ELSEVIER

Neurobiology of Aging 33 (2012) 2774–2781

NEUROBIOLOGY OF AGING

www.elsevier.com/locate/neuaging

Determinants of cerebellar and cerebral volume in the general elderly population

Yoo Young Hoogendam[a,b], Jos N. van der Geest[c], Fedde van der Lijn[b,d], Aad van der Lugt[b], Wiro J. Niessen[b,d], Gabriel P. Krestin[b], Albert Hofman[a], Meike W. Vernooij[a,b], Monique M.B. Breteler[a], M. Arfan Ikram[a,b,*]

[a] *Department of Epidemiology, Erasmus MC University Medical Center, Rotterdam, the Netherlands*
[b] *Department of Radiology, Erasmus MC University Medical Center, Rotterdam, the Netherlands*
[c] *Department of Neuroscience, Erasmus MC University Medical Center, Rotterdam, the Netherlands*
[d] *Department of Medical Informatics, Erasmus MC University Medical Center, Rotterdam, the Netherlands*

Received 21 October 2011; received in revised form 20 January 2012; accepted 11 February 2012

Abstract

In a population-based study of 3962 community-dwelling nondemented elderly we investigated the relation of age, sex, cardiovascular risk factors, and the presence of infarcts with cerebellar volume, and its interrelationship with cerebral volumes. Cerebellar and cerebral gray and white matter were segmented using Freesurfer version 4.5 (http://surfer.nmr.mgh.harvard.edu/). We used linear regression analyses to model the relationship between age, sex, cardiovascular risk factors, brain infarcts, white matter lesions (WMLs) and cerebellar and cerebral volume. Smaller cerebellar volumes with increasing age were mainly driven by loss of white matter. Diabetes, higher serum glucose and lower cholesterol levels were related to smaller cerebellar volume. No association was found between hypertension, smoking, apolipoprotein E (ApoE) genotype, and cerebellar volume. Supratentorial lacunar infarcts and WMLs were related to smaller cerebellar volume. Infratentorial infarcts were related to smaller cerebellar white matter volume and total cerebral volume. This study suggests that determinants of cerebellar volume do not entirely overlap with those established for cerebral volume. Furthermore, presence of infarcts or WMLs in the cerebrum can affect cerebellar volume.

Keywords: Cohort study; Cerebellum; Cerebrum; Aging; Brain volume; Magnetic resonance imaging; Cerebrovascular disease; Infarcts; White matter lesions; Cardiovascular risk factors

1. Introduction

The cerebellum is a complex structure, containing more than 50% of all neurons in the brain. It is organized in a different manner than the cerebrum (Kandel et al., 2000; Voogd, 2003). Recently, research has emphasized the role the cerebellum is likely to play in cognitive processing, next to its well-studied contributions to motor skills (Schmahmann, 2010; Stoodley, 2011). It is therefore important to study determinants of cerebellar volume in an elderly population.

Most structural magnetic resonance (MR) imaging studies with large sample sizes have focused on the cerebrum only or the entire brain (DeCarli et al., 2005; Good et al., 2001; Ikram et al., 2008). Studies that specifically assessed the cerebellum showed inconsistent results. Some studies reported that cerebellar volume remains relatively stable with aging (Bergfield et al., 2010; Rhyu et al., 1999; Smith et al., 2007), whereas others found strong effects of age on cerebellar atrophy (Jernigan et al., 2001; Pagani et al., 2008; Raji et al., 2009; Raz et al., 2001, 2010; Walhovd et al., 2005). A histological study of the cerebellum showed that

* Corresponding author at: Department of Epidemiology, Erasmus MC University Medical Center, PO Box 2040, 3000 CA Rotterdam, the Netherlands. Tel.: +31 10 70 43930; fax: +31 10 70 44657.

E-mail address: m.a.ikram@erasmusmc.nl (M.A. Ikram).

0197-4580/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
10.1016/j.neurobiolaging.2012.02.012

smaller weight and volume were found, and fewer neurons were counted in the cerebellum of older persons than in those of younger persons (Andersen et al., 2003). Drawbacks of this previous work are the relatively small sample sizes and use of preselected populations. An important aspect that is underexposed in current literature is how the cerebellum is affected by cardiovascular factors. Cardiovascular risk factors have extensively been associated with atrophy of the cerebrum (DeCarli et al., 2005; Ikram et al., 2008). Moreover, various studies have shown strong relations of cortical and lacunar infarcts, as well as white matter lesions with cerebral atrophy (DeCarli et al., 2005; Godin et al., 2009; Ikram et al., 2008; Raji et al., 2012). Still, how cardiovascular risk factors and cerebrovascular disease relate to cerebellar volumes, remains unclear. Therefore, there is a need to study cardiovascular risk factors and characteristics of cerebrovascular disease as determinants of cerebellar volume in a population-based elderly population.

The aim of our study was to investigate structural characteristics of the cerebellum with aging, and how cardiovascular factors and cerebrovascular disease affect cerebellar volume. Moreover, we compared determinants of cerebellar volume to determinants of cerebral volume.

2. Methods

2.1. Participants

The study is based on the Rotterdam Study (Hofman et al., 2011), a population-based study in middle-aged and elderly participants that started in 1990, investigating causes and consequences of age-related disease. All participants provided written informed consent for all aspects of the study and the medical ethical committee of the Erasmus MC University Medical Center, The Netherlands, approved of the study. The cohort was expanded in 2000 and 2006. From 2005 onward, standardized brain magnetic resonance imaging (MRI) scanning was implemented in the core protocol of the study (Ikram et al., 2011). From a total of 4898 persons, 30 persons with a diagnosis of prevalent dementia were excluded from the study and 389 persons were considered noneligible for MRI (due to, e.g., pacemakers or claustrophobia). The remaining 4479 persons were invited, of whom 4082 (91%) agreed to participate. Due to physical constraints (e.g., back pain), imaging was not performed or completed in 44 individuals. In total, 4038 complete MRI examinations were obtained.

2.2. MRI acquisition and image analysis

Magnetic resonance imaging of the brain was performed on a 1.5-T MRI scanner (Signa Excite II; General Electric Healthcare, Milwaukee, WI, USA). The MRI protocol included a high-resolution axial T1-weighted 3-dimensional fast radio frequency spoiled gradient recalled acquisition in steady state with an inversion recovery prepulse (FASTSPGR-IR) sequence (repetition time [TR] = 13.8 ms, echo time [TE] = 2.8 ms, inversion time [TI] = 400 ms, field of view [FOV] = 25 cm^2, matrix = 416 × 256, flip angle = 20°, number of excitations [NEX] = 1, bandwidth [BW] = 12.50 kHz, 96 slices with slice thickness 1.6 mm 0-padded to 0.8 mm). Furthermore a fluid-attenuated inversion recovery (FLAIR) sequence was acquired (TR = 8000 ms, TE = 120 ms, TI = 2000 ms, FOV = 25 × 25 cm^2, matrix = 320 × 224, NEX = 1, BW = 31.25 kHz, 64 slices with slice thickness 2.5 mm) and a proton density-weighted sequence (TR = 12,300 ms, TE = 17.3 ms, FOV = 25 cm [rectangular], matrix 416 × 256, NEX = 1, BW = 17.86 kHz, 90 slices with slice thickness 2.5 mm). All slices were contiguous.

According to our standard acquisition protocol images were resampled to 512 × 512 × 192 voxels (voxel size: 0.5 × 0.5 × 0.8 mm^3) (Ikram et al., 2011).

A nonuniformity correction was performed (Sled et al., 1998). Segmentation and labeling of brain structures was performed by Freesurfer version 4.5 (http://surfer.nmr.mgh.harvard.edu/) (Fig. 1) (Fischl et al., 2002). This procedure automatically assigns a neuroanatomical label to each voxel in an MRI volume based on probabilistic information obtained from a manually labeled training set. This yielded intracranial volume (ICV) and gray and white matter volumes for cerebellum and cerebrum. A trained observer inspected a sample of random individuals (n = 192) and all outliers (n = 170) with an intracranial, cerebral, or cerebellar volume outside a range of ± 2.58 SD from the mean, stratified by sex. These scans were blindly rated on segmentation quality. Three scans of the random sample were excluded from the study. Two of these scans contained arachnoid cysts and in 1 scan a large meningioma was present, both interfering with tissue segmentation results. Seventy-three scans of the outlier sample were excluded, because the segmentation quality was insufficient. Problems in the segmentation were due to either technical problems (n = 62, e.g., motion artifacts, susceptibility artifacts due to dental implants) or pathology (n = 11, e.g., large arachnoid cysts, meningiomas) that could influence the volume estimates, resulting in 3962 scans that were included in our analyses. The total of 76 persons that were excluded, were on average older (68.4 ± 12.73 years vs. 60.2 ± 8.58 years) and more often had hypertension (67.1% vs. 54.2%) than those included in the analysis.

The evaluation of infarcts was based on fluid-attenuated inversion recovery, proton density, and T1-weighted sequences, by 5 experienced raters under supervision of a neuroradiologist. The rating protocol has been described elsewhere (Vernooij et al., 2008). Because the primary aim of the study was to investigate the cerebellum as a separate structure, we classified infarcts into 4 mutually exclusive categories. These categories entailed infratentorial infarcts only, supratentorial lacunar only, supratentorial cortical only, or multiple area infarcts. Multiple area infarcts could be supratentorial and infratentorial. Supratentorial white matter lesion volumes were obtained using a k-nearest-