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Differences between chronological and brain age are related to education and self-reported physical activity

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ABSTRACT

This study investigated the relationship between education and physical activity and the difference between a physiological prediction of age and chronological age (CA). Cortical and subcortical gray matter regional volumes were calculated from 331 healthy adults (range: 19–79 years). Multivariate analyses identified a covariance pattern of brain volumes best predicting CA (R^2 = 47%). Individual expression of this brain pattern served as a physiologic measure of brain age (BA). The difference between CA and BA was predicted by education and self-report measures of physical activity. Education and the daily number of flights of stairs climbed (FOSC) were the only 2 significant predictors of decreased BA. Effect sizes demonstrated that BA decreased by 0.95 years for each year of education and by 0.58 years for 1 additional FOSC daily. Effects of education and FOSC on regional brain volume were largely driven by temporal and subcortical volumes. These results demonstrate that higher levels of education and daily FOSC are related to larger brain volume than predicted by CA which supports the utility of regional gray matter volume as a biomarker of healthy brain aging.

1. Introduction

Gray matter volume decline is a highly visible aspect of the chronological aging process resulting from neural shrinkage and neuronal loss (Terry et al., 1987). These neural changes are detectable with magnetic resonance imaging (MRI) as volumetric declines in subcortical regions and throughout the cortical mantel (Dale et al., 1999; Sowell et al., 2004). Although volumetric decline is a common aspect of aging, the rate and degree of decline is highly variable across regions of the brain and between individuals (Raz et al., 2010). Furthermore, differences in lifetime exposures, such as years of education or physical activity, have been associated with differential amounts of gray matter volumetric decline with advancing age (Ahlskog et al., 2011; Erickson et al., 2010; Nithianantharajah and Hannan, 2009).

Interindividual variability in genetics and development along with positive and negative effects of lifetime exposure will result in different quantities of brain volume loss. Several investigators have suggested the concept of physiological brain age (BA) where the difference between chronological age (CA) and predicted age, based on brain measures, serves as a more informative marker of brain health than CA alone (Franke et al., 2010; Irimia et al., 2014). Regional brain volume measures would be useful for calculating a physiological BA measurement.

In this study, we used regional measures of gray matter volume from 331 healthy adults across the life span to derive a biomarker of BA. We defined the difference between CA and BA as a marker of whether the brain is younger or older than expected. We then investigated whether this difference was related to lifetime exposures including years of education and self-reported assessments of physical activity. Such relationships would suggest that certain lifetime exposures help maintain the brain in a more "youthful" state.

2. Materials and methods

2.1. Participants

Data from 331 healthy adults between the ages of 19 and 79 were included in this study. Participants were drawn from 3

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different studies from our laboratory using the same testing apparatus, procedures, and MRI. Table 1 lists the number of participants by decade, sex, and study. Participants were recruited using market-mailing procedures from within 10 miles of our northern Manhattan, NY, USA site to equalize the recruitment approaches across the life span. Participants who responded to the mailing were telephone screened to ensure that they met basic inclusion criteria (right handed, English speaking, no psychiatric or neurologic disorders, normal, or corrected-to-normal vision). All participants found eligible via the initial telephone screen were further screened in person with structured medical, neurologic, psychiatric, and neuropsychological evaluations to ensure that they had no neurologic or psychiatric disease or cognitive impairment. The screening procedure included a detailed interview that excluded individuals with a self-reported history of major or unstable medical illness, significant neurologic history (e.g., epilepsy, brain tumor, stroke), history of head trauma with loss of consciousness for >5 minutes or history of Axis I psychiatric disorder (Association, A. P, 1994). Individuals taking psychotropic medications were also excluded. Global cognitive functioning was assessed with the Mattis Dementia Rating Scale, on which a score of at least 133 was required for retention in the study (Mattis, 1988). This study was approved by the Internal Review Board of the College of Physicians and Surgeons of Columbia University, and written informed consent was obtained from all participants prior to study participation and after the purpose and risks of the study were explained. Participants were compensated for their participation in the study.

2.2. Measures of lifetime exposures

Lifetime exposures included measures of education and physical activity. Education was assessed as the number of years engaged in formal education. Physical activity was assessed using a questionnaire containing 9 questions about the amount of time spent doing various physical activities. These activities included walking/hiking, jogging, running, bicycling, aerobic exercise, lap swimming, tennis/squash/racquetball, low intensity exercise, and flights of stairs climbed daily (FOSC). The FOSC daily was coded as follows: none, 1–2, 3–4, 5–9, 10–14, and >15. These values were coded as 0, 1.5, 3.5, 7, 12, and 16. The other questions referred to the amount of time spent within 1 week and were coded as follows: none, 1–19 minutes, 20–50 minutes, 1 hour, 1.5 hours, 2–3 hours, 4–6 hours, and >7 hours. This questionnaire is similar to that used in other assessments of physical activity (Chao et al., 2004; Thacker et al., 2008). For all physical activities, these measures were converted to metabolic equivalent of task (MET) (Ainsworth et al., 2000; Bassett et al., 1997) and a total MET score was calculated.

2.3. Image acquisition procedure

MRI images were acquired in a 3.0T Philips Achieva Magnet using a standard quadrature head coil. A T1-weighted scout image was acquired to determine the participant's position. One hundred sixty-five contiguous 1-mm coronal T1-weighted images of the whole brain were acquired for each participant with an Magnetization Prepared Rapid Acquisition Gradient Echo sequence using the following parameters: TR 6.5 ms, TE 3 ms; flip angle 8°, acquisition matrix 256 × 256, and 240 mm field of view. A neuroradiologist reviewed the anatomic scans to identify any potentially clinically significant findings.

Table 1
Sample sizes split by decade, sex, and study

Age group	Total N F/M	Study 1 N F/M	Study 2 N F/M	Study 2&3 N F/M	Study 3 N F/M
>30	43/21	9/4	10/5	10/3	14/9
30–39	32/19	3/1	2/1	4/1	23/16
40–49	14/19	0/0	0/0	0/0	14/19
50–59	20/23	0/0	1/0	0/1	19/22
60–69	46/45	7/9	16/10	15/19	8/7
70 and older	27/22	1/0	4/2	2/2	20/18
Total	182/149	20/14	33/18	31/26	98/91

2.4. FreeSurfer methods

Each participant's structural T1 scans were reconstructed using FreeSurfer (Fischl, 2012) (http://surfer.nmr.mgh.harvard.edu/). The accuracy of Freesurfer's subcortical segmentation and cortical parcellation (Fischl et al., 2002, 2004) has been reported to be comparable with manual labeling. Each participant's white and gray matter boundaries as well as gray matter and cerebrospinal fluid boundaries were visually inspected slice by slice by an experienced user, manual control points were added in the case of any visible discrepancy, and reconstruction was repeated until we reached satisfactory results within every participant. The subcortical structure borders were plotted by FreeView visualization tools and compared against the actual brain regions. In case of discrepancy, they were corrected manually. In total, this procedure quantified 84 regions, 16 subcortical and 68 cortical.

2.5. Scaled subprofile modeling

We used the scaled subprofile modeling (Moeller et al., 1987; Spetsieris and Eidelberg, 2010) approach to calculate physiological BA based on regional gray matter volumes from cortical and subcortical locations using the principal components analysis toolbox (http://groups.google.-com/group/gcva) (Habeck and Stern, 2007; Habeck et al., 2005). Briefly, the 84 gray matter volume regions of interest were subjected to a principal component analysis. This produced a series of principal component images, v_i, and their respective subject scaling factors (SSF_i), which are each individual's expression of that respective principal component. The number of components comprising approximately 95% of the variance of the structural data was retained. Predicted Age (pAge) was calculated by regressing the SSF's taken from this subset of principal components against CA controlling for total intracranial volume, study (which of the studies they were recruited for), and sex:

$$pAge = \beta_0 + SSF_1\beta_1 + SSF_2\beta_2 + SSF_3\beta_3 + \ldots + \beta_x TIV + \beta_y Study + \beta_z Sex + \varepsilon$$

Both sex and study were dummy-coded, with female and study 1 as the references. The weights from the SSF variables were used to combine the respective eigenimages, v_i, to produce an age-related brain covariance pattern. This was then projected back into the original data to calculate the expression of this pattern for each participant. This value served as the BA measure. The stability of the regions within the resultant pattern was assessed using 1000 bootstrap resamples and tested with bias-corrected, accelerated confidence intervals.

For each individual, chronological age and brain age (CA-BA) indicated whether their BA was older or younger than their CA. Positive values indicate their BA was younger than their CA would predict, whereas a negative value indicates the BA was older than their CA. We then tested whether the measures of education and physical activity were related to this difference.

Similar to assessing regional contributions to the BA map, regional contributions to the CA-BA relationship with education