Gender-specific effects of health and lifestyle markers on individual BrainAGE

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***Abstract*—This study quantifies the effects of health and lifestyle markers on individual brain aging in dementia-free elderly subjects, revealed by a relevance vector regression approach. In males, markers of metabolic syndrome as well as alcohol abuse were significantly related to increased *BrainAGE* scores of up to 9 years. In females, markers of healthy liver and kidney functions and an adequate supply of nutrients were significantly related to decreased *BrainAGE* scores.**

Keywords: Aging; Alzheimer's disease; BrainAGE; Lifestyle; Magnetic resonance imaging; Voxel-based morphometry

I. Introduction

Early identification of neuroanatomical changes deviating from the normal age-related atrophy pattern has the potential to improve clinical outcomes in neuropsychiatric and neurodegenerative disorders through early treatment or prophylaxis [3]. Especially Alzheimer's disease (AD), the most common form of dementia, is widely linked to pathological brain aging [4-9].

Though neuroanatomical aging is characterized by a widespread but rather specific pattern of alterations [10, 11], multiple factors affect and modify those individual trajectories. Several markers of poor health and an inappropriate lifestyle were shown to be associated with the risk of cognitive decline, greater brain atrophy, and even dementia, including the metabolic syndrome, hypertension, diabetes, nicotine and alcohol abuse, elevated serum total homocysteine (tHcy), and lower levels of vitamin B12 [12-14]. Furthermore, combination of risk factors was found to further boost the risk [15]. In contrast, a healthy and well-balanced lifestyle, including physical activity, normal body weight, smoking cessation, intake of unsaturated fatty acids, and moderate alcohol intake, was shown to lower the risk of cognitive decline and dementia [16-18].

Assuming AD to be preceded by precocious / accelerated brain aging [6, 19], a straightforward and efficient solution is to model healthy brain aging on the one hand, and to identify pathological brain atrophy on the other. The recently presented *BrainAGE* approach takes into account the widespread, sequential brain tissue loss associated with aging. Based on single time-point structural magnetic resonance images (MRI), the complex, multidimensional aging patterns across the whole brain are aggregated to one single value, i.e. the estimated brain age (Fig. 1A). Consequently, although using only one MRI scan per subject, the deviation in brain atrophy from normal brain aging can be directly quantified (Fig. 1B).

II. Methods

A. Data source

We utilized data obtained from the ADNI database (www.loni.ucla.edu/ADNI), including all healthy subjects for whom MRI data as well as a battery of physiological and clinical parameters at baseline were available (n=211). The male sample consisted of 107 healthy subjects, aged 60–88 years, with a mean age of 75.7 years (SD=5.3 years). The female sample contained 104 healthy subjects, aged 62–90 years, with a mean age of 76.1 years (SD=4.8 years).

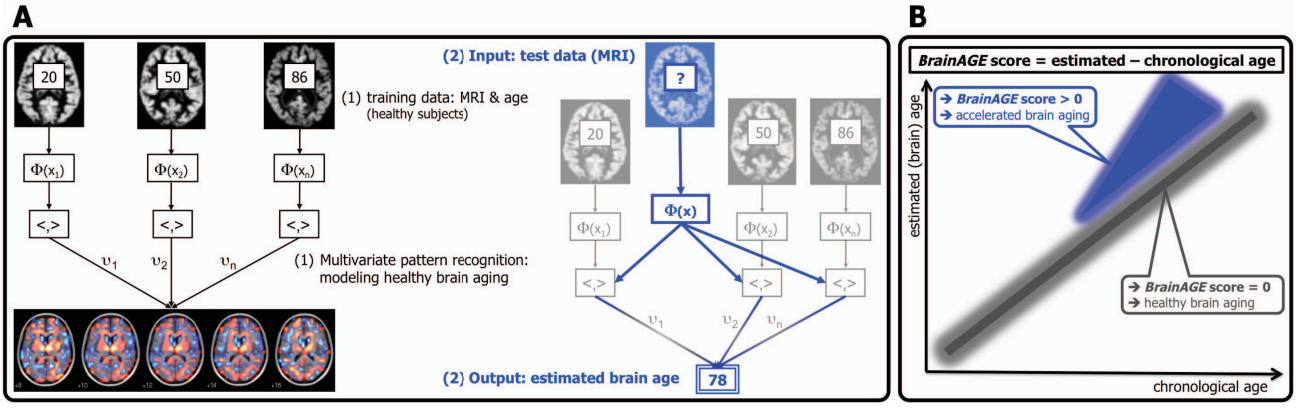

Figure 1. Depiction of the *BrainAGE* concept. [Image modified from [1], with permission from Hogrefe Publishing, Bern.]
(A) The model of healthy brain aging is trained with the chronological age and preprocessed structural MRI data of a training sample (left, with an exemplary illustration of the most important voxel locations that were used by the age regression model). Subsequently, the individual brain ages of previously unseen test subjects are estimated, based on their MRI data (blue; picture modified from [2]). *(B)* The difference between the estimated and chronological age results in the *BrainAGE* score. Consequently, positive *BrainAGE* scores indicate accelerated brain aging (blue area).

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B. Preprocessing of MRI data and data reduction

As described in [1, 20], preprocessing of the T1-weighted MR images was done using the SPM8 package (http://www.fil.ion.ucl.ac.uk/spm/) and the VBM8 toolbox (http://dbm.neuro.uni-jena.de). The images were processed with affine registration and smoothed with 8-mm full-width-at-half-maximum (FWHM) smoothing kernels. Spatial resolution was set to 8 mm. Data reduction was performed by applying principal component analysis (PCA), utilizing the "Matlab Toolbox for Dimensionality Reduction" (http://ict.ewi.tudelft.nl/~lvandermaaten/Home.html).

C. BrainAGE framework

The age estimation model [20] was trained with preprocessed grey matter (GM) images of healthy subjects, aged 20–86 years, from the IXI cohort (www.brain-development.org) by applying a high-dimensional learning machine, namely relevance vector regression (RVR) [2, 21] with a linear kernel. It was separately trained on male and female subjects, utilizing the freely available toolbox "The Spider" (www.kyb.mpg.de/bs/people/spider/main.html).

Then, the individual brain ages of the test sample from the ADNI database were estimated. The difference between the estimated and the true age resulted in the brain age gap estimation (*BrainAGE*) score. Consequently, positive *BrainAGE* scores indicate accelerated brain aging.

D. Statistical analysis

The relationships between *BrainAGE* score and laboratory data was analyzed with the help of the multivariate linear regression model. To quantify the effects of the physiological and clinical chemistry parameters under consideration on the *BrainAGE* scores, the 1st quartile (lowest 25% of values) vs. 4th quartile (highest 25% of values) of each parameter was compared via t-tests. Using MATLAB, statistical testing was performed separately on males and females to account for gender-specific patterns.

TABLE I. COMPARISON OF *BRAINAGE* SCORES BETWEEN 1ST QUARTILE VS. 4TH QUARTILE GROUPS WITHIN THE MALE SAMPLE

Male Sample (n=107)	Mean *BrainAGE* score (years)		
	1st	4th	p-value
Albumin (g/dl)	1.00	-0.02	n.s.
ALT (U/l)	1.23	0.48	n.s.
AST (U/l)	1.60	-0.84	n.s.
Total Bilirubin (mg/dl)	0.83	1.62	n.s.
SBP (mmHg)	-2.55	1.29	n.s.
DBP (mmHg)	**-3.51**	**3.56**	**0.0028**
BMI (kg/m²)	**-3.44**	**5.39**	**0.0001**
Cholesterol (mg/dl)	-0.92	1.80	n.s.
Creatinine (mg/dl)	0.83	1.52	n.s.
GGT (U/l)	**-2.13**	**3.58**	**0.0197**
Glucose (mg/dl)	-0.87	1.62	n.s.
MCV (fL)	-2.42	-1.71	n.s.
TSH (µIU/mL)	1.39	-2.24	n.s.
tHcy (µmol/l)	-0.83	0.55	n.s.
Triglycerides (mg/dl)	-0.40	-0.20	n.s.
Uric Acid (mg/dl)	**-4.34**	**1.87**	**0.0154**
Vitamin B12 (ng/l)	0.18	-0.51	n.s.

Abbreviations: ALT, alanin-aminotransferase; AST, aspartat-aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; GGT, γ-glutamyltransferase; MCV, mean erythrocyte cell volume; SBP, systolic blood pressure; TSH, thyroid stimulating hormone; tHcy, total homocysteine; n.s. = not significant

III. RESULTS

The *BrainAGE* scores did not differ between males (0.0 ± 8.4 years) and females (0.0 ± 7.5 years). Men and women did not differ with respect to albumin, aspartat-aminotransferase (AST), systolic (SBP) and diastolic blood pressure (DBP), body mass index (BMI), γ-glutamyltransferase (GGT), glucose, mean erythrocyte cell volume (MCV), thyroid stimulating hormone (TSH), and triglycerides. Men showed significantly higher parameter levels than women in alanin-aminotransferase (ALT), total bilirubin, creatinine, tHcy, and uric acid, whereas women show significantly higher levels than men in cholesterol and vitamin B12.

For men, when combining all measured physiological and clinical chemistry parameters by applying a multivariate regression model, 39% of variance within the *BrainAGE* score was attributed to the physiological and clinical chemistry parameters under consideration (R^2=0.39, p<0.001). When quantifying the effects of health and lifestyle markers on *BrainAGE*, several significant differences were observed between the lowest (1st) vs. the highest (4th) quartile group of each physiological and clinical chemistry parameter (Table 1): for BMI, the absolute difference of the mean *BrainAGE* scores was 8.8 years; for DBP, the result was 7.1 years; GGT, 5.7 years; and for uric acid, 6.2 years. Combining these four parameters, the effects of "healthy" vs. "poor" lifestyle markers on *BrainAGE* were even accumulating, resulting in mean *BrainAGE* scores of -8.09 vs. 6.79 years, respectively (p=0.015; Figure 2). Taken together, the results indicate a strong link between physiological and clinical health and lifestyle markers and acceleration in brain aging in men.

For women, the multivariate regression model combining all measured parameters was capable of explaining 32% of *BrainAGE* variance (R^2=0.32, p<0.01). Comparing the

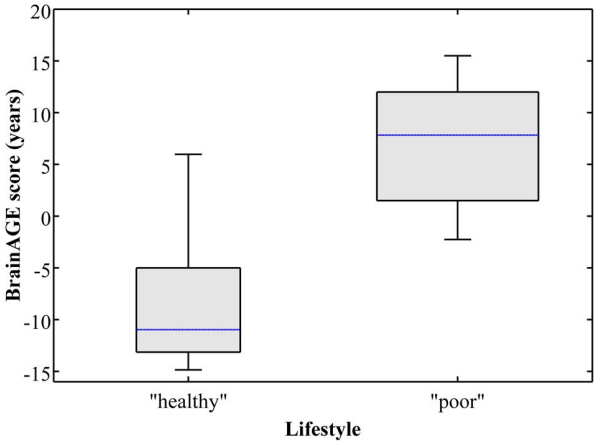

Figure 2. Box plots with *BrainAGE* scores of male subjects with markers of „healthy" (values equal to or below the medians of BMI, DBP, GGT, and uric acid; n=9) vs. „poor" lifestyle (values equal to or above the medians of BMI, DBP, GGT, and uric acid; n=14; p<0.05).

lowest quartile with the highest quartile of each physiological and clinical chemistry parameter in female individuals, a different pattern of significant differences was observed (Table 2). For GGT, the absolute difference of the mean *BrainAGE* scores was 6.1 years; for ALT, it resulted in 5.2 years; for AST, 4.2 years; and for uric acid, 4.9 years. For MCV and B12, higher levels were associated to negative *BrainAGE* scores (MCV: 5.7 years; B12: 4.9 years). Combining these parameters, the effects of "healthy" vs. "risky" lifestyle markers on brain aging observed in women were also accumulating, resulting in mean *BrainAGE* scores of -3.47 vs. 7.42 years, respectively (p=0.006; Figure 3). Again, these results indicate a significant link between physiological and clinical health markers and pathological brain aging in women.

IV. Discussion

The scope of this study was the implementation of a novel MRI-based biomarker based on the recently presented *BrainAGE* framework [20] to quantify the effect of several common physiological and clinical health and lifestyle markers on individual brain aging. Using structural MRI data, the fully automated age estimation model aggregates the complex, multidimensional aging patterns across the whole brain to one single value (i.e. the *BrainAGE* score) and finally identifies pathological brain aging on an individual level. This method already showed the advantage of accurately and reliably estimating the age of the brain with minimal preprocessing and parameter optimization [1, 20], using a single anatomical scan. Regarding the relevance within the clinical context, higher *BrainAGE* scores were recently demonstrated to be closely related to measures of clinical disease severity in AD patients, as well as prospective worsening of cognitive functioning in subjects who converted to AD [1].

The present study with healthy elderly subjects provides evidence that a number of environmental and in particular nutrition- or lifestyle-related factors and health parameters have a significant effect on brain aging, hence likely affecting the onset of dementia in healthy humans. The set of serum markers under consideration could explain 39% of variance in *BrainAGE* in men and 32% in women.

In males, components of the metabolic syndrome, i.e., elevated values in BMI, DBP, and uric acid, as well as markers of alcohol abuse, i.e., elevated GGT and uric acid, were significantly associated with an increased *BrainAGE* score of nearly 9 years. Furthermore, when combining the observed risk parameters, the effects on brain aging were even accumulating. This is consistent with previous studies that associated lower total brain volume as well as an increased risk of later dementia with a higher BMI and [12] the metabolic syndrome [13].

In females a different pattern was found. In particular, markers of liver and kidney functions, i.e., GGT, ALT, AST, and uric acid, were significantly related to *BrainAGE* scores. Furthermore, female subjects with a sufficient supply of vitamin B12 and possibly iron, as indicated by low MCV values, showed lower *BrainAGE* scores, suggesting a protective effect of these nutrients on brain aging. As already observed in the male sample, the effects on accelerated brain aging were accumulating, when combining the female-specific risk parameters. These results are consistent with recent studies that also found gender-specific relationships between lifestyle-related health markers and GM atrophy [22] or even risk for AD [12].

Because this study was cross-sectional, it remains unclear whether health and lifestyle factors represent cause or consequence of the associations found. Nevertheless, it strongly supports previously published results relating overall health with brain structure. Further research is needed

TABLE II. Comparison of *BrainAGE* scores between 1st Quartile vs. 4th Quartile Groups within the Female Sample

Female Sample (n=104)	Mean *BrainAGE* score		
	1st	4th	p-value
Albumin (g/dl)	0.55	-1.21	n.s.
ALT (U/l)	**-2.88**	**2.29**	**0.0085**
AST (U/l)	**-1.67**	**2.57**	**0.0426**
Total Bilirubin (mg/dl)	-2.54	1.26	n.s.
SBP (mmHg)	-1.31	0.35	n.s.
DBP (mmHg)	-1.50	2.20	n.s.
BMI (kg/m^2)	-0.77	2.08	n.s.
Cholesterol (mg/dl)	1.71	0.26	n.s.
Creatinine (mg/dl)	-0.92	0.37	n.s.
GGT (U/l)	**-3.88**	**2.18**	**0.0056**
Glucose (mg/dl)	-0.45	1.81	n.s.
MCV (fL)	**2.67**	**-3.02**	**0.0074**
TSH (µIU/mL)	0.55	-0.92	n.s.
tHcy (µmol/l)	-1.41	1.04	n.s.
Triglycerides (mg/dl)	0.43	-0.71	n.s.
Uric Acid (mg/dl)	**-3.63**	**1.25**	**0.0188**
Vitamin B12 (ng/l)	**1.80**	**-3.07**	**0.0249**

Abbreviations: ALT, alanin-aminotransferase; AST, aspartat-aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; GGT, γ-glutamyltransferase; MCV, mean erythrocyte cell volume; SBP, systolic blood pressure; TSH, thyroid stimulating hormone; tHcy, total homocysteine; n.s. = not significant

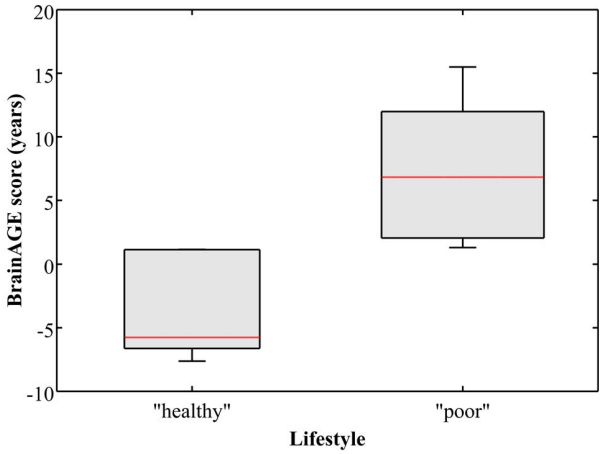

Figure 3. Box plots with *BrainAGE* scores of female subjects with markers of „healthy" (values equal to or below the medians of GGT, ALT, AST, uric acid, and values equal to or above the medians of MCV and B12; n=5) vs. „poor" lifestyle (values equal to or above the medians of GGT, ALT, AST, uric acid, and values equal to or below the medians of MCV and B12; n=6; p<0.01).

to quantify the gender-specific relation between individual brain aging and miscellaneous risk factors (i.e. genetic effects, cognitive development, personal health markers, and modifiable lifestyle factors) in larger samples. Furthermore, it should be explored how the duration of exposure to risk factors affects the risk of accelerated brain aging and dementia in higher age, and how changes in nutrition and lifestyle could decrease that risk.

Taken together, accelerated brain aging in healthy elderly subjects is related to several markers of impaired health or inappropriate lifestyle, whereas a protective effect on brain aging is observed for markers of good health, including a healthy lifestyle. Since accelerated brain atrophy was shown to precede cognitive impairment in AD [8, 9], this study suggests that a healthy lifestyle can prevent or at least slow down brain aging. However, gender-specific mechanisms should be taken care of in future studies.

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