Measuring Brain Age Algorithm Night-to-Night Stability

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Introduction

Changes in sleep electroencephalogram patterns with increasing age are clearly established (Mander et al., 2017; Scullin, 2017), and recent efforts have been made to calculate brain-age using both MRI and EEG (Franke et al., 2010, Sun et al., 2018). A recent study proposed the use of Brain-Age Index (BAI) as a sign of overall brain health and possible biomarker for diseases including diabetes, neurological disorders, and HIV-AIDS.

However, while patient brain ages five years apart have been compared, the night-to-night variability of the brain-age algorithm has yet to be studied. Night-to-night EEG variability could stem from previous sleep deprivation, interrupted sleep due to outside factors such as light or noise, and other disruptions. To determine the clinical applicability of BAI (Brain Age – Chronological Age) as a biomarker of disease, the night-to-night variability in model performance must be quantified. This study aims to:

(1) determine the night-to-night variability of BAI in individual patients

(2) establish thresholds to determine the probability that a patient's actual Brain Age (BA) differs from their Chronological Age (CA) based on a limited number of observations.

Patient Cohort

Eligible patients included any adult (≥18 years) patient who underwent continuous EEG (cEEG) monitoring at the EMU at the Massachusetts General Hospital during a 5 years period between May 1, 2014, and May 1, 2019 who had

(1) at least two consecutive nights of EEG recordings;

(2) "normal" EEG recordings (i.e., showed no signs of epileptiform EEG activity as such abnormalities would affect the calculation of brain age) as assessed by a certified epileptologist; and

(3) >5 hours of cEEG data (Figure 1). Ninety-five patients met these criteria.

Methods

Artifact Removal

Artifact Removal:

(1) 30-second segments with greater than 6 blinks where the EEG was classified as awake were removed (the algorithm was trained on sleep-lab data).

(2) 30-second segments with ≥ 2 seconds of saturated signal (amplitude > 500 uV) were removed

(3) 30-second segments with ≥ 2 seconds of flat EEG signal were removed

EEG Filtering

Remaining segments were filtered with:

(1) bandstop filter at 60 Hz to remove line noise

(2) bandpass filter between .5 and 20 Hz

Brain Age Calculation

Each 30-second segment was classified independently using two sleep-staging algorithms, and results were compared. Sleep-stage results and EEG features were used as inputs to a linear brain-age prediction model. Brain age estimates were calculated separately for each epoch.

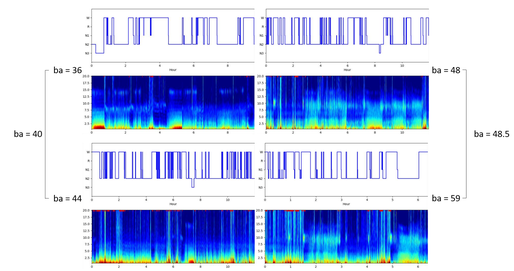

Figure 1
Brain age estimate for two patients. Left-patient with low variability

Night-to-Night Variability

The standard deviation was calculated for each patient using all brain age estimates for that patient. To determine if multiple estimates gave a more stable brain age prediction:

(1) patient brain age estimates were divided into groups of size *n*

(2) the mean BA of each epoch was calculated

(3) the standard deviation between mean BA values was calculated. To simulate random samples of size *n*, 1,000 permutations were created for each patient and these permutations were sliced into segments of size *n*. The average brain age was calculated for each segment, and one standard deviation was calculated for each permutation. Patient standard deviation for *n* nights were calculated as the mean standard deviation across the 1,000 permutations.

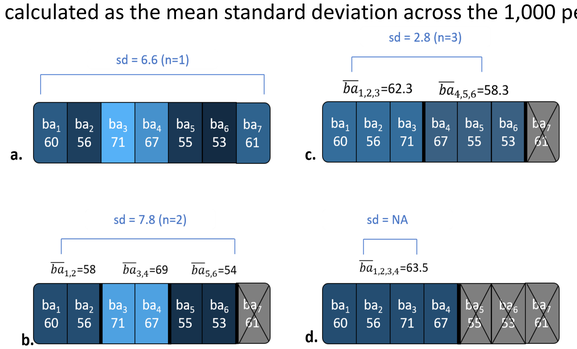

Figure
2a. Standard deviation calculated using all nights once
2b-d Method for calculating standard deviation for the average of 2, 3 and 4 nights respectively.

Results

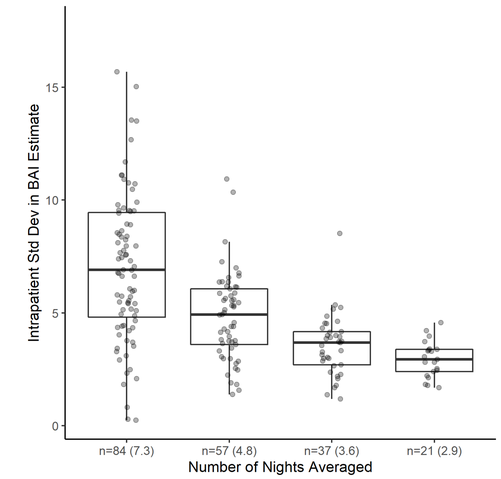

Figure 3- Intrapatient standard deviation with increasing number of nights.
X axis- *n patients* (mean standard deviation)
Y axis- standard deviation in predicted Brain Age Index (years)

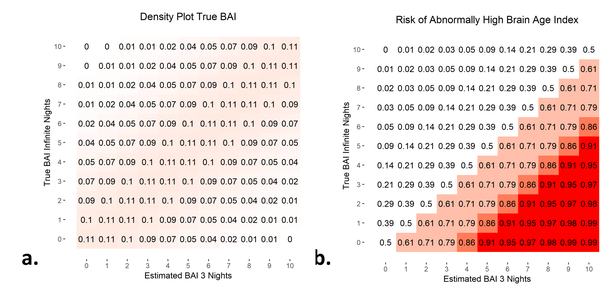

Figure 4a. Probability density table. Probability that the true BAI = y if estimated BAI = x.
4b. Probability that a patient's actual BAI is ≥ y if their estimated BAI = x.

Discussion

Our study results show that the previously developed machine learning brain age algorithm provides a stable BAI estimate if three nights are averaged (sd = 3.6). The fact that results are similar when two separate sleep staging algorithms are used (sd = 3.6 vs. sd = 3.7), support the robustness of the brain age prediction algorithm. By assuming that brain age estimates vary night-to-night around a true brain age value, we show that patients with a high average BAI are likely to have a high true BAI. When averaging BAI from 3 nights, patients with a BAI ≥ 9 have over a 90% chance that their true brain age is ≥ 4. This is similar in magnitude to the difference between healthy patients and those with diabetes and could be a clinical biomarker of chronic disease or neurodegeneration.