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# Brain structural differences between 73- and 92-year olds matched for childhood intelligence, social background, and intracranial volume

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ABSTRACT

Fully characterizing age differences in the brain is a key task for combating aging-related cognitive decline. Using propensity score matching on 2 independent, narrow-age cohorts, we used data on childhood cognitive ability, socioeconomic background, and intracranial volume to match participants at mean age of 92 years ($n = 42$) to very similar participants at mean age of 73 years ($n = 126$). Examining a variety of global and regional structural neuroimaging variables, there were large differences in gray and white matter volumes, cortical surface area, cortical thickness, and white matter hyperintensity volume and spatial extent. In a mediation analysis, the total volume of white matter hyperintensities and total cortical surface area jointly mediated 24.9% of the relation between age and general cognitive ability (tissue volumes and cortical thickness were not significant mediators in this analysis). These findings provide an unusual and valuable perspective on neurostructural aging, in which brains from the 8th and 10th decades of life differ widely despite the same cognitive, socioeconomic, and brain-volumetric starting points.



## 1. Introduction

Many changes in brain structure occur during normal aging. Understanding and characterizing these age-related differences are important because they have been linked to aging-related cognitive decline, a pervasive phenomenon with a substantial predicted effect on aging societies (Brayne, 2007; Luengo-Fernandez et al., 2010). A fuller understanding of later-life brain changes will aid in the search for interventions to ameliorate this decline (Raz and Lindenberger, 2013). Relatively few studies have modeled both brain and cognitive age differences, and fewer have included participants over the age of 90 years (Dickie et al., 2013). In the present study, we quantified age differences in a variety of neurostructural measures using an unusual design: we compared closely matched participants from 2 independent narrow-aged samples in later life,

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1 aged 73 years and the other 92 years. We then tested the extent to which neuroanatomical differences could explain the large age-related cognitive differences between the 2 samples.

The most-studied neuroanatomical measure with reference to aging is brain volume. Volume peaks in early adulthood, before a period of relatively mild decline through midlife, and more rapid degeneration in older age (Fjell and Walhovd, 2010). In non-pathological aging, adults aged more than 60 years experience around a 0.5% decline in total brain volume per year (Fotenos et al., 2005), with volumetric declines seen in both gray matter and white matter, in regions across the entire brain (Dickie et al., 2015; Giorgio et al., 2010; Kruggel, 2006; Raz et al., 2005; Walhovd et al., 2011; Ziegler et al., 2011). Cortical surface area follows a similar trajectory of decline (Hogstrom et al., 2013), and most regions of the brain exhibit cortical thinning with age, with the loss of up to ~0.6 mm of cortical thickness per decade (Thambisetty et al., 2010; see also Fjell et al., 2009; Shaw et al., 2016a,b). Finally, the volume of white matter hyperintensities (WMHs) tends to increase with advancing age (Morris et al., 2009; Ritchie et al., 2015a). These hyperintensities, which are commonly seen on fluid-attenuated inversion recovery (FLAIR) brain magnetic resonance imaging (MRI) scans of older people and vary in their extent between individuals, are indicators of pathology thought to be related to small vessel disease, though debate continues on their precise etiology (see Wardlaw et al., 2015, for detailed discussion).

Deteriorations in the above-listed brain measures have been linked, in longitudinal studies, to declines in key cognitive faculties such as fluid intelligence, reasoning, mental speed, and memory, which decline on average throughout adulthood (Salthouse, 2004). For example, Schmidt et al. (2005) showed that declining brain volume was related to loss of cognitive skills such as memory and visuopractical abilities (see also Jokinen et al., 2012; Persson et al., 2016; Ritchie et al., 2015a). In a meta-analysis, Kloppenborg et al. (2014) showed that advancing WMH levels were related to decrements in all measured cognitive abilities.

There is relatively little evidence on which of these neuroanatomical variables are the most relevant for explaining cognitive aging, since few studies have analyzed multiple imaging variables simultaneously. In a previous study of one of the cohorts involved in the present analysis (Ritchie et al., 2015b), we measured multiple neuroanatomical measures and related them to a broad latent variable of general cognitive ability (so-called "*g*") measured at the age of 73 years. Total brain volume made the largest contributions to explaining variance in *g*, but other variables such as WMH and cortical thickness made additional, incremental contributions (see also Kievit et al., 2012). Thus, it is likely that several different aspects of brain structure are independently relevant to understanding the aging of cognitive abilities. However, these studies focus on cognitive ability level, rather than the age-related differences in these abilities.

In testing the extent to which brain structure can account for age differences in cognitive functioning, the present study took the approach of Kievit et al. (2014). They used structural equation model–based mediation analysis to test whether the age variance in cognitive ability could, in part, be explained by different neuroanatomical measures. They showed, for instance, that fractional anisotropy of the forceps minor and the volume of Brodmann area 10 were parallel mediators (explaining 18.2% in total) of the association between age and fluid intelligence in a sample with an age range of 18–89 years. Although the selection of brain regions included in that analysis was limited (2 cortical regions and 2 tracts), their results contributed to our understanding of the multifaceted nature of brain aging and its relation to key cognitive outcomes. That, in addition to a detailed characterization of aging across various brain imaging measures, was the aim of the present study.

### 1.1. The present study

Here, we extensively characterized whole and regional brain differences between 2 narrow-age cohorts of older people, 1 aged around 73 years and the other around 92 years. Unusually, both cohorts had data available on the same well-validated general cognitive ability test taken at the age of 11 years, as well as retrospective data on their socioeconomic status from childhood and adulthood. We used propensity score matching on these background variables, as well as on a measure of maximal brain size (their intracranial volume), to reduce confounding in the comparison of the 2 cohorts in later life. Because socioeconomic and early cognitive differences may influence the intercept (if not necessarily the slope) of aging-related changes (e.g., Barulli and Stern, 2013; Tucker-Drob et al., 2009), it was important to compare participants who have been matched on these variables.

Using these well-matched cohorts, we ran the following 3 analyses. First, we characterized the extent of the 19-year age differences in multiple broad brain volumetric measures: total brain volume, gray and white matter volumes, and the volume of WMHs. Second, we examined the gray matter in more detail, using parcellation to map volume and surface area differences in each of 54 gray matter regions of interest between the 73- and 92-year olds. We also used a vertex-wise method to examine the cohort differences in cortical thickness across the entire brain. Third, we used mediation analyses to test whether differences in *g* (indicated by the same 3 cognitive tests taken by both cohorts) between the samples could be accounted for by differences in brain structure.

## 2. Method

### 2.1. Participants

Members of both the Lothian Birth Cohort 1921 (LBC1921; Deary et al., 2004b) and the Lothian Birth Cohort 1936 (LBC1936; Deary et al., 2007, 2012) studies were included in the present analysis. Both cohorts are studies of aging that follow up individuals who, at the age of 11 years, took part in the Scottish Mental Survey of 1932 or 1947. The cohorts have been followed up at multiple waves in later life; for the present study, we focus on data from the fifth wave of the LBC1921 (total $n = 59$, mean age = 92.1 years, standard deviation [SD] = 0.34) and the second wave of the LBC1936 (total $n = 866$, mean age = 72.5 years, SD = 0.71). At these waves, $n = 53$ members of the LBC1921 and $n = 731$ members of the LBC1936 attended for a structural MRI scan (as described below, the final matched sample involved $n = 42$ LBC1921 members and $n = 126$ LBC1936 members). In the LBC1921 cohort, cognitive/medical testing and brain scanning were completed on the same day in all but a few cases (mean gap = 0.04 days, SD = 0.27). In the LBC1936, the participants all made 2 separate visits (mean gap = 65.04 days, SD = 39.57).

Approval for the LBC1921 study was obtained from the Lothian Research Ethics Committee (wave 1: LREC/1998/4/183; wave 3: 1702/98/4/183) and the Scotland A Research Ethics Committee (waves 4 and 5: 10/S1103/6). Approval for the LBC1936 study was obtained from the Multicentre Research Ethics Committee of Scotland (wave 1: MREC/01/0/56), the Lothian Research Ethics Committee (wave 1: LREC/2003/2/29), and the Scotland A Research Ethics Committee (waves 2 and 3: 07/MRE00/58). All participants provided written, informed consent before any measurements were taken.

### 2.2. Measures

#### 2.2.1. Brain MRI acquisition and volumetric processing

Brain MRI acquisition parameters were described in detail for the LBC1936 by Wardlaw et al. (2011). All subjects (from both