Higher Neurovascular Signal Entropy is Associated with Accelerated Brain Ageing

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The Irish Longitudinal Study on Ageing

BACKGROUND

Increased complexity in neurocardiovascular signals has been shown to be associated with poorer cognitive performance and physical frailty status.[1,2] Ageing is a heterogeneous process across individuals, and often chronological age is not the most accurate marker of an individual's health status.[3] In neuroimaging, machine learning can be used to quantify the relationship between structural MRI data and chronological age, to estimate an individual's 'brain age', which, when subtracted from chronological age, provides a brain predicted-age difference score (BrainPAD).[4] This measure reflects the biological ageing of the brain.

References

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AIM

To evaluate how the complexity of frontal-lobe oxygenation (tissue saturation index (TSI)) data may be associated with BrainPAD, in a large cohort of community-dwelling older adults.

METHODS

Neurovascular Measurements

TSI was measured non-invasively in the left frontal lobe (approximately the FP1 position of the 10 to 20 electrode system (3 cm lateral and 3.5 cm superior to the nasion)) using near-infrared spectroscopy (NIRS; *Portalite*; Artinis Medical Systems, Zetten, Netherlands). TSI data were acquired continuously during five minutes of supine rest and the last minute (down sampled to 5Hz) was utilized in this analysis.

Sample Entropy (SampEn)

Complexity of the signals was quantified using sample entropy (SampEn).[5] SampEn was calculated as:

$$\mathrm{SampEn}(m,r,N) := \log\left(\sum_{i=1}^{N-m} C_i^m(r)\right) - \log\left(\sum_{i=1}^{N-m-1} C_i^{m+1}(r)\right)$$

In this study, *m* (the embedding dimension; the length of the data segment being compared) was set to 2 and *r* (the similarity criterion) to 0.15. The number of data points used (*N*) was 300 (1min at 5Hz).

BrainPAD

To calculate BrainPAD, machine learning (Elastic Net model with 10-fold cross-validation, repeated 25 times) was applied to grey matter density values from 54,869 voxels in 1359 T1-weighted MRI scans drawn from various open-access repositories.[4] This model was then applied to T1 MRI data (3T *Achieva*, Philips Medical Systems, Netherlands) from wave 3 of The Irish Longitudinal Study on Ageing (TILDA).

Statistical Analysis

Multivariable linear regression modelling was performed in STATA 15.1 (StataCorp, USA), controlling for chronological age, sex, education, antihypertensive medications, diabetes, cardiovascular conditions, smoking, alcohol, depression, BMI, physical activity (IPAQ), and seated blood pressure.

SAMPLE

In total data from 397 individuals (age: 67.9±7.7 years; 53.7% female), enrolled in TILDA, were included in this study. TILDA is a population-based longitudinal study of ageing. Data from wave 3 (2014/2015) of this study was utilised in the present work. Ethical approval was obtained from the Faculty of Health Sciences Research Ethics Committee at Trinity College Dublin, Ireland. All participants provided written informed consent.

RESULTS

- **In total, 397 individuals were included in this study (age: 67.9±7.7 years; 53.7% female)**
- **Demographics and full regression results are presented in Table 1**
- **Mean BrainPAD score was -7.2 ± 7.3 years**
- **Mean SampEn was 0.26 ± 0.11**
- **An increase in TSI SampEn of 0.1 was associated with an increase in BrainPAD of 0.9 years (*P*=0.007, 95%CI: 0.3 to 1.6), as illustrated in Figure 1**
- **Similar results were found with and without the inclusion of chronological age in the models**

Table 1: Demographic characteristics of the study cohort and regression results from statistical analysis

	Demographics	Regression Results	
	(N=397)	β (95% CI)	*P* Value
BrainPAD [years]	-7.2 ± 7.3 years		
TSI SampEn	0.26 ± 0.11	9.1 (2.6 to 15.6)	**0.007**
Age	67.9 ± 7.7 years	-0.11 (-0.23 to 0.003)	0.055
Sex			
Male	46.3% (n=184)	*Reference*	
Female	53.7% (n=213)	3.1 (1.6 to 4.5)	**≤0.001**
Education			
Primary/None	19.7% (n=78)	*Reference*	
Secondary	35.0% (n=139)	-0.67 (-2.7 to 1.5)	0.525
Third/Higher	45.3% (n=180)	-0.63 (-2.6 to 1.3)	0.521
Antihypertensive Meds			
No	59.7% (n=237)	*Reference*	
Yes	40.3% (n=160)	0.27 (-1.3 to 1.9)	0.740
Diabetes			
No	91.4% (n=363)	*Reference*	
Yes	8.6% (n=34)	3.5 (0.46 to 6.6)	**0.024**
No. CV Conditions			
0	52.9% (n=210)	*Reference*	
1	40.3% (n=160)	0.24 (-1.3 to 1.8)	0.758
2+	6.8% (n=27)	-2.0 (-4.9 to 0.84)	0.165
Smoker			
Never	51.6% (n=205)	*Reference*	
Past	41.6% (n=165)	0.49 (-1.0 to 2.0)	0.518
Current	6.8% (n=27)	1.3 (-1.3 to 2.7)	0.318
CAGE Alcohol Scale			
CAGE < 2	80.1% (n=318)	*Reference*	
CAGE ≥ 2	7.8% (n=31)	2.5 (0.14 to 4.9)	**0.038**
No response	12.1% (n=48)	0.7 (-1.3 to 2.7)	0.486
Depression (CESD)			
Non-depressed	90.7% (360)	*Reference*	
Depressed (≥9)	9.3% (n=37)	1.9 (-0.7 to 4.5)	0.154
BMI	27.7 ± 4.3 kg/m^2	-0.03 (-0.2 to 0.1)	0.729
Physical Activity			
Low	32.5% (n=129)	*Reference*	
Moderate	39.0% (n=155)	-1.9 (-3.6 to -0.2)	**0.029**
High	23.9% (n=95)	-0.2 (-2.0 to 1.7)	0.860
No data	4.6% (n=18)	-	-
Seated sBP	133 ± 18 mmHg	0.03 (-0.02 to 0.07)	0.237

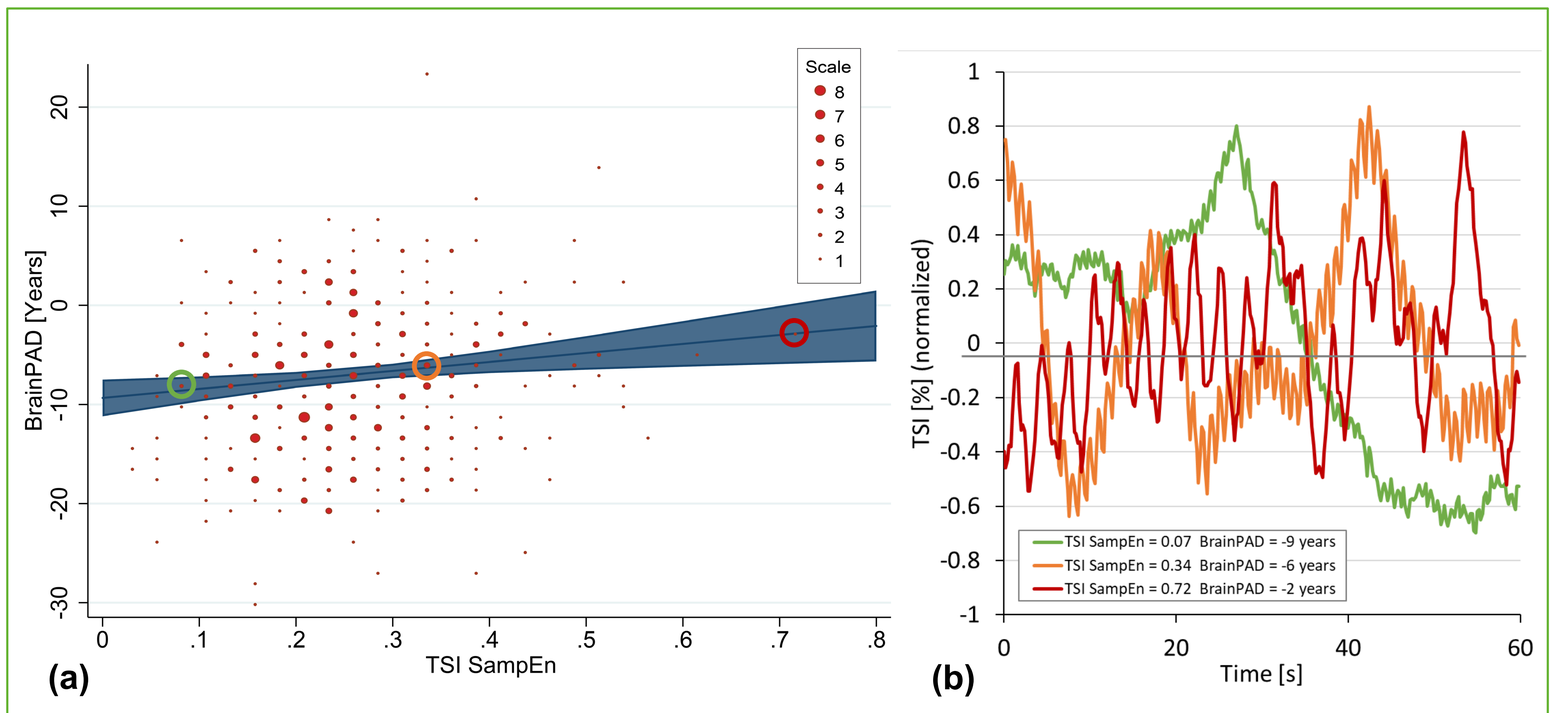

Figure 1: (a) Marginal plots for brain predicted-age difference score (BrainPAD) verses tissue saturation index (TSI) sample entropy (SampEn) measures. Scatter density plot of raw data points also shown. (b) Example plots of raw TSI data from three participants (highlighted in (a)) with high, medium, and low SampEn.

CONCLUSION

This study demonstrated significant associations between increased complexity in peripherally measured frontal lobe oxygenation levels and accelerated brain ageing.

RESOURCES

Calculate **SampEn** for your own data

Calculate **BrainPAD** for your own data

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