Title: Structural brain changes in medically refractory focal epilepsy resemble premature brain aging

Running Head: Premature brain aging in focal epilepsy

Authors: Heath R. Pardoe PhD[1], James H. Cole PhD[2], Karen Blackmon PhD[1], Thomas Thesen D. Phil[1], Ruben Kuzniecky MD[1], for the Human Epilepsy Project Investigators

1. Comprehensive Epilepsy Center, Department of Neurology, New York University School of Medicine, 223 East 34th St, New York City, New York, 10016, USA
2. Computational, Clinical, and Cognitive Neuroimaging Laboratory, Department of Medicine, Imperial College London, London, United Kingdom

Corresponding author:

Heath Pardoe

Comprehensive Epilepsy Center

New York University School of Medicine

223 East 34th St

New York City, New York 10016, USA

Email: heath.pardoe@nyumc.org

Telephone: +1 646 754 5320

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Abstract

Objective

We used whole brain T1-weighted MRI to estimate the age of individuals with medically refractory focal epilepsy, and compared with individuals with newly diagnosed focal epilepsy and healthy controls. The difference between neuroanatomical age and chronological age was compared between the three groups.

Methods

Neuroanatomical age was estimated using a machine learning-based method that was trained using structural MRI scans from a large independent healthy control sample (N = 2001). The prediction model was then used to estimate age from MRI scans obtained from (i) newly diagnosed focal epilepsy patients (N = 42), medically refractory focal epilepsy patients (N = 94) and healthy controls (N = 74).

Results

Individuals with medically refractory epilepsy had a difference between predicted brain age and chronological age that was on average 4.5 years older than healthy controls ($p = 4.6 \times 10^{-5}$). No significant differences were observed in newly diagnosed focal epilepsy. Earlier age of onset was associated with an increased brain age difference in the medically refractory group ($p = 0.034$).

Significance

Medically refractory focal epilepsy is associated with structural brain changes that resemble premature brain aging.

1. Introduction

Medically refractory focal epilepsy is associated with decreased brain-wide volumetric measures and cognitive function, both of which are also observed in normal aging[1-4]. Prior studies have noted that epilepsy-related neuroanatomical and cognitive changes are greater than those observed in normal aging and therefore may be conceptualized as accelerated aging[5-8].

Evidence for an association between chronic focal epilepsy and brain atrophy has primarily come from analyses of cortical thickness changes or local gray matter volume in temporal lobe epilepsy. Medically refractory temporal lobe epilepsy has been shown to be associated with brain-wide reductions in regional cortical thickness or volume[7; 9-12]. A modest number of studies have identified brain changes beyond the primary lesion in focal cortical dysplasia, however reported extra-lesional changes in these studies are not typically atrophic[13; 14].

In this study, the difference between predicted and chronological age was cross-sectionally compared in three groups, comprising (i) individuals with medically refractory localization-related epilepsy being assessed for epilepsy surgery, (ii) newly diagnosed localization related epilepsy cases enrolled in the Human Epilepsy Project, and (iii) healthy matched controls imaged contemporaneously with epilepsy subjects. We used a previously validated multivariate machine-learning method for analysis of whole brain structural MRI to predict the age of individuals with focal epilepsy[15]. This methodological framework allowed us to test the hypothesis that the brains of individuals with medically refractory epilepsy resemble those of older

healthy individuals, as well as explicitly estimating the magnitude of the hypothesized aging effect. In addition to the primary analysis investigating increased neuroanatomical age in medically refractory cases, we also investigated whether age of seizure onset and epilepsy duration were related to the difference between predicted and chronological neuroanatomical age.

2. Methods

2.1 Participants

Two epilepsy groups were included in the study. The first group comprised consecutively recruited individuals with medically refractory epilepsy referred for imaging as part of pre-surgical assessment at the NYU Comprehensive Epilepsy Center between 2007 and 2015. Investigations included clinical semiology, video-EEG monitoring, clinical MRI, neuropsychological assessment, and PET/SPECT when deemed appropriate by clinical investigators. Age of epilepsy onset was obtained from clinical records for these epilepsy patients.

The second group of epilepsy participants were recruited for the Human Epilepsy Project, an ongoing prospective study of newly diagnosed focal epilepsy. Participants were recruited if they were between 12 and 60 years of age and had a clinical history consistent with focal epilepsy and had two confirmed spontaneous seizures within the previous 12 months.

Healthy controls were recruited by community advertisement. Control participants were excluded if they reported prior history of psychiatric or neurological disorders, head injury or substance abuse.

For all participants whole brain T1 weighted MRI was obtained on a 3T Siemens Allegra scanner using an MPRAGE volumetric acquisition (voxel size 1.3 × 1 × 1.3 mm, echo time = 3.25 ms, repetition time = 2530 ms, inversion time = 1100 ms, flip angle = 7°).

2.2 Image analysis

The age of each individual was predicted using Pattern Recognition for Neuroimaging Toolbox (PRoNTo, http://www.mlnl.cs.ucl.ac.uk/pronto[16]). The prediction model was developed using T1-weighted MRI of healthy individuals obtained from 14 publicly available neuroimaging databases (total N = 2001, mean age = 36.95 ± 18.12 years, range 18 – 90, 1016 male, 985 female, see supplementary material for database list and demographic information[17-30]). Each T1 weighted MRI scan was segmented into gray matter and white matter and spatially warped into a common space to ensure voxelwise correspondence between individuals. The SPM software package was used for segmentation, non-linear (DARTEL) registration and resampling into Montreal Neurological Institute (MNI) 152 template space [31]. Images were smoothed with a 4mm FWHM kernel and modulated to ensure final images retained localised volumetric information from the original images. Each voxel in the final images thus represents a regional estimate of gray or white matter volume. A Gaussian Processes Regression (GPR) machine learning algorithm was then trained to predict chronological age using the gray matter and white matter maps[32]. The prediction accuracy of the GPR model was then assessed using k-fold cross-validation with k = 10, to generate predicted age values on all training images.

The accuracy of the model was quantified using the correlation between chronological age and predicted, the amount of variance in age explained by the model (R^2), the mean absolute error (MAE) and the root mean squared error (RMSE). The model was then applied to the GM and WM segments to provide an estimated age for all individuals in the study (medically refractory epilepsy, newly diagnosed epilepsy and the study-specific healthy control group).

The difference between the predicted age of the individual and their chronological age was calculated, where a positive value corresponded to an increased estimated neuroantomical age relative to chronological age. These values were then compared between the three groups using a general linear model, with age and sex included as covariates. We also investigated the effect of (i) age of onset and (ii) epilepsy duration on the difference between predicted and chronological age after controlling for age at the time of scan.

3. Results

Ninety-four individuals with refractory epilepsy, forty-two individuals with newly diagnosed epilepsy and seventy-four healthy controls were included in our study (Table 1). For the medically refractory epilepsy group, seizures were localized to the temporal lobe in forty-seven patients (50%), frontal lobe in eighteen patients (19%), parietal lobe in four patients (4 %) and the occipital lobe in two patients (2%). The remaining twenty-three cases had adjacent multilobar seizure onset. Twelve of the forty-seven temporal lobe cases had histopathologically confirmed mesial temporal sclerosis, and twenty-two participants had focal cortical dysplasia. For the medically refractory group, seizure onset age ranged from one to fifty-three years of age

(mean = 17.4; SD = 12.2 years) and epilepsy duration ranged from one to forty-five years (mean = 15.9; SD = 11.8 years). In the newly diagnosed epilepsy group, seizure onset age was between eleven and sixty (mean = 29.3, SD = 11.5 years) and epilepsy duration ranged from zero to nineteen years (mean = 2.1, SD = 3.9 years).

Cross-validation in the training dataset indicated that the model was able to accurately predict age ($r = 0.938$, $R^2 = 0.88$, MAE = 5.01, RMSE = 6.31), based on combined GM and WM volume images (permutation corrected $p = 0.001$). Accuracy estimates in the independent healthy control test dataset were: $r = 0.74$, $R^2 = 0.54$, MAE = 5.73, RMSE = 7.34.

Individuals with medically refractory epilepsy had a difference between predicted brain age and chronological age that was on average 4.5 years older than healthy controls (Figure 1, $p = 4.6 \times 10^{-5}$). Although individuals with newly diagnosed epilepsy had a brain age 0.9 years older than their chronological age, this difference was not statistically significant ($p = 0.55$). There was a statistically significant relationship between age of onset and the difference in neuroanatomical and chronological age (-0.15 years difference per year, $p = 0.034$, $r = 0.5$). This finding indicates that the difference between predicted and chronological age is larger in individuals with earlier epilepsy onset. No significant relationship was observed between the amount of time someone had refractory epilepsy and the difference between their neuroanatomical and chronological age (0.13 years difference per year with epilepsy, $p = 0.083$). No relationship was observed between age of onset ($p = 0.29$) or epilepsy duration ($p = 0.29$) and the difference between

neuroanatomical and chronological age in the newly diagnosed epilepsy group. No significant association was observed between the difference in neuroanatomical and chronological age and the presence of hippocampal sclerosis or focal cortical dysplasia when these were included as additional covariates in the statistical model, suggesting that the observed brain aging effect in refractory epilepsy is not driven by lesional cases (hippocampal sclerosis p = 0.47, focal cortical dysplasia p = 0.57).

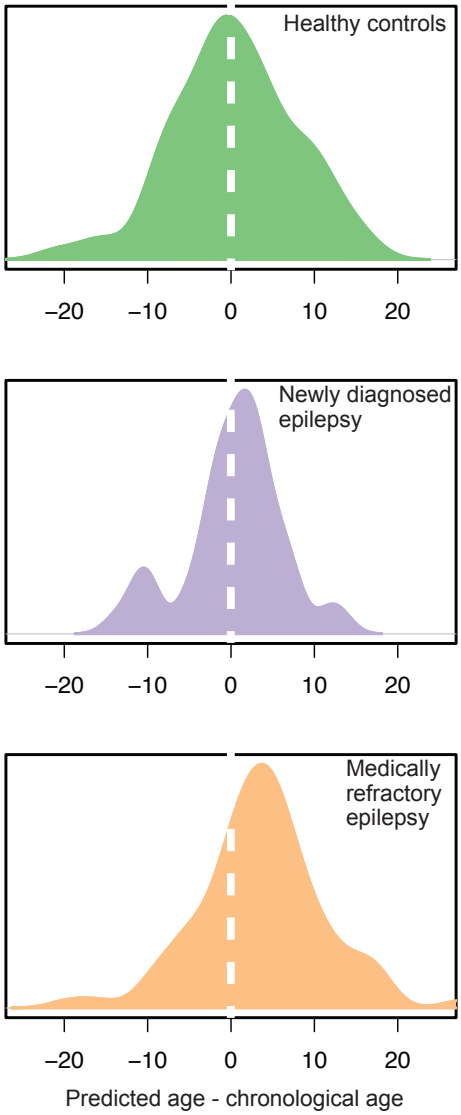

Figure 1. Long term medically refractory epilepsy is associated with an average increased brain age of 4.5 years. The figure shows the distribution of differences between predicted neuroanatomical age and chronological age in healthy controls (top row, green), newly diagnosed epilepsy patients (middle row, purple) and intractable epilepsy patients (bottom row, orange).

4. Discussion

We have demonstrated that medically refractory chronic epilepsy is associated with an increased brain age of 4.5 years, when estimated using whole brain T1-weighted MRI. This finding suggests that long-term medically refractory focal epilepsy disrupts the typical trajectory of aging in the brain. The biological mechanism underlying the brain aging effect observed in our study is unknown at this stage. It is unclear if the neuroanatomical changes that cause the brain of an individual with medically refractory epilepsy to appear older are due to the early onset of the same biological mechanisms that are associated with aging in healthy adults or reflect different pathological effects that mimic the atrophic volumetric changes that occur in aging brains.

Previous studies have shown that medically refractory epilepsy is associated with cognitive decline, and others have conceptualized this phenomenon as accelerated cognitive aging[5]. Because the neuroanatomical changes observed in medically refractory epilepsy cases resemble increased aging, these changes provide a potential biological mechanism to explain epilepsy-related cognitive decline. It is interesting to note that our secondary analysis of age of onset and epilepsy duration

in the medically refractory group suggest that age of onset makes more of a contribution to increased brain aging than the duration of epilepsy. These findings parallel previous work that suggests age of onset may be more important than epilepsy duration for global cognitive impairment in temporal lobe epilepsy[33]. Our findings of a greater influence of age of onset vs. epilepsy duration should be interpreted with caution since these variables are correlated; in our study individuals with an earlier age of onset had epilepsy for a longer period of time. Furthermore the significance of the link between brain age and epilepsy duration was marginally statistically significant ($p = 0.083$). Prospective future studies would be required to confirm these relationships between age of epilepsy onset, epilepsy duration and neuroanatomical aging. Similarly future studies should assess both structural changes and cognition in refractory epilepsy in order to determine if cognitive and neuroanatomical aging effects in epilepsy are related.

The one-year average increase in brain age observed in the newly diagnosed focal epilepsy group, although not statistically significant over the whole group, suggests that a subset of individuals with recent onset epilepsy also have an increased brain age. Approximately one third of newly diagnosed focal epilepsy patients will develop medically refractory epilepsy[34]. Because the newly diagnosed epilepsy patients will be longitudinally followed as part of the Human Epilepsy Project, we will be able to determine if the subset of newly diagnosed patients with increased brain age comprise the medically refractory portion of the group. If so, neuroanatomical age estimation using MRI may be a useful clinical marker for predicting intractability early in the course of an individual's epilepsy.

It is possible that the aging effect we have observed is not due to the underlying epilepsy or ongoing seizures but may be a result of long term antiepileptic medication use. Previous studies have reported brain volume reductions are associated with antiepileptic medication use[35; 36]. It is important to note that patients with newly diagnosed epilepsy in our study also showed a trend towards increased brain age, and AED use had only been recently started in these individuals. This provides supporting evidence that our observed brain age differences are not due to AED use at the time of scanning. A relatively simply way to investigate this question would be to assess brain aging in a group of epilepsy patients with long term but well controlled epilepsy or by using a larger sample size that controls for AED type.

This study contributes to the growing literature that applies machine learning techniques to imaging data to identify epilepsy-related structural and functional brain abnormalities and predict health outcomes[37-45]. Machine learning-based methods for estimating age using MRI have found a range of application in other clinical populations, including increased brain age in schizophrenia, diabetes, following traumatic brain injury and as a marker of risk for development of Alzheimer's disease[15; 46-48]. The overarching theme of these studies is that brain maturation may be disrupted by neurological insult or disease. Age estimation based on brain structure provides additional information compared with chronological age, and may allow us to non-invasively assess how events over the lifespan impact brain structure.

In summary, we have demonstrated that the brains of individuals with medically refractory focal epilepsy resemble the brains of older healthy individuals. These

findings are consistent with cognitive deficits observed in individuals with medically refractory epilepsy. Neuroanatomical age assessment using structural MRI may be a useful clinical tool for assessing how ongoing seizures impact brain development and maturation across the lifespan.

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