NeuroImage 134 (2016) 508–513

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Estimating brain age using high-resolution pattern recognition: Younger brains in long-term meditation practitioners

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ARTICLE INFO

Article history:
Received 9 October 2015
Revised 24 March 2016
Accepted 4 April 2016
Available online 11 April 2016

Keywords:
Aging
Brain
Gray matter
Meditation
Mindfulness
MRI

ABSTRACT

Normal aging is known to be accompanied by loss of brain substance. The present study was designed to examine whether the practice of meditation is associated with a reduced brain age. Specific focus was directed at age fifty and beyond, as mid-life is a time when aging processes are known to become more prominent. We applied a recently developed machine learning algorithm trained to identify anatomical correlates of age in the brain translating those into one single score: the BrainAGE index (in years). Using this validated approach based on high-dimensional pattern recognition, we re-analyzed a large sample of 50 long-term meditators and 50 control subjects estimating and comparing their brain ages. We observed that, at age fifty, brains of meditators were estimated to be 7.5 years younger than those of controls. In addition, we examined if the brain age estimates change with increasing age. While brain age estimates varied only little in controls, significant changes were detected in meditators: for every additional year over fifty, meditators' brains were estimated to be an additional 1 month and 22 days younger than their chronological age. Altogether, these findings seem to suggest that meditation is beneficial for brain preservation, effectively protecting against age-related atrophy with a consistently slower rate of brain aging throughout life.

1. Introduction

Meditation is attracting increasing interest in relation to health and wellbeing but its biological effects are not well understood. Although publication bias and methodological limitations are strong concerns in this emerging field, meditation has been shown to induce increases in brain tissue, even after relatively short periods of time, such as weeks or months (Fox et al., 2014). Complementing these short-term effects, brains of long-term meditators have been reported to be structurally different, with thicker, better connected, and more complex cortical sections, larger volumes, areas and dimensions of specific brain regions, as well as more local brain tissue than in brains of healthy controls (Luders et al., 2013a, 2015; Fox et al., 2014).

Since normal aging is known to be accompanied by loss of brain substance (Raz et al., 2010; Pfefferbaum et al., 2013), the question arises as to whether meditation may have a protective effect against age-related brain atrophy, where effects might accumulate over time and become evident especially in later years of life. The present study was designed to examine whether the practice of meditation manifests as a seemingly reduced brain age in meditators. Specific focus was directed at age fifty and beyond, as mid-life is a time when aging processes are known to become more salient as well as more functionally significant (Fraser et al., 2015).

We utilized a recently developed and validated high-dimensional pattern recognition approach which allows estimating, automatically and objectively, the age of any given brain based on a single T1-weighted brain image (Franke et al., 2010, 2012). Importantly, in people aged 19–86 years, this method has been shown to predict brain age with a mean error of as little as 4.98 years (Franke et al., 2010). Moreover, as also evaluated previously (Franke et al., 2010), the 95% confidence interval for the prediction of brain age is stable across the entire age range, even in older adults (e.g., age [mean $\pm$ SD] $= 20 \pm 11.6$ years vs. age [mean $\pm$ SD] $= 80 \pm 11.7$ years). This is especially relevant for our current sample, which is composed of 100 subjects (50 meditators/50 controls) ranging in age between 24 and 77 years.

The applied method effectively translates the complex, multidimensional aging pattern across the whole brain into one single score: the brain age (BrainAGE) index. The polarity of the index indicates if brains appear younger (negative score) or older (positive score) than their chronological age, and the numeric value specifies the magnitude of the difference (in years) between estimated age and chronological age. For example, estimating the brain ages of individuals with mild Alzheimer's disease in a previous study revealed a mean BrainAGE

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http://dx.doi.org/10.1016/j.neuroimage.2016.04.007
1053-8119/

index of +10 (Franke et al., 2010). These striking findings suggested significantly accelerated brain aging in Alzheimer's patients compared to normal aging in healthy controls (Franke et al., 2010). In contrast, for the current study focusing on the potential brain-preserving effect of long-term meditation, we predicted decelerated brain aging in meditators compared to normal aging in healthy controls. With respect to the *magnitude* of the effect, the deviation from 'normality' may range between a few days to several years.

2. Methods

2.1. Subjects

Note that this was a re-analysis of data overlapping, fully or in part, with those used in prior studies (Luders et al., 2009, 2011, 2012a,b, 2013a,b, 2014, 2015; Kurth et al., 2015a,b). The study sample included 50 meditation practitioners (28 men, 22 women) and 50 control subjects (28 men, 22 women). Meditators and controls were closely matched for chronological age, ranging between 24 and 77 years with a mean age of 51.4 years in both groups (SD = 12.8 years in meditators; SD = 11.8 years in controls). Meditators were recruited from various venues in the greater Los Angeles area and had close to twenty years of meditation experience on average (mean: 19.8 years; SD = 11.4 years; range: 4–46 years). A detailed overview with respect to each subject's individual practice has been previously provided (Luders et al., 2012a). Brain scans for the control subjects were obtained from the ICBM database of normal adults (http://www.loni.usc.edu/ICBM/Databases/). All subjects gave their informed consent in accordance with the policies and procedures of UCLA's Institutional Review Board.

2.2. Image Acquisition

All subjects were scanned at the same site, using the same scanner, and following the same scanning protocol. Specifically, magnetic resonance images were acquired on a 1.5 Tesla Siemens Sonata scanner (Erlangen, Germany) using an 8-channel head coil and a T1-weighted magnetization-prepared rapid acquisition gradient echo sequence with the following parameters: 1900 ms repetition time, 4.38 ms echo time, 15° flip angle, 160 contiguous sagittal slices, 256×256 mm^2 field-of-view, and $1 \times 1 \times 1$ mm^3 voxel size.

2.3. Data Preprocessing

All T1-weighted images were processed in Matlab (http://www.mathworks.com/products/matlab/) utilizing SPM8 (http://www.fil.ion.ucl.ac.uk/spm) and the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm.html), as recently described (Gaser et al., 2013). Briefly, images were bias corrected, spatially normalized, and classified into gray matter, white matter, and cerebrospinal fluid, all within the same generative model (Ashburner and Friston, 2005). The segmentation procedure was extended by accounting for partial volume effects (Tohka et al., 2004), applying adaptive maximum *a posteriori* estimations (Rajapakse et al., 1997), and using a hidden Markov Random Field model (Cuadra et al., 2005). The resulting gray matter partitions were then smoothed using an 8 mm full-width-at-half-maximum (FWHM) Gaussian kernel. Subsequently, image resolution was set to 8 mm, and further data reduction was performed via principal component analysis utilizing the "Matlab Toolbox for Dimensionality Reduction" (http://lvdmaaten.github.io/drtoolbox/), using the maximal number of principal components that equals to the size of the training sample, minus 1. Finally, using the gray matter data, the individual brain ages were predicted utilizing "Spider for Matlab" (http://www.kyb.mpg.de/bs/people/spider/main.html). For this purpose, we leveraged a recently developed BrainAGE estimation framework, as detailed below.

2.4. The BrainAGE Estimation Framework

The BrainAGE framework uses relevance vector regression (RVR), a machine learning approach based on pattern recognition. It has been successfully applied in a range of studies (Franke et al., 2010, 2012, 2013; Gaser et al., 2013; Franke et al., 2014, 2015) and was originally developed to model the healthy aging patterns of the brain, as detailed elsewhere (Franke et al., 2010, 2012). Briefly, the initial model has been trained using the preprocessed gray matter segments in a sample of more than 650 subjects, aged between 19 and 86 years. Information on the most important brain regions used by the RVR for estimating the individual brain ages has been provided in the accompanying methods paper (Franke et al., 2010). When applied to new brain scans, specifically the preprocessed gray matter segments extracted from T1-weighted images, the trained algorithm generates an estimated brain age. The concept of the brain age estimation is illustrated in Fig. 1. The difference between estimated age and true chronological age yields the so-called brain age gap estimate (BrainAGE). The absolute BrainAGE index is large if estimated brain age and chronological age are far apart; it is small if both values are close together. The BrainAGE index is negative if a brain is estimated younger than its chronological age (decelerated brain aging); it is positive if a brain is estimated older than its chronological age (accelerated brain aging). For example, if the algorithm computes a BrainAGE index of +5 for the brain of a 50-year-old, this individual shows the typical aging pattern of a 55-year-old. Conversely, if the algorithm computes a BrainAGE index of −5 for the brain of a 50-year-old, this individual shows the typical aging pattern of a 45-year-old. The BrainAGE methodology has been validated across datasets, age ranges and scanner types and was found to be robust and reliable (Franke et al., 2010).

2.5. Main Analyses

First, we computed the BrainAGE index (i.e., the difference between estimated brain age and chronological age) for all 100 subjects, as described above. Then, the association between BrainAGE, chronological age and meditation was investigated using multiple regression analysis, where chronological age was centered on 50 years. BrainAGE was entered as dependent variable and chronological age and group (meditators/controls) as predictors, while controlling for sex and handedness using a factorial design testing all two-way interactions. The model was then reduced to only include significant/influential components. The final model included the following predictors: age, group, sex, handedness, age × group, age × sex, age × handedness,

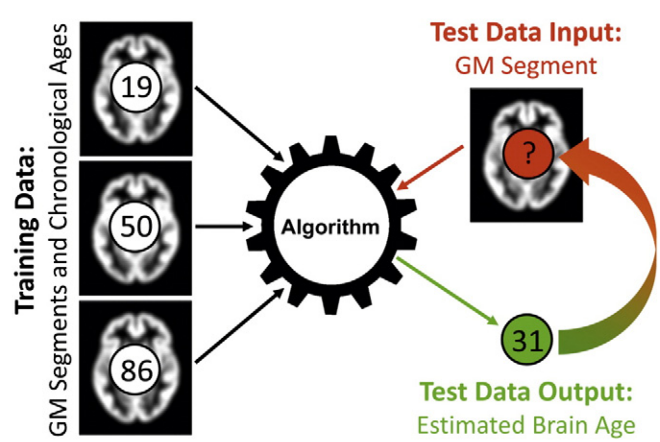

Fig. 1. The brain age estimation concept. First, the algorithm is trained using preprocessed gray matter (GM) segments as well as the individual chronological ages (e.g., 19, 50, and 86 years) from a large training sample. Then, feeding the trained algorithm with the preprocessed GM segments (input data) from a new test sample will provide the estimated brain ages for each subject (e.g., 31 years) as the desired output data.