Brain Age Index Predicts Mortality

Luis Paixao [1, 2], Haoqi Sun [1, 2], Robert J. Thomas [2, 3], Sydney S. Cash [1, 2], M. Brandon Westover [1, 2]

[1] Department of Neurology, Massachusetts General Hospital, Boston, MA [2] Harvard Medical School, Boston, MA [3] Pulmonary, Critical Care & Sleep, Department of Medicine, BIDMC, Boston, MA

INTRODUCTION

- **Healthy aging** constitutes one of the most pressing global issues.
- **Aging markers** are urgently needed to understand aging mechanisms, to identify individuals at increased risk of age-related cognitive impairment and death, and to develop tools to improve brain health and extend healthspan.
- **"Brain age"** represents the age predicted by comparing brain measurements from an individual with age norms.
- **Critical unmeet need** to develop a brain age biomarker that is low-cost, patient-friendly, and broadly-accessible.

AIMS

- **Introduce and evaluate the clinical utility of an electroencephalogram (EEG)-based biomarker of brain age.**
- **Hypothesis**: **Brain age index** (BAI = BA, EEG-Based Brain Age – CA, Chronological Age) independently predicts mortality.

METHODS

- **Preliminary work**: developed a machine learning model that can predict brain age based on 510 features per sleep EEG. Model based on 3,100 subjects (2,100 in training set + 1,000 in testing set) who underwent overnight sleep EEG.
- **In this retrospective study**, we used the above machine learning model to determine the brain age index of ≥ 39 year old adults belonging to a subset of patients from the Sleep Heart Health Study (N=1,736) with complete sleep EEGs.
- **Outcome:** time to event and covariates-adjusted estimate of mortality during 15 years follow-up.
- **Statistical Analysis:** Kaplan-Meier curves & Cox proportional hazards survival analysis regression models.

RESULTS

Table 1. Baseline characteristics, mortality, and follow-up times (N=1,736)

Age, years	60.0 ± 9.0
Female, %	55.5
Black race, %	4.8
Body mass index, kg/m²	28.2 ± 4.8
Diabetes, %	4.4
Hypertension, %	35.2
Smoking status (current), %	9.0
Smoking status (never), %	48.6
> 10 years of education, %	94.0
Deaths, n (%)	137 (8)
Follow up time, y, median (IQR)	11.9 (1.4)
EEG-predicted brain age, years	60.0 ± 11.4

Above values reported are mean ± SD unless otherwise specified

Table 2. Multivariable cox proportional hazards regression analysis for all-cause mortality (N=1,736)

	Adjusted HR	95% CI	Adjusted P-value
Brain Age Index, y	1.033	1.006-1.060	.017
Female	0.553	0.379-0.806	.002
Black race	0.584	0.264- 1.292	.184
Diabetes	1.665	0.971-2.853	.064
Hypertension	1.259	0.880-1.803	.208
Body mass index, kg/m2	1.028	0.985-1.073	.200
Current smoker	2.691	1.626-4.451	<.001
Education level (>10 y)	1.003	0.557-1.804	.993

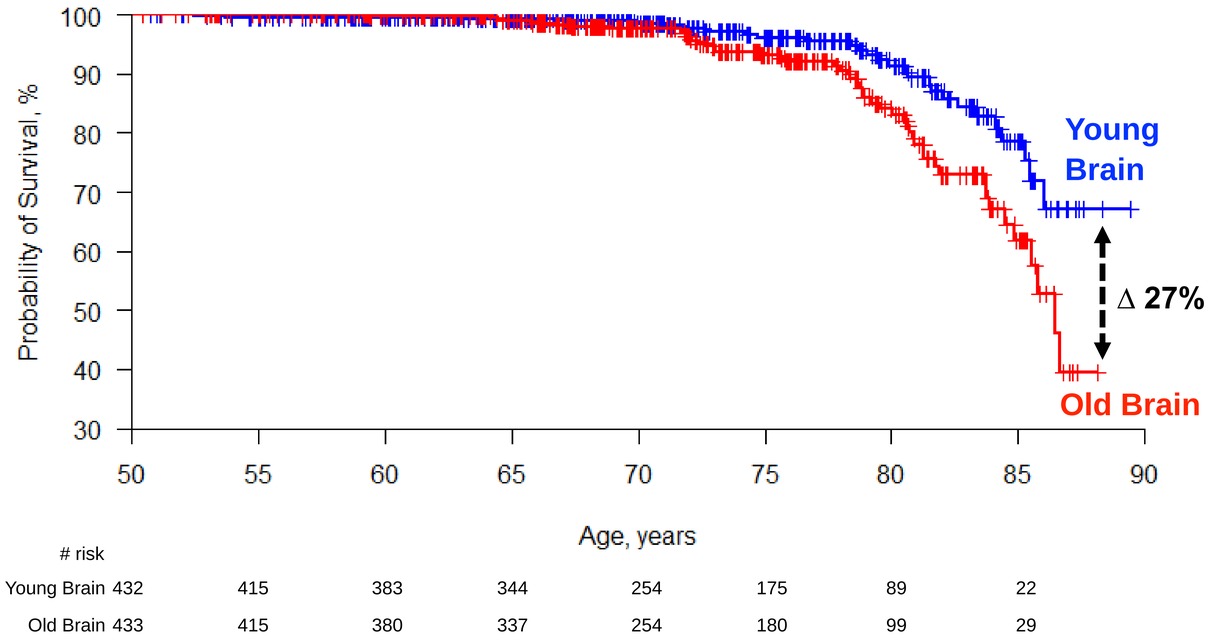

Figure 1. Kaplan-Meier survival curves according to brain age index (BAI). The two lines represent a quartile split based on BAI score. Old brain (red line) represents highest quartile BAI whereas young brain (blue line) represents lowest quartile BAI. Log-rank chi-square statistic = 8.1; P < .01.

.

- **Kaplan-Meier curve showed significantly higher mortality among patients with an old brain** compared to a young brain (P < .01). Patients with an old brain relative to patients with a young brain had a 27% relative increase in the risk of death at 88 years old.
- Having a **higher brain age index score** (i.e. brain age older than one's chronological age) **was significantly associated with increased mortality risk**, even after adjusting for sex, race, smoking status, body mass index, diabetes, hypertension, and education level (adjusted hazard ratio, 1.033; 95% confidence interval, 1.006-1.060; p-value < .05).
- **Each extra year of brain age index** (i.e. having an EEG-based brain age – chronological age of +1) **yielded a 3.3% relative increase in the risk of death.**

CONCLUSIONS

- Brain age index (BAI), an EEG-based brain age biomarker, is an independent predictor of mortality, with higher BAI (i.e. an older brain) being associated with increased mortality.
- This helps to validate BAI as a novel, non-invasive, clinically-relevant biomarker of a subject's brain health that may hold important insights into the individual aging process and provide more accurate prediction of functional capability and life span than chronological age alone.

ACKNOWLEDGMENTS

- NIH-NINDS (1K23NS090900)
- MBW is a Breakthroughs in Gerontology Grant recipient, supported by the Glenn Foundation for Medical Research and the American Federation for Aging Research

REFERENCES

[1] Sun FW et al. Youthful Brains in Older Adults: Preserved Neuroanatomy in the Default Mode and Salience Networks Contributes to Youthful Memory in Superaging. J. Neurosci. 2016; 36(37):9659–9668.
[2] Purdon PL et al. The Ageing Brain: Age-dependent changes in the electroencephalogram during propofol and sevoflurane general anaesthesia. Br. J. Anaesth. 2015; 115:i46–i57.

CONTACT

- LP: ldecarvalhopaixao@mgh.harvard.edu
- HS: hsun8@mgh.harvard.edu
- MBW: mwestover@mgh.harvard.edu