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Excess brain age in the sleep electroencephalogram predicts reduced life expectancy

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Abstract

The brain age index (BAI) measures the difference between an individual's apparent “brain age” (BA; estimated by comparing EEG features during sleep from an individual with age norms), and their chronological age (CA); that is BAI = BA–CA. Here, we evaluate whether BAI predicts life expectancy. Brain age was quantified using a previously published machine learning algorithm for a cohort of participants ≥40 years old who underwent an overnight sleep electroencephalogram (EEG) as part of the Sleep Heart Health Study (n = 4877). Excess brain age (BAI >0) was associated with reduced life expectancy (adjusted hazard ratio: 1.12, [1.03, 1.21], $p = 0.002$). Life expectancy decreased by −0.81 [−1.44, −0.24] years per standard-deviation increase in BAI. Our findings show that BAI, a sleep EEG-based biomarker of the deviation of sleep microstructure from patterns normal for age, is an independent predictor of life expectancy.

Keywords

Brain age; Mortality; EEG; Sleep; Life expectancy; Biomarker

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Disclosure statement

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurobiolaging.2019.12.015.

1. Introduction

Healthy neurological aging is a major global challenge. Biomarkers of brain aging are urgently needed to understand aging mechanisms, design effective tools to improve brain health, and identify individuals at increased risk of age-associated neurological disorders, cognitive decline, and death. Several aging biomarkers have been proposed, including molecular-cellular level biomarkers such as leukocyte telomere length (Kruk et al., 1995) and DNA methylation status (Bocklandt et al., 2011; Chen et al., 2016; Horvath, 2013). Among organ-system level biomarkers, the concept of “brain age” has emerged recently, which represents the age predicted by analyzing age-related patterns in brain structure (from brain MRI images) (Cole et al., 2017b; Cole and Frank, 2017; Franke et al., 2010; Franke and Gaser, 2012) and function (from EEG signals) (Al Zoubi et al., 2018; Purdon et al., 2015; Sun et al., 2019; Touchard et al., 2019). The sleep state is uniquely attractive for computational analysis because it exhibits a rich set of features that are distinct for each sleep stage, are conserved across individuals, and change systematically with age.

Sleep EEG signals exhibit several characteristics that are stable within an individual. Classic features of non–rapid eye movement (NREM) sleep, such as spindles, K-complexes, and slow waves show substantial genetic determination and heritability (Gorgoni et al., 2019; Rusterholz et al., 2018). Strong trait-like differences are also well documented in response to experimental sleep loss, stress, and different types of sleep apnea (McGuire et al., 2016; Zinchuk and Yaggi, 2019). What is not known is the extent to which these phenotypic differences predict clinically meaningful health-related outcomes.

We recently showed that an individual's age can be predicted from the pattern of brain activity recorded during an overnight sleep EEG using machine learning methods (Sun et al., 2019). We define the difference between how old an individual's brain “looks” to the machine learning algorithm (sleep EEG-predicted brain age, BA) and their chronological age (CA) as the brain age index, BAI = BA–CA. Our prior work demonstrates that BAI is increased in neurological and psychiatric disease, diabetes, and hypertension (HTN) (Sun et al., 2019). In the present study, we further investigate the utility of BAI as a biomarker of brain health and general health, by testing whether increased BAI independently predicts life expectancy (LE).

2. Materials and methods

2.1. Design and participants

A retrospective cohort study was designed based on the SHHS Visit 1 data set from the Sleep Heart Health Study (SHHS). This visit included participants enrolled between November 1995 and January 1998. Outcomes were collected in 2011. Exclusion criteria included age <40 years, unwillingness, and physical, social, or mental conditions precluding a home polysomnogram (PSG). PSG data were collected using the Compumedics P Series System (Abbotsford, Victoria, Australia) device at a sample rate of 500 Hz. EEG was recorded from 2 electrodes, placed at locations C3A2 and C4Al. Additional non-EEG signals recorded as part of PSG were not included in our analysis. In total, 4877 participants from the SHHS were included in our final analysis (Quan et al., 1997).

2.2. Covariates

The primary outcome was median survival time, also known as LE. LE was estimated using survival analysis. Survival data provided the chronological age at death or last contact. The primary exposure was BAI, scaled by (divided by) its standard deviation in the cohort. We estimated the dependence of LE on BAI and compared LE in participants with high BAI (i.e., predicted brain age older than chronological age) versus low BAI. The survival model was adjusted for a variety of other covariates available in the SHHS data set (Quan et al., 1997). The following were included as binary covariates: sex (male or female), race (white/other or black), marital status (widowed/divorced/separated/never married/unknown/refused or married), diabetes (no or yes), HTN (no or yes), cardiovascular disease (CVD) (no or yes), smoking status (former/never or current), and education level (>10 years or <10 years). BAI (years), body mass index (BMI) (kg/m^2), and apnea-hypopnea index (AHI, the average number of breathing pauses [apneas] and reductions [hypopneas] per hour of sleep) were included as continuous covariates.

We also conducted a secondary sensitivity analysis, in which the multivariate model mentioned previously was augmented with 2 additional sleep “macrofeatures” which prior literature (Smagula et al., 2016) suggests may also be associated with mortality: REM % (percentage of total sleep time spent in REM sleep) and sleep fragmentation (measured by the number of minutes awake after sleep onset, WASO). This analysis was performed to ascertain whether BAI provides “extra information” beyond these traditional sleep measures.

2.3. Calculation of the brain age index (BAI)

BAI was calculated as described in our previous work (Sun et al., 2019). Briefly, brain age is estimated using a penalized linear regression machine learning model. The model was developed on a training data set of overnight sleep EEGs from 2330 healthy participants in the MGH Sleep data set (Biswal et al., 2018; Sun et al., 2019). The model first divides the EEG into a series of consecutive 30-second-long segments. From each segment, the algorithm extracts summary statistics of the signal that serve as features (95th-percentile range, min, mean, SD of spectral power for delta, theta, and alpha bands; ratios of spectral band powers; kurtosis of band powers, etc.). Using these features, an automated algorithm (Sun et al., 2017) assigns a sleep stage (Wake, NREM 1, 2, 3, or REM) to each 30-second segment. The algorithm then computes an average feature vector for each sleep stage, and concatenates the features from the 5 stages to create a set of $102 \times 5 = 510$ features. These features are finally multiplied by weights and added together to yield the predicted brain age. The weights were determined by optimizing an objective function to predict participants' chronologic age.

In this study, we applied the model to overnight sleep EEG data from participants in the SHHS (n = 4877) (Quan et al., 1997). BAI was calculated by subtracting chronological age from the sleep EEG-predicted brain age.

2.4. Statistical analysis

Descriptive statistics for participant demographics include frequencies, percentages, means, standard deviations, medians, and interquartile ranges. Categorical variables are reported as

% (n), normally distributed continuous variables are reported as mean ± SD (standard deviation), and nonparametric continuous variables are reported as median [interquartile range (IQR)]. To assess associations with mortality, we used univariate and adjusted (multivariate) Cox proportional hazards (PH) regression, allowing for right censoring. The results are reported as unadjusted and adjusted mortality hazard ratios. Variables were adjusted for in the multivariate model when $p < 0.05$ in the corresponding univariate model. Variables considered for model adjustment were covariates available at the time of SHHS visit 1, as described previously.

To estimate the effect of BAI on LE, we fit the baseline survival rate in the Cox-PH model with a Weibull model. Specifically, the Cox-PH model approximates the survival function as $S(t, x) \approx [S_0^{KM}(t)]^{z(x)}$, where $S_0^{KM}(t)$ is the empirical (Kaplan-Meier) survival curve, and the exponent $z(x) = \exp(\beta_0 + \beta_1 x_1 + \ldots + \beta_n x_n)$ contains the model coefficients β_i for the covariates x_i. This model is used to calculate the adjusted hazard rates for each covariate as $HR_i = \exp^{\sigma_i \beta_i}$, where σ_i is a unit-change in covariate x_i, which we take as one standard deviation for continuous-valued covariates, and one for binary-valued covariates.

To extend the baseline survival model $S_0^{KM}(t)$ out until death of the entire cohort, we fit a parametric, namely the Weibull curve $S_0^{W}(t) = \exp(-[\lambda t]^p)$. We confirmed goodness of fit graphically, by plotting $\log S_0^{KM}(t)$ and $\log S_0^{W}(t)$ together on the same plot to confirm that they are approximately equal. After confirmation, we used the model $S(t, x) \approx [S_0^{W}(t)]^{z(x)}$. The area under this Weibull proportional hazards curve is our estimate of LE, i.e. $LE(x) \approx Area[S(t, x)]$. To characterize how LE depends on BAI, we set all values of the covariates x (other than BAI) to their median values, and varied only BAI. This creates a graph $LE(BAI)$, whose slope we report as the change in LE per standard-deviation change in BAI.

Confidence intervals for reported statistics were estimated using bootstrapping (1000 rounds), and are reported using the format: X [Y, Z]. All analyses were performed using MATLAB (Natick, MA) software, and p values of <0.05 were considered statistically significant. The code needed to produce all figures and tables is available on request from the authors.

3. Results

Data from 4877 participants were analyzed from the Sleep Heart Health Study during SHHS visit 1. Participant demographics are presented in Table 1. The median follow-up period was 11.9 years (IQR 2.0), during which 17.2% (n = 839) of participants died. Individuals in this cohort had a mean age of 61.2 years (SD 10.0) and a mean BAI of 0.8 years (SD 15.2). The median BMI was 27.6 kg/m^2 (IQR 6.1) and the median AHI was 12.8 apneas or hypopneas per hour of sleep (IQR 16.7). 53.2% (n = 2597) of participants were female, 8.0% (n = 389) were of black race, 78.4% (n = 3824) were married, 6.5% (n = 303) had diabetes, 40.0% (n = 1953) had HTN, 19.6% (n = 818) had CVD, 10.0% (n = 486) were current smokers, and 6.2% (n = 301) had less than ten years of education (Table 1).

Unadjusted and adjusted hazard ratios (aHRs) for all-cause mortality are presented in Table 2. After adjusting for covariates in the Cox regression model (brain age index, sex, race, marital status, BMI, diabetes, HTN, CVD, smoking status, education level, and AHI), participants with a higher BAI had a significantly increased mortality risk compared with those with a lower BAI (aHR 1.12, [1.03, 1.21], $p = 0.002$), where the hazard expresses the increased relative risk per standard-deviation change in BAI (Table 2).

Other variables significantly associated with increased mortality risk in the adjusted model included diabetes (aHR 1.52, [1.23, 1.85], $p < 0.001$), HTN (aHR 1.20, [1.04, 1.40], $p = 0.023$), CVD (aHR 1.83, [1.57, 2.14], $p < 0.001$), current smoking status (aHR 2.29, [1.82, 2.98], $p < 0.001$), and BMI (aHR 1.08, [0.99, 1.19], $p = 0.001$). Female sex (aHR 0.68, [0.59, 0.80], $p = 0.002$) was associated with decreased risk of death. Associations with mortality that did not reach statistical significance in the multivariate model included race, marital status, education level, and AHI (Table 2).

The change in LE is plotted as function of BAI in Fig. 1. LE is estimated as the area under a baseline multivariate survival model that is adjusted for the effects of covariates. For these plots, all baseline covariates are set to their median values in the cohort, except BAI, which is allowed to vary. Comparing extremes of BAIs, we see that participants with sleeping brain activity that “looks” substantially younger than their chronological age (BAI = −3 standard deviations) have a LE 5.0 years longer than participants with substantially older-appearing sleeping brain activity (BAI = +3 standard deviations). For each standard-deviation increase in BAI, LE decreased by −0.81 [−1.44, −0.24] years (Fig. 1).

In sensitivity analysis, we adjusted the multivariate model for 2 additional conventional macro sleep features: fragmentation (measured by WASO) and REM%. WASO was not associated with LE ($p = 0.50$). By contrast, REM was associated with LE ($p = 0.02$); however, the association between BAI and LE changed minimally (reduction in LE of 5.0 years without adjusting vs 4.9 years while adjusting for REM%, per 3 SD change in BAI).

4. Discussion

Our findings show that individuals with sleeping brain activity characteristic of individuals with an older chronological age (i.e., a higher BAI score) have a significantly reduced LE compared to those with younger-appearing brains, with each standard-deviation increase in BAI yielding a decrease in LE of almost one year, or equivalently, an adjusted hazard for all-cause mortality of 1.12. This result was obtained after controlling for covariates of sex, race, marital status, BMI, diabetes, HTN, CVD, smoking status, education level, and AHI. Thus, BAI is an EEG-based biomarker of the risk of death.

BAI shares similarities with other recently developed biomarkers of aging. Kruk et al. (1995) found that a decline in telomere repair is connected to the process of aging. Bocklandt et al. (2011) found that DNA methylation patterns at specific sites in the genome that are known to correlate with age predict an individual's epigenetic bio-age. These patterns change with increasing age and aging-associated disease. Horvath (2013) further examined DNA methylation age and developed a multitissue predictor to estimate the age of

body tissues and cell types. A meta-analysis by Chen et al. (2016) built on this work and found that epigenetic age assessed in blood cell composition predicts all-cause mortality independent of chronological age, even after adjusting for additional risk factors.

Several studies have used neuroimaging to predict brain age (Cole and Franke, 2017). Franke et al. (2010) used T1-weighted MRI scans to predict an individual's brain age, and found that accelerated aging correlates with accelerated brain atrophy, as indicated in Alzheimer's disease (AD). Franke and Gaser (2012), Gaser et al. (2013), and Löwe et al. (2016) demonstrated that this neuroimaging-derived biomarker follows the progression of mild cognitive impairment to AD based on pathological brain aging patterns, even when the status of a participant's APOE status is unknown. Cole (2017) and Cole et al. (2017b) further found that raw T1-weighted MRI data using machine learning methods can function as a brain aging biomarker. Age-related alterations in brain structure that make the brain appear “older” are associated with increased risk of Down syndrome, AD, and mortality, based on differences in the rate of mild cognitive impairment and beta amyloid deposition (Cole et al., 2017a, 2018). In one study of MRI-based brain age (Cole et al., 2018), a model adjusted for age and sex found that each extra year of brain-predicted age (equivalent to our concept of BAI) was associated with a 6.1% relative increase in the risk of death between age 72 and 80 years (HR 1.06 [1.031, 1.091]). These effect sizes, although similar to ours, are not directly comparable, because our model adjusted for multiple other variables (e.g., diabetes, HTN) and involved a large, more diverse cohort. Nevertheless, this concordance of findings supports the overall value of distinguishing chronologic from biologic age.

While the aforementioned biomarkers have scientific value, their potential clinical use is limited by cost, time, and accessibility. EEG-based biomarkers of brain aging have the advantage of being easily deployable, noninvasive, low-cost, and easily repeatable. Purdon et al. (2015) observed general anesthesia-induced brain dynamics in areas related to aging in the EEG, and found that age-dependent changes in the EEG parallel neurological changes in typical aging. Touchard et al. (2019) demonstrated that this EEG-based cerebral physiological age (i.e., brain age) can function as a marker of cerebral fragility, and predict postoperative cognitive changes in age and burst suppression in individuals under general anesthesia. Outside of anesthesia, Al Zoubi et al. (2018) found that machine learning approaches can be used to infer an individual's age from awake EEG signals. Our previous work by Sun et al. (2019) developed a specific machine learning model to predict brain age from sleep EEGs, which was found to be higher in individuals with neurological and psychiatric disease, HTN, and diabetes. Our current work links this model with LE.

There have been prior studies linking aspects of sleep with mortality. A study of 185 healthy older adults in their 60s through 80s, with no history of mental illness, sleep complaints, or current cognitive impairment, reported associations with death of certain “macro” features of sleep, derived from the sequence of overnight sleep stages (“sleep hypnogram”) (Dew et al., 2003). After controlling for age, gender, and baseline medical burden, features that predict increased risk of death include sleep latency >30 minutes (aHR 2.14, [1.25, 3.66]), sleep efficiency <80% (aHR 1.93, [1.14, 3.25]), and low or high (<16.1 or >25.7%) REM sleep percentage (aHR 1.71, [1.01, 2.91]). Associations were also found in a large study (n = 2531) of community-dwelling older men between mortality and increased sleep

fragmentation (aHR = 1.32, [1.12–1.57]) and a lower percentage of REM sleep (aHR per s.d. = 0.90, [0.93–0.97]) (Smagula et al., 2016). Similarly, a study that included this cohort and 2 other cohorts of older adults (men and women, n = 8668 total) found that combinations of certain sleep macro-features (i.e., time in bed, hours spent napping, and wake-up time) correlate with increased risk of death (Wallace et al., 2019). This latter study did not report hazard ratios, thus effect sizes cannot be compared directly with those in the present study. In sensitivity analysis, we also found that lower percentage of REM was independently associated with mortality, while sleep fragmentation was not; nevertheless, adjusting for REM percentage did not substantively alter our main findings. By contrast to our present study, none of the studies cited previously investigated the relationship between EEG oscillations (sleep “microstructure”) and mortality. Taken together, these prior studies and the present study strongly suggest that both micro- and macro-features of sleep are associated with mortality. Nevertheless, effect sizes should be compared with caution, given the differences in cohorts and analysis methods. Moreover, the clinical significance of these different findings (e.g., the extent to which each is modifiable, and the extent to which modifying each factor might also alter LE) remains an important area in need of further study.

The connection between brain age and mortality established herein makes BAI a potentially attractive tool to support the search for ways to enhance brain health and well-being of the aging population. Our hypothesis for what pathologies cause an “older brain” extends from potential risk factors not analyzed in this study, including substance use, neurological or psychiatric disease, metabolic dysfunction, and environmental insults (i.e., socioeconomic status), to lifestyle habits including poor nutrition, medication use, and sedentary behavior. Conversely, our data do not show whether “older sleep” is a cause of poor brain health, versus merely a readout. There are plausible mechanisms by which an “older” brain may be hostile to the younger body. The older brain is associated with greater sleep fragmentation, which is correlated with metabolic dysregulation (Reutrakul and Van Cauter, 2018). Blood pressure nondipping occurs in states of fragmented sleep (Sieminski et al., 2017; Sieminski and Partinen, 2016). Increased sympathetic activity is associated with lighter sleep and over a lifetime can induce endothelial dysfunction and HTN from “excessively aged sleep” alone (Saxena et al., 2018).

Our results have important limitations. First, our current BAI algorithm is trained on a large data set of raw sleep EEG data, but it is constrained by its linear structure. More advanced methods might provide a biomarker that correlates even better with brain health. For example, while the presented evidence suggests that BAI is meaningful at the population level, the sources and relative contributions to variation at the individual level have yet to be defined (i.e., night-to-night variation vs. biological effects connected to brain health). Second, we cannot exclude the possibility of unmeasured confounding, which is likely present given the nonrandomized nature of the SHHS data. Nevertheless, the large sample size (n = 4877), long duration of follow-up (median 11.9 years), and availability of a relatively large number of relevant variables (i.e., diabetes, HTN, CVD, smoking, female sex, and black race) are strengths of our work. Finally, while many measures in the SHHS are self-reported, the data set nonetheless has high validity and reliability, decreasing the risk of bias (Quan et al., 1997).

5. Conclusions

Our study shows that the BAI, a sleep EEG-based biomarker, is an independent and significant predictor of LE. This work further validates BAI as a biomarker of brain health.

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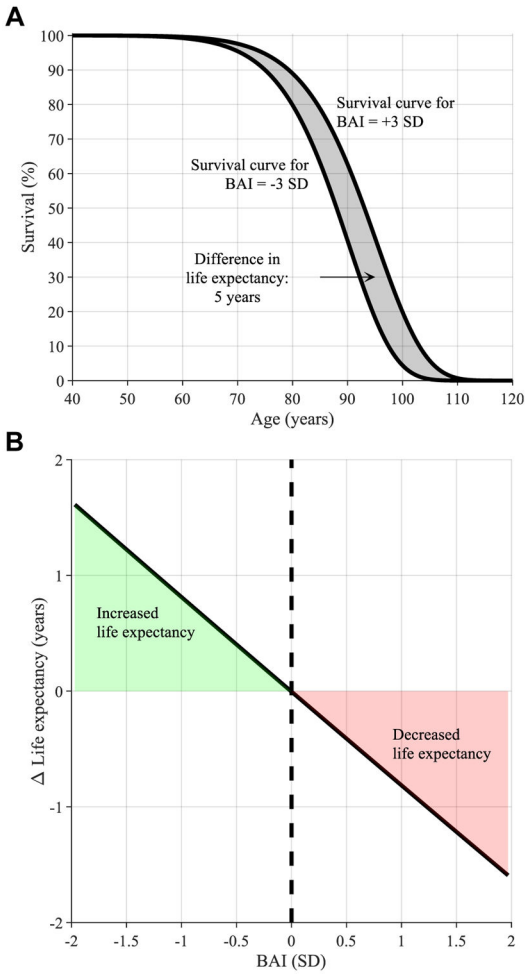

Fig. 1.

(A). Survival curves (multivariate Weibull regression models) for a participant with BAI = +36.8 versus BAI = −36.8 years (+/− 3 standard deviations of BAI). The area under each survival curve is the life expectancy. The difference in area under the 2 curves is 5.1 years. (B). The change in life expectancy as a function of BAI, relative to a baseline BAI = 0. For an increase in BAI of one standard deviation (12.3 years), life expectancy decreases by 0.85 years. Similarly, for participants with younger-appearing sleeping brain activity (negative BAI), life expectancy is increased. Abbreviations: BAI, brain age index.

Table 1

Baseline demographic characteristics, mortality, and follow-up time in a subset population from the Sleep Heart Health Study, 1995–1998 (N = 4877)

Category	
Age, y +SD	61.2 ± 10.0
Female % (n)	53.2 (2597)
Black race, % (n)	8.0 (389)
Marital status (married) %, (n)	78.4 (3824)
Body mass index, kg/m^2, median [IQR]	27.6 [6.1]
Diabetes, % (n)	6.5 (303)
Hypertension % (n)	40.0 (1953)
Cardiovascular disease % (n)	19.6 (818)
Smoking status, current % (n)	10.0 (486)
Education level <10 y, % (n)	6.2 (301)
Apnea-hypopnea index (#/h), median [IQR]	12.8 [16.7]
Brain age index (BAI), y, median [SD]	0.8 [15.2]
Deaths % (n)	17.2 (839)
Follow-up time, y, median [IQR]	11.9 [2.0]
Sleep EEG-predicted brain age, y, median [IQR]	62.0 ± 18.6

Table 2

Univariate and multivariate Cox proportional hazards analyses for all-cause mortality in a subset population from the Sleep Heart Health Study followed for a median of approximately 12 y (N = 4877)

Outcome predictor	Unadjusted hazard ratio[b] HR	*p* Value	Adjusted hazard ratio[c] aHR [95% CI]	Adjusted *p* value
Diabetes	1.94	<0.001	1.52 [1.23, 1.85]	<0.001[a]
Female	0.67	<0.001	0.68 [0.59, 0.80]	0.002[a]
Cardiovascular disease	2.11	<0.001	1.83 [1.57, 2.14]	<0.001[a]
Current smoker	2.06	<0.001	2.29 [1.82, 2.98]	<0.001[a]
Hypertension	1.32	<0.001	1.20 [1.04, 1.40]	0.023[a]
Brain age index, y	1.12	0.002	1.12 [1.03, 1.21]	0.002[a]
Body mass index, kg/m^2	1.10	0.014	1.08 [0.99, 1.19]	0.001[a]
Apnea-hypopnea index	1.09	0.009	0.98 [0.90, 1.07]	0.119
Married	0.89	0.150	–	–
Education <10 y	0.91	0.436	–	–
Black race	1.08	0.487	–	–

Data are unadjusted hazard ratio HR (95% CI) and adjusted hazard ratio aHR (95% CI).

Key: y, years; HR, hazard ratio; CI, confidence interval.

[a] Statistically significant ($p < 0.05$).

[b] Univariate analyses.

[c] Adjusted for brain age index, sex, race, marital status, body mass index, diabetes, hypertension, cardiovascular disease, smoking status, and education level.