NeuroImage 59 (2012) 3862–3870

Contents lists available at SciVerse ScienceDirect

NeuroImage

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

Brain tissue volumes in the general population of the elderly☆ The AGES-Reykjavik Study

Sigurdur Sigurdsson [a,*], Thor Aspelund [a,b], Lars Forsberg [a], Jesper Fredriksson [c], Olafur Kjartansson [a], Bryndis Oskarsdottir [a], Palmi V. Jonsson [a,b], Gudny Eiriksdottir [a], Tamara B. Harris [f], Alex Zijdenbos [d], Mark A. van Buchem [e], Lenore J. Launer [f], Vilmundur Gudnason [a,b]

[a] The Icelandic Heart Association, Kopavogur, Iceland
[b] The University of Iceland, Reykjavik, Iceland
[c] Rafonninn Inc, Reykjavik, Iceland
[d] Biospective Inc, Montreal, Canada
[e] Department of Radiology, Leiden University Medical Center, Leiden, The Netherlands
[f] Laboratory of Epidemiology, Demography, and Biometry, National Institute on Aging, National Institutes of Health, Bethesda, MD, USA

ARTICLE INFO

Article history:
Received 13 April 2011
Revised 3 November 2011
Accepted 4 November 2011
Available online 13 November 2011

Keywords:
Brain volume
White matter hyperintensities
Atrophy
Magnetic resonance imaging
Population based
AGES-Reykjavik study

ABSTRACT

Imaging studies have reported conflicting findings on how brain structure differs with age and sex. This may be explained by discrepancies and limitations in study population and study design. We report a study on brain tissue volumes in one of the largest cohorts of individuals studied to date of subjects with high mean age (mean ± standard deviation (SD) 76 ± 6 years). These analyses are based on magnetic resonance imaging (MRI) scans acquired at baseline on 4303 non-demented elderly, and 367 who had a second MRI, on average 2.5 ± 0.2 years later. Tissue segmentation was performed with an automatic image analysis pipeline. Total brain parenchymal (TBP) volume decreased with increasing age while there was an increase in white matter hyperintensities (WMH) in both sexes. A reduction in both normal white matter (NWM)- and gray matter (GM) volume contributed to the brain shrinkage. After adjusting for intra-cranial volume, women had larger brain volumes compared to men (3.32%, $p<0.001$) for TBP volume in the cross-sectional analysis. The longitudinal analysis showed a significant age-sex interaction in TBP volume with a greater rate of annual change in men (−0.70%, 95%CI: −0.78% to −0.63%) than women (−0.55%, 95%CI: −0.61% to −0.49%). The annual change in the cross-sectional data was approximately 40% less than the annual change in the longitudinal data and did not show significant age–sex interaction. The findings indicate that the cross-sectional data underestimate the rate of change in tissue volumes with age as the longitudinal data show greater rate of change in tissue volumes with age for all tissues.

Introduction

It is well known that the human brain atrophies with age. Generally, this atrophy reflects a decrease in gray- and white matter tissue combined with an increase in white-matter hyperintensities (WMH) and cerebrospinal fluid (CSF) (Pfefferbaum et al., 1994; Courchesne et al., 2000; Good et al., 2001; Jernigan et al., 2001; Resnick et al., 2003; Taki et al., 2004; DeCarli et al., 2005; Enzinger et al., 2005; Fotenos et al., 2005; Walhovd et al., 2005; Ikram et al., 2008). However, reports vary on the trajectory of these tissue changes with age. In studies based on older populations the volume of WM has been shown to decrease (Jernigan et al., 2001; Resnick et al., 2003; Walhovd et al., 2005; Greenberg et al., 2008; Ikram et al., 2008), or not change significantly with age (Good et al., 2001; Taki et al., 2004). A reduction in GM volume with age has been shown in most (Good et al., 2001; Jernigan et al., 2001; Resnick et al., 2003; Taki et al., 2004; Walhovd et al., 2005; Godin et al., 2009) but not all studies (Greenberg et al., 2008; Ikram et al., 2008). Studies that include broader age ranges have reported WM volume to increase through adulthood, peaking in volume in the age range of 40–60 years, followed by a rapid decline at the age around 60. In contrast, GM volume was shown to decline throughout adulthood and old age at more or less linear rate (Allen et al., 2005; Walhovd et al., 2005). Gray-white matter ratios have

Abbreviations: AGES, Age Gene/Environment Susceptibility; WMH, white matter hyperintensities; CSF, cerebrospinal fluid; SD, standard deviation; WM, white matter; TWM, total white matter; GM, gray matter; TBP, total brain parenchyma; CI, confidence interval; SNR, signal-to-noise ratio; CNR, contrast-to-noise ratio; 3D-SPGR, three dimensional spoiled gradient echo, FLAIR, fluid attenuated inversion recovery; BET, brain extraction tool; ICV, intra-cranial volume; r, intra-class correlation, CoV, coefficient of variation; GM/WM, GM-to-WM ratio.

☆ Equal contribution of co-authors: Lenore J. Launer, Vilmundur Gudnason.

* Corresponding author at: The Icelandic Heart Association, 201 Kopavogur, Iceland. Fax: + 354 5351801.
E-mail address: sigurdur@hjarta.is (S. Sigurdsson).

1053-8119/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2011.11.024

been found to vary widely in the literature, from approximately 1 to 3 dependent on age, generally declining non-linearly from age 20–50, then increasing linearly in elderly subjects (Harris et al., 1994; Guttmann et al., 1998; Resnick et al., 2000; Good et al., 2001). As the trajectory of these tissues depends on the age-ranges examined, methods assuming linearity or even mono-tonicity of the age-functions should be interpreted with caution (Jernigan and Gamst, 2005).

Inconsistent results have also been reported in studies of sex related differences and age-sex interactions in brain volumes. Generally the whole brain, and in some instances both GM- and WM volumes, have been reported to be larger in men than women (Courchesne et al., 2000; Good et al., 2001; Greenberg et al., 2008) without correction for head size. Some but not all studies with head size correction suggest that GM- or WM volumes or both tissue types are smaller or not significantly different in men as compared to women (Ge et al., 2002; Brickman et al., 2008; Greenberg et al., 2008; Ikram et al., 2008; Barnes et al., 2010). These discrepancies are expected since men have generally larger heads than women as they are larger in stature, making head size correction a logical approach in brain volume research (Greenberg et al., 2008). Significant age–sex interactions have been reported showing that the brain shrinks more rapidly with age in men than women (Xu et al., 2000; Good et al., 2001). Other studies including recent studies on relatively large samples did not observe any age–sex interactions at all (Resnick et al., 2003; Greenberg et al., 2008; Ikram et al., 2008).

These conflicting results in the literature reflect differences in the range of participant age, health based inclusion/exclusion criteria, cross-sectional or longitudinal study design, lack of correction for intra-cranial volume, different image quality including varying levels of signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR), different post processing methods, as well as variations in the degree of manual intervention in computerized post-processing algorithms and in particular, sample sizes. Many of the studies referred to above are based on sample sizes of less than 250 subjects with a broad age range of 15–99 years and include only a small number of older individuals (Allen et al., 2005; Enzinger et al., 2005; Walhovd et al., 2005; Greenberg et al., 2008). The selection of participants with respect to health status also varies across studies, from only selecting very healthy individuals, without any neurological, psychiatric, or other medical condition (Good et al., 2001) to limiting exclusions to individuals with dementia (Ikram et al., 2008; Godin et al., 2009). Furthermore, there are inconsistent findings regarding cross-sectional and longitudinal brain volume changes where some studies have shown good agreement between cross-sectional and longitudinal estimates (Resnick et al., 2003; Fotenos et al., 2005), where as others (Raz et al., 2003; Raz et al., 2005) have shown greater longitudinal change than predicted from cross-sectional estimates. Secular changes and subsequent cohort affects confound results of age effects based on cross-sectional studies, possibly leading to a mismatch between cross-sectional and longitudinal estimates (Fotenos et al., 2005). Several other longitudinal studies on brain volumes have been reported (Resnick et al., 2000; Tang et al., 2001; Scahill et al., 2003; Enzinger et al., 2005; Fjell et al., 2009; Sluimer et al., 2010). In general, these studies are based on more selected samples that are not population based.

Advances in post-processing procedures make it possible to analyze a large sample with an automated classification pipeline. These methods require little manual intervention so unreliability due to manual intervention is reduced (Zijdenbos et al., 2002; Taki et al., 2004). Further, it is also possible to estimate different brain tissue types including WMH (Walhovd et al., 2005; Ikram et al., 2008), which is an important component of brain pathology in aging brains; some studies have not accounted for WMH (Resnick et al., 2003; Fotenos et al., 2005).

Here, we report brain tissue volumes in the largest population-based cohort to date consisting of men and women who participated in the Age Gene/Environment Susceptibility-Reykjavik Study (AGES-Reykjavik Study). We present cross-sectional data of 4303 non-demented subjects as well as longitudinal data based on a 9% sub-sample. Tissue segmentation was performed using a validated automatic image analysis pipeline based on a multi-spectral tissue classification described in Image processing pipeline–Validation of tissue volumes sections. We hypothesize that GM- and WM atrophy as well as gray-white matter ratio and WMH volume in this elderly cohort increases linearly with age, more in men compared with women. Furthermore, we hypothesize that longitudinal changes in brain volumes with age are different from that predicted from cross-sectional estimates.

Material and methods

Study population

The AGES-Reykjavik Study is a continuation of the Reykjavik Study. The Reykjavik Study was initiated in 1967 by the Icelandic Heart Association and included men and women born in 1907–1935 and living in the Reykjavik area. From September 2002 to February 2006, new data were collected for the AGES-Reykjavik Study, aimed to investigate the genetic and environmental factors contributing to clinical and subclinical disease at older age. The study design and initial assessments of the cohort have been described previously (Harris et al., 2007; Saczynski et al., 2009). As part of the assessments at the research center, a questionnaire was administered, a clinical examination was performed, and images were acquired of the brain, musculoskeletal system, body composition, vasculature and heart. From June 2006 to March 2007 a sub-sample of the cohort was re-imaged. The AGES-Reykjavik Study has been approved by the Icelandic National Bioethics Committee, which acts as the Institutional Review Board for the Icelandic Heart Association, and by the Institutional Review Board for the Intramural Research Program of the National Institute on Aging, National Institutes of Health, USA. Informed consent was obtained from all participants. All MR images were screened by a neuroradiologist for evidence of brain pathology that warranted medical follow-up.

MR image acquisition

MR images were acquired on a single research-dedicated 1.5 T Signa Twinspeed EXCITE system (General Electric Medical Systems, Waukesha, WI) using a multi-channel phased array head cap coil. The structural image protocol included a T1-weighted three dimensional spoiled gradient echo (3D-SPGR) sequence (TE (time to echo), 8 ms; TR (time repetition), 21 ms; FA (flip angle), 30°; FOV (field of view), 240 mm; matrix, 256×256). Each volume consisted of 110 slices with 1.5 mm slice thickness and in-plane pixel size of 0.94 mm x 0.94 mm. A proton density (PD)/T2 - weighted fast spin echo (FSE) sequence (TE1, 22 ms; TE2, 90 ms; TR, 3220 ms; echo train length, 8; FA, 90°; FOV, 220 mm; matrix, 256×256), and a fluid attenuated inversion recovery (FLAIR) sequence (TE, 100 ms; TR, 8000 ms, inversion time, 2000 ms, FA, 90°; FOV, 220 mm; matrix, 256×256). These latter two sequences were acquired with 3-mm thick slices and in-plane pixel size of 0.86 mm x 0.86 mm. All images were acquired to give full brain coverage and were localized at the AC/PC commissure line.

Image processing pipeline

Following MRI acquisition, all images were transferred to a dedicated 52-CPU Linux processing cluster and processed using an image analysis pipeline derived from the Montreal Neurological Institute (MNI) pipeline described in detail by Zijdenbos et al. (2002). The pipeline, referred to here as the AGES-RS/MNI pipeline, is divided into 45 processing modules. The algorithm segments the whole brain