG leads, and 1 EMG lead), and the target output was the CA of the patients.
  - Our employed model architecture contained a combination of 1-D convolution, long-short term memory (lstm), and dense layers. The model contained over 21 million learned parameters, tuned across 30 epochs of training, (see Figure 1).
- To assess model performance, we ran both deming regression and bland-altmann plots (Figure 2) on EnsoHistorical and KP Test Datasets.
- We then tested the OLS associations with BAI on both test datasets, (shown in Figure 3 & Table 1).

Results

What is the Brain Age Index (BAI)?

- The trained model can take a full night recording of 8 raw channels and predict the age of the patient.
- The predicted age (BA) together with the CA were used to derive representative indices that were correlated with canonical sleep architecture statistics (e.g., N3 % of total sleep time).
- We've calculated the brain age index (BAI) using the following equation: BAI=BA -CA
- The BAI allows for the evaluation of the directionality (i.e., higher is "worse") of the deviation between the BA and CA.

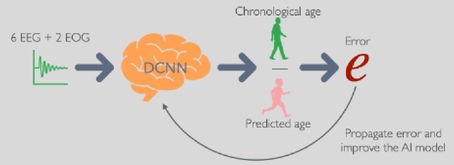

Figure 1. The Training Process. The DCNN model was trained to predict the CA of a patient. During each iteration, the model generates a prediction for the age based on the raw signals and optimizes an error function such that the predicted age will match the CA as much as possible.

Brain Age Index Model Performance

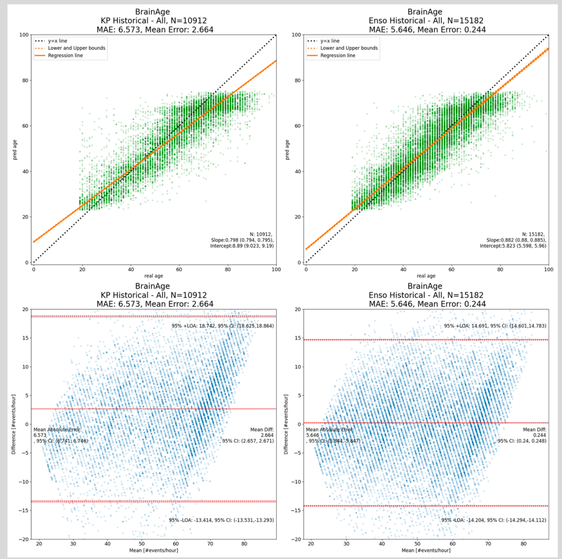

Figure 2. BrainAge Model Performance. Left and right columns correspond to performance on KP Historical and EnsoData Historical Test Datasets, respectively. The top row shows the deming regression plot, where the linear fit to BA (y) from CA (x) is in orange and y=x reference is in black. The bottom row shows the bland-altmann agreement plot, where the x-axis is the mean of the two (CA + BA) ages, and the y-axis is the difference between (CA - BA) for that sample.

Results Continued

Ordinary Least Squares (OLS) Parameter Estimates

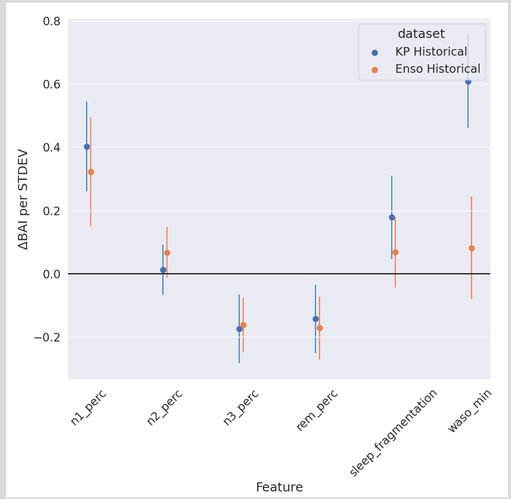

Figure 3. Sleep Architecture & BAI Association Effect Sizes. The x-axis separates all features used in the OLS analysis. The y-axis marks the effect size, in units of change in BAI per unit standard deviation. Each effect is color-coded by either the KP Historical (blue) or Enso Historical (orange) Dataset analysis. The black line marks zero, or no effect.

Ordinary Least Squares (OLS) Parameter Estimates

Feature	KP Historical Dataset Effect (CI)	Enso Historical Dataset Effect (CI)
Total Explained Var.	R2 = 0.340	R2 = 0.201
N1 Percentage	*0.4019 (0.260, 0.544), p<0.001	*0.3226 (0.150, 0.495), p<0.001
N2 Percentage	0.0126 (-0.067, 0.092), p=0.757	0.0674 (-0.013, 0.148), p=0.101
N3 Percentage	*-0.1737 (-0.283, -0.065), p=0.002	*-0.1609 (-0.248, -0.074), p<0.001
REM Percentage	*-0.1423 (-0.250, -0.034), p=0.01	*-0.1710 (-0.271, -0.071), p=0.001
Sleep Fragmentation	*0.1781 (-0.042, 0.178), p=0.008	0.0681 (-0.042, 0.178), p=0.227
WASO	*0.6084 (0.461, 0.756), p<0.001	0.0822 (-0.080, 0.244), p=0.319

Table 1. OLS Parameter Estimates. Left and right columns correspond to performance on KP Historical and Enso Historical Test Datasets, respectively. The top row shows the explained variance (R2) of all variables together. Each row shows that feature's parameter estimate. Rows that are highlighted in green denote features that were significant (p<0.01) for both testing datasets.

Conclusions

- This analysis highlights the robustness of the applied BAI model; we show comparable performance (+/- 1 in MAE) across large, multi-site/device datasets.
- Increased N1% of total sleep correlates with an increased (i.e., worse) BAI, specifically ~0.35 years per standard deviation.
  - This effect was both large in magnitude and consistent across testing datasets, which is in line with previous work [2,5].
  - N1 is a marker of "light sleep" and its percentage of total sleep increases with healthy aging [3].
- Decreased N3% and REM% of total sleep correlates with increased (i.e., worse) BAI.
  - These effects were not as pronounced as the N1 effect.
- While sleep fragmentation and WASO were significantly associated with BAI in the KP Historical dataset, we did not replicate those findings in the Enso Historical Dataset.
- The total explained variance of the sleep architecture features is a minority (R2<0.35) of those signal-derived features extracted from deep learning.

Future Work

- A fundamental question regarding the healthcare impact of the BAI remains: can a high BAI be reversed with behavioral or pharmacological intervention?
- Decreased N3 and REM sleep have been reported in multiple neurodegenerative disorders [6], and their association with BAI suggests shared mechanistic action.
  - Linking neurodegenerative processes (e.g., amyloid-beta deposition) to BAI would clarify this hypothesis.

References

1. Brink-Kjaer, et al. Predicting Age with Deep Neural Networks from Polysomnograms. 2020 42nd Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC). 2020. doi:10.1109/embc44109.2020.9176254
2. Sun H, et al. Brain age from the electroencephalogram of sleep. Neurobiology of Aging. 2019;74:112-120. doi:10.1016/j.neurobiolaging.2018.10.016
3. Ohayon, M. M., Carskadon, M. A., Guilleminault, C. & Vitiello, M. V. Meta-Analysis of Quantitative Sleep Parameters From Childhood to Old Age in Healthy Individuals: Developing Normative Sleep Values Across the Human Lifespan. Sleep 27, 1255–1273 (2004).
4. Nygate, Y. et al. 543 EEG-Based Deep Neural Network Model for Brain Age Prediction and Its Association with Patient Health Conditions. Sleep 44, A214–A214 (2021).
5. Brink-Kjaer, A. et al. Age estimation from sleep studies using deep learning predicts life expectancy. Npj Digital Medicine 5, 103 (2022).
6. Petit D, Gagnon J-F, et al. Sleep and quantitative EEG in neurodegenerative disorders. Journal of Psychosomatic Research. 2004;56(5):487-496. doi:10.1016/j.jpsychores.2004.02.001