Neurobiology of Aging 39 (2016) 202–209

Contents lists available at ScienceDirect

Neurobiology of Aging

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

Age-related cortical thinning in cognitively healthy individuals in their 60s: the PATH Through Life study

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ARTICLE INFO

Article history:
Received 3 May 2015
Received in revised form 10 December 2015
Accepted 18 December 2015
Available online 23 December 2015

Keywords:
Aging
Healthy
MRI
Cortical thickness
Longitudinal
Sex differences

ABSTRACT

Although it is recognized that the human cortex thins with age, longitudinal estimates of thinning patterns specific to healthy young-old age (<75 years) individuals are lacking. Importantly, many neurodegenerative disorders first manifest between midlife and old age, and normative estimates may provide a reference for differential change associated with such disorders. Here, we provide longitudinal estimates of cortical thinning observed over 12 years in a large group (n = 396) of healthy individuals, aged 60–66 years at baseline scan, who were scanned with magnetic resonance imaging (1.5T) on 4 occasions. Longitudinal age-related thinning was observed across most of the cortices, with a mean change of −0.3% per year. We measured significant thinning in heteromodal association cortex, with less thinning in regions expected to atrophy later in life (e.g., primary sensory cortex). Men showed more extensive thinning than women. Our comparison of cross-sectional and longitudinal estimates adds to growing evidence that cross-sectional designs may underestimate age-related changes in cortical thickness.

1. Introduction

Aging results in widespread structural change in the human brain, including cortical thinning (Fjell and Walhovd, 2010; Salat et al., 2004). Studying these changes is of interest for understanding age-related changes in cognitive abilities, as well as for identifying the early manifestation of neurodegenerative disorders, including Alzheimer's disease (AD). Studies of age-related cortical thinning to date, however, have largely been cross-sectional and thus potentially confounded by cohort effects. Estimates of cortical thinning can only be obtained from examining change within individuals over time. An example of divergent results obtained with longitudinal and cross-sectional estimates on the same data was given recently (Fjell et al., 2014). The authors measured different rates of annual thinning based on cross-sectional (−0.30%) compared to longitudinal (−0.59%) analysis on the same data set. Furthermore, regions that appeared to be preserved or even thickening based on cross-sectional analysis, including anterior cingulate and insula, showed significant thinning based on longitudinal analysis.

Of the few longitudinal studies of age-related cortical thinning carried out to date, individuals studied have largely been older. For example, 4 of 5 recent studies were based on individuals aged 69+ years (Fjell et al., 2014; Jiang et al., 2014; Storsve et al., 2014; Thambisetty et al., 2010; Yao et al., 2012). However, recent evidence suggests that the rate of cortical atrophy changes with age, depending on the brain region. For example, although thinning has been consistently observed in inferior parietal cortex (Fjell et al., 2014; Sowell et al., 2003; Thambisetty et al., 2010; Yao et al., 2012) and lateral temporal cortex (Fjell et al., 2013, 2014; Thambisetty et al., 2010; Yao et al., 2012), a growing number of studies suggest there are regions of accelerating and decelerating change (Driscoll et al., 2009; Pfefferbaum et al., 2013). Thinning in orbitofrontal cortex, for example, was shown to decrease with increasing age (Fjell et al., 2014; Sowell et al., 2003), whereas medial temporal thinning has been shown to increase with increasing age (Pfefferbaum et al., 2013; Raz et al., 2005). Storsve et al. concluded that atrophy in medial temporal cortex is most likely evident toward age 70+ years (Sowell et al., 2003).

Some researchers have attempted to identify overarching principles that explain these age-dependent regional vulnerabilities. For example, the "last in, first out" model predicts earliest decline in regions that mature relatively late in life including prefrontal and association cortex (Raz, 2000). An extended "development-sensory" model predicts earlier atrophy in heteromodal association

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0197-4580/$ – see front matter
http://dx.doi.org/10.1016/j.neurobiolaging.2015.12.009

cortex and later atrophy in primary sensory, primary motor, and paralimbic cortices (McGinnis et al., 2011). To further investigate these models, longitudinal studies of cortical thinning across the life span are needed.

For the present study, we investigated age-related cortical thinning in a large group of healthy early-old age individuals (aged 60–66 years at baseline) scanned up to 4 times longitudinally with magnetic resonance imaging (MRI) over a 12-year period. We hypothesized that we would see cortical thinning in heteromodal association cortex, including prefrontal, inferior parietal, and lateral temporal cortex. We expected to see a lack of cortical thinning in regions thought to decline later in life, including medial temporal and primary sensory cortex. We also sought to test whether sex differences in cortical atrophy were present in this age group. Recent longitudinal studies suggest greater age-related change in men compared to women (Driscoll et al., 2009; Thambisetty et al., 2010). Finally, we carried out a comparison of cross-sectional versus longitudinal atrophy estimates.

2. Participants

2.1. Study population

Participants were sampled from the Personality and Total Health (PATH) Through Life project, a large longitudinal study of aging aimed at investigating the course of mood disorders, cognition, health, and other individual characteristics across the life span (Anstey et al., 2012). PATH surveys 2530 individuals aged 40–44 years at baseline (44–49 years at first MRI) and 2551 individuals aged 60–66 years at baseline (60–66 years at first MRI), who are residents of the city of Canberra and the adjacent town of Queanbeyan, Australia, and who were randomly recruited through the electoral roll. Enrollment to vote is compulsory for Australian citizens, making this cohort representative of the population. The study was approved by the Australian National University Ethics Committee, and all participants provided written informed consent. Follow-up is every 4 years, and here, we analyzed the first 4 waves of data collection in the 60–66 year olds.

Of the 2551 randomly selected PATH participants aged 60–66 years included in the study at wave 1, 2076 consented to be contacted regarding an MRI scan. Of these, a randomly selected subsample of 622 participants was offered an MRI scan and 479 were eventually scanned. Of these, 1 scan was lost, and 78 scans were excluded because of a history of epilepsy (3), Parkinson's disease (9), stroke (12), mild cognitive impairment (35), dementia (1), or on the basis of the individual's Mini–Mental State Examination (MMSE) score (18) (Folstein et al., 1975) (MMSE $<$ 27 at any wave). This high MMSE cutoff was based on a validation study of the use of MMSE to estimate probable dementia in population studies (Anstey et al., 2010) and was used to minimize the chance of including participants with dementia. A further 13 MRI scans failed FreeSurfer processing. For the remaining 387 participants (199 men, 51%), there were no significant differences in mean age, race, or gender balance compared to the original PATH sample, but participants of the study sample had more years of education (14.4 vs. 13.8, $p <$ 0.01), as well as higher MMSE scores (29.5 vs. 29.1, $p < 0.0001$) and a smaller percentage of current smokers (6.9% vs. 11%, $p < 0.01$) compared to the original PATH sample.

At the second wave of data collection, 377 participants were rescanned. Of these, 4 scans were lost and 61 scans were excluded because of a history of epilepsy (1), Parkinson's disease (8), stroke (9), mild cognitive impairment (30), dementia (1), or MMSE $<$ 27 at any wave (12), and 21 scans failed FreeSurfer processing, resulting in 291 MRI scans (161 male, 55%). Cohort statistics for the second wave of data collection did not differ in years of education, gender balance, or baseline MMSE scores compared to the first wave.

At the third wave of data collection, 314 participants were rescanned. Of these, 1 scan was lost and 3 were excluded due to poor scan quality. A further 49 scans were excluded because of Parkinson's disease (7), stroke (7), mild cognitive impairment (25), or MMSE $<$ 27 at any wave (10), and 20 scans failed FreeSurfer processing, resulting in 241 MRI scans (132 men, 55%). Cohort statistics for the third wave of data collection did not differ in years of education, gender balance, or baseline MMSE scores, compared to cohort statistics at the first wave.

At the fourth wave, 275 participants were rescanned. Of these, 48 scans were excluded because of a history of epilepsy (1), Parkinson's disease (4), stroke (6), mild cognitive impairment (26), dementia (1), or MMSE $<$ 27 at any wave (10). A further 7 scans failed FreeSurfer processing, resulting in 220 MRI scans (128 men, 58%). Cohort statistics for the fourth wave of data collection did not differ in years of education, gender balance, or baseline MMSE scores, compared to cohort statistics at the first wave.

In summary, our final analyses were based on 387 participants scanned at wave 1 (51% men, age range: 60.3–66.0 years), 291 participants scanned at wave 2 (55% men, age range: 64.4–70.1 years), 241 participants scanned at wave 3 (55% men, age range: 68.6–73.8 years), and 220 participants scanned at wave 4 (58% men, age range: 72.8–78.0 years). Out of a total of 396 participants, 179 were scanned on all 4 occasions, 74 were scanned on 3 occasions, 58 were scanned on 2 occasions, and 85 participants were scanned just once.

2.2. MRI scan acquisition

T1-weighted 3-dimensional structural MRI scans were obtained for all volunteers using 1.5T MRI scanners. For the first 2 waves of data collection, MRI scans were acquired using a Philips Gyroscan ACS-NT scanner (Philips Medical Systems, Best, the Netherlands) in coronal orientation using a fast-field echo sequence. For wave 1, the repetition time (TR), echo time (TE), flip angle, and slice thickness were 28.05 ms/2.64 ms/30°, and 2 mm, respectively, with matrix size 256 × 256. For wave 2, TR, TE, flip angle, and slice thickness were 8.93 ms/3.57 ms/8°, and 1.5 mm, respectively, with matrix size 256 × 256. For wave 3, participants were scanned on a Siemens 1.5T Avanto scanner (Siemens Medical Solutions), and scans were acquired in sagittal orientation with TR, TE, flip angle, and slice thickness equal to 1160 ms/4.17 ms/15°, and 1 mm respectively, with matrix size 512 × 512. For wave 4, participants were scanned on a Siemens 1.5T Espree scanner with TR, TE, flip angle, and slice thickness equal to 1160 ms/4.24 ms/15°, and 1 mm, respectively, with matrix size 512 × 512. To account for variance due to changes in scanner and scan parameters between waves of data collection, we orthogonalized the thickness data with respect to a scanner covariate, as a data preprocessing step (see the following for more details).

2.3. Image processing

Further image analysis was carried out using FreeSurfer, version 5.3, including the estimation of the cortical surfaces and the cortical thickness for each participant (Fischl, 2012). Processing quality control was implemented through an in-house script which identified outlier scans based on total gray and white matter volumes. These scans were visually checked, and if confirmed to have failed FreeSurfer processing, removed from further analysis (numbers provided in study population). We used the longitudinal FreeSurfer pipeline, where a within-subject template is created, which allows equal treatment of all input images, thus limiting processing bias associated with the use of a particular time point as the reference