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Brain white matter damage in aging and cognitive ability in youth and older age☆

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ABSTRACT

Cerebral white matter hyperintensities (WMH) reflect accumulating white matter damage with aging and impair cognition. The role of childhood intelligence is rarely considered in associations between cognitive impairment and WMH. We studied community-dwelling older people all born in 1936, in whom IQ had been assessed at age 11 years. We assessed medical histories, current cognitive ability and quantified WMH on MR imaging. Among 634 participants, mean age 72.7 (SD 0.7), age 11 IQ was the strongest predictor of late life cognitive ability. After accounting for age 11 IQ, greater WMH load was significantly associated with lower late life general cognitive ability ($\beta = -0.14$, $p < 0.01$) and processing speed ($\beta = -0.19$, $p < 0.001$). WMH were also associated independently with lower age 11 IQ ($\beta = -0.08$, $p < 0.05$) and hypertension. In conclusion, having more WMH is significantly associated with lower cognitive ability, after accounting for prior ability, age 11IQ. Early-life IQ also influenced WMH in later life. Determining how lower IQ in youth leads to increasing brain damage with aging is important for future successful cognitive aging.

1. Introduction

White matter hyperintensities (WMH) are a common sign of cerebrovascular disease visible on brain imaging in older people (O'Sullivan, 2008). WMH contribute substantially to loss of independence at older ages through a 3-fold increased risk of stroke and a 2-fold increased risk of dementia (Debette and Markus, 2010); in addition, WMH accelerate aging-related cognitive decline (Debette and Markus, 2010; O'Sullivan, 2008; Schmidt et al., 2007). Although previously regarded as clinically "silent," WMH are now recognized to be associated with subtle neurological symptoms (Haley et al., 2009) and subjective awareness of cognitive decline (Silbert et al., 2009). It is generally considered that the cognitive impairment seen with WMH (Almkvist et al., 1992) is caused by the WMH and not related to premorbid cognitive ability.

Childhood intelligence is the strongest predictor of late-life cognitive ability (Deary et al., 2003) and may protect against the effects of cognitive aging (Stern, 2009). Higher childhood intelligence is also associated with many health outcomes across the life course, including a lower risk of vascular dementia (Deary et al., 2009, 2010b). Similarly, higher educational attainment is also associated with decreased incidence of dementia (Dufouil et al., 2003), an association that is as yet unexplained. Early-life cognitive ability might therefore influence the risk of developing cerebrovascular disease including WMH.

Many longitudinal studies show that WMH progression is associated with worsening cognition at older ages and that WMH progression is worst in those with more WMH at inception (Bartres-Faz et al., 2001; Debette and Markus, 2010; Schmidt et al., 2007) (we summarize other longitudinal studies not included in those reviews in Supplementary Table 1). Most studies adjusted for educational level and other confounds (Bartres-Faz et al., 2001; Schmidt et al., 2007) (Supplementary Table 1), but most did not examine whether prior cognitive ability or educational level modified the longitudinal WMH–cognition association or was associated with cross-sectional WMH burden. In 1 study of 800

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individuals, the association between WMH and impaired cognition in older age was strongest in those with lower educational level (Dufouil et al., 2003). In another study, increased duration of education was associated with less executive dysfunction, but not with WMH severity, in 475 patients with stroke (Ojala-Oksala et al., 2012); however, this study may have been underpowered to detect any education–WMH burden association.

A few studies of WMH and cognition were able to control for prior cognitive ability using a validated mental test obtained in youth (Deary et al., 2003), but these were modestly powered, given the expected effect sizes (e.g., about 100 individuals of nearly 80 years of age (Deary et al., 2003; Murray et al., 2012), or 233 to 249 participants nearly 70 years of age (Murray et al., 2011, 2012) and did not consider the effect of stroke. Although these showed an important association between IQ at age 11 years and late-life cognitive ability, along with the well-documented association between WMH and late-life cognitive decline, they did not find (and were probably underpowered to do so) an association between age 11 IQ and WMH or other factors that might explain why lower childhood intelligence may increase the risk of vascular dementia (Deary et al., 2010b).

We hypothesized that childhood IQ would account not just for much of cognitive ability in older age, but would explain some of the apparent cross-sectional WMH–cognitive ability association in later life, and that lower childhood IQ would be associated with increased WMH. We used both qualitative (visual scores) and quantitative (WMH volume) indicators of white matter damage, examined 3 key cognitive domains, and used a large, narrow-age cohort to minimise the powerful effect of age on progressing vascular disease.

2. Methods

2.1. Participants

The LBC1936 are community-dwelling surviving members of the Scottish Mental Survey of 1947, who were all born in 1936 and sat the Moray House Test No. 12 (MHT) of general intelligence at age 11 years. Most were resident in Edinburgh and the surrounding Lothians when initially recruited at a mean age of 70 years (Deary et al., 2007). Here, we use data from the second wave of testing (mean age = 72.7 years, SD = 0.7 years), at which time 700 participants underwent brain structural magnetic resonance imaging (MRI). Of the 700, 672 had all relevant sequences to assess WMH volumes (detailed below) (Wardlaw et al., 2011). Participants with Mini Mental State Examination scores <24 were excluded as scores below this level are commonly taken to be indicative of possible pathological cognitive impairment. The current analyses (see below) required complete data for all covariates, resulting in a final sample of 634 adults (men, n = 337, 53.2%).

Written informed consent was obtained from all participants under protocols approved by the Lothian (REC 07/MRE00/58) and Scottish Multicentre (MREC/01/0/56) Research Ethics Committees. The study was conducted according to the STROBE criteria (www.equator-network.org).

The participants provided their history of hypertension, diabetes, hypercholesterolemia (in each case, a medical diagnosis or current medication for these conditions), smoking status (which we classified as current/former smoker or never smoked) and of vascular disease including medically confirmed myocardial infarction and of stroke. Details were checked with the study medical advisor and family doctor or hospital records where necessary. Details of the full LBC 1936 assessment protocol have been published (Deary et al., 2007).

2.2. MRI brain image acquisition and processing

All MRI data were acquired using a 1.5T GE Signa Horizon HDxt clinical scanner (General Electric, Milwaukee, WI) operating in research mode and using a self-shielding gradient set with maximum gradient of 33 mT/m, and an 8-channel phased-array head coil. We acquired T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR) and T2* axial structural sequences, the full details of which have been published previously (Wardlaw et al., 2011) but are provided in Supplementary Table 2.

All analyses were performed with the analysts blinded to cognitive and all clinical data, and, along with the validation, are described in detail in Supplementary Table 2. We defined "WMH" as the collective term for punctate or diffuse areas in the white matter and deep gray matter of the cerebral hemispheres or in the brainstem that were 3 mm or larger in diameter and hyperintense with respect to normal-appearing white and gray matter on T_2-weighted and FLAIR images; some hypointensity on T_1-weighted MRI was allowed, as long as this was not as hypointense as cerebrospinal fluid (CSF). We appreciate that not all would agree with including deep gray and white matter hyperintensities in the term WMH, but we are simply using it as an operational term in this instance. We defined infarcts as cortical or large subcortical areas of hyperintensity on T2-weighted or FLAIR, consistent with cerebromalacea and in a vascular distribution. Areas of tissue loss and replacement by CSF due to infarcts (including lacunes) were also included in the stroke lesion volume. Where stroke lesions were occasionally contiguous with WML, the boundary between the 2 was determined by evaluation of the WML and underlying anatomy in the contralateral hemisphere and neuroradiological knowledge.

We co-registered each subject's structural MRI scans using FLIRT (http://www.fmrib.ox.ac.uk/fsl) and measured intracranial volume (ICV), total brain tissue volume, cerebrospinal fluid (CSF) volume, and WMH volume using a validated semi-automated image processing tool, MCMxxxVI (available for download at http://sourceforge.net/projects/bric1936/), which implements multispectral color fusion and minimum variance quantization (Valdes Hernandez et al., 2010) and performs at least as well as other multispectral methods (Valdes Hernandez et al., 2012a). MCMxxxVI maps 2 or more different MRI sequences (e.g., FLAIR and T2*) that display the tissues/lesions at different signal intensity levels to the red/green/blue (RGB) color space. It then reduces the color levels of the fused image to 32 clusters using minimum variance quantisation. To segment the WMH, the T2*-weighted sequence was mapped to the red and FLAIR was mapped to the green color space. The subarachnoid space and ventricles appear in red and WMH and any cortical or other discrete hyperintense infarcts appear in yellow. Further details of the tissue segmentation are given in Supplementary data.

We visually inspected all segmented images and manually edited any incorrectly classified tissues. We also identified and masked separately any visible cortical, cerebellar, or subcortical infarcts or lacunes to exclude them from erroneously influencing the WMH or CSF volumes. Neuroradiological experts identified these infarcts according to established diagnostic criteria as wedge-shaped or rounded lesions, conforming to a vascular territory, with tissue atrophy and signal characteristics consistent with malacic change. Infarcts, defined as above, were separated from WMH manually by thresholding the FLAIR sequences using a region-growing algorithm from Analyze 10.0 (http://www.analyzedirect.com/Analyze/).

Three different WMH volume measures ("WMH volume," "percentage of WMH volume in ICV," and "percentage of WMH volume in brain tissue volume") all correlated very highly (0.99 to 1.00), so we used only the "percentage of WMH in ICV" in the statistical analysis. Separately, and blinded to all other data, an expert neuroradiologist provided a WMH visual Fazekas score in periventricular and subcortical areas (Fazekas et al., 2003) using FLAIR- and T2-weighted sequences.