Structural brain MRI trait polygenic score prediction of cognitive abilities

Structural brain MRI trait polygenic score prediction of cognitive abilities

Michelle Luciano*[a,b] , Riccardo E Marioni[a,c,d], Maria Valdés Hernández[a,e,f,g], Susana Munoz Maniega[a,e,f, g], Iona F Hamilton[a,e,f, g] Natalie A. Royle[a,e,f,g], Generation Scotland[h], Ganesh Chauhan[i,j] , Joshua C. Bis[k,l], Stephanie Debette[i,j,m,n], Charles DeCarli[o], Myriam Fornage[p,q], Reinhold Schmidt[r], M. Arfan Ikram[s], Lenore J. Launer[t], Sudha Seshadri[m,u], the CHARGE Consortium[m,u], Mark E. Bastin[a,e,f,g], David J. Porteous[a,h], Joanna Wardlaw[a,e,f,g], Ian J Deary[a,b]

a. Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK

b. Department of Psychology, University of Edinburgh, Edinburgh, UK

c. Medical Genetics Section, Centre for Genomic and Experimental Medicine, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK

d. Queensland Brain Institute, The University of Queensland, Brisbane, Australia

e. Brain Research Imaging Centre, University of Edinburgh, Edinburgh, United Kingdom

f. Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, United Kingdom

g. Scottish Imaging Network, A Platform for Scientific Excellence (SINAPSE) Collaboration, Department of Neuroimaging Sciences, University of Edinburgh, Edinburgh, United Kingdom

h. Medical Genetics Section, Centre for Genomic and Experimental Medicine, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK

i. Inserm Research Center for Epidemiology and Biostatistics (U897) - Team Neuroepidemiology, Bordeaux, France

j. University of Bordeaux, Bordeaux, France

k. Cardiovascular Health Research Unit, University of Washington, Seattle, WA

l. Department of Medicine, University of Washington, Seattle, WA

m. Department of Neurology, Boston University School of Medicine, Boston, Massachusetts, USA

n. Department of Neurology, Bordeaux University Hospital, Bordeaux, France

o. Department of Neurology and Center for Neuroscience, University of California at Davis, Davis, CA

p. Brown Foundation Institute of Molecular Medicine, Division of Epidemiology, School of Public Health, University of Texas Health Science Center at Houston, Houston, TX

q. Human Genetics Center, Division of Epidemiology, School of Public Health, University of Texas Health Science Center at Houston, Houston, TX

r. Department of Neurology, Medical University Graz, Graz, Austria

s. Departments of Epidemiology, Radiology and Neurology at Erasmus MC University Medical Center, Rotterdam, The Netherlands

t. Laboratory of Epidemiology, Demography, and Biometry, National Institute on Aging, Bethesda, MD, USA

u. Framingham Heart Study

* Corresponding author: michelle.luciano@ed.ac.uk, Psychology, University of Edinburgh, 7 George Square, EH8 9JZ, UK

Keywords

Polygenic prediction; white matter hyperintensities, brain infarct, intracranial volume, hippocampal volume, total brain volume, general cognitive ability

Structural brain magnetic resonance imaging (MRI) traits share part of their genetic variance with cognitive traits. Here, we use genetic association results from large meta-analytic studies of genome-wide association for brain infarcts, white matter hyperintensities, intracranial, hippocampal and total brain volumes to estimate polygenic scores for these traits in three Scottish samples: Generation Scotland: Scottish Family Health Study (GS:SFHS), and the Lothian Birth Cohorts of 1936 (LBC1936) and 1921 (LBC1921). These five brain MRI trait polygenic scores were then used to 1) predict corresponding MRI traits in the LBC1936 (numbers ranged 573 to 630 across traits) and 2) predict cognitive traits in all three cohorts (in 8,115 to 8,250 persons). In the LBC1936, all MRI phenotypic traits were correlated with at least one cognitive measure; and polygenic prediction of MRI traits was observed for intracranial volume. Meta-analysis of the correlations between MRI polygenic scores and cognitive traits revealed a significant negative correlation (maximal r=0.08) between the hippocampal volume polygenic score and measures of global cognitive ability collected in childhood and in old age in the Lothian Birth Cohorts. The lack of association to a related general cognitive measure when including the GS:SFHS points to either type 1 error or the importance of using prediction samples that closely match the demographics of the genome-wide association samples from which prediction is based. Ideally, these analyses should be repeated in larger samples with data on both MRI and cognition, and using MRI GWA results from even larger meta-analysis studies.

Structural brain MRI traits and cognitive abilities are heritable, with over 50% of the variance for some MRI traits, e.g, frontal lobe volumes and white matter hyperintensities, being due to genes (Deary *et al.* 2009; Peper *et al.* 2007). Some of these MRI traits have been shown to share genetic variance with cognitive measures (Betjemann *et al.* 2010; Bohlken *et al.* 2014; Posthuma *et al.* 2002). Here, we test whether the additive effect of common DNA single nucleotide polymorphisms (SNPs) influencing cerebral white matter hyperintensities burden (WMH), brain infarcts (BI), hippocampal (HV), total brain (TBV) and intracranial (ICV) volumes predict variance in measures of cognitive ability. These MRI polygenic scores will be based on the results of four genome-wide association (GWA) studies (Bis *et al.* 2012; Debette *et al.* 2010; Fornage *et al.* 2011; Ikram *et al.* 2012), and estimated in three Scottish cohorts who have been measured on processing speed, memory, verbal and executive function. Firstly, we will establish whether the brain MRI polygenic scores predict their respective MRI trait in one of the cohorts who have MRI data. Where this is confirmed, we expect that common SNPs influencing these MRI traits will explain variance in the cognitive traits.

Various brain MRI structural traits are associated with cognitive ability (Andreasen *et al.* 1993; Haier *et al.* 2004). The most investigated of these is TBV, which correlates 0.33 with intelligence, as estimated from a meta-analysis of 37 samples (n=1530) (McDaniel 2005). Twin studies have supported complete genetic mediation of this relationship in adults (Posthuma *et al.* 2002); and in children, genetic overlap has been shown between measures of TBV, neocortex, white matter and prefrontal cortex with a range of cognitive indices (IQ, reading ability, processing speed) (Betjemann *et al.* 2010). ICV, which might be considered as a premorbid/maximal brain size measure, has been associated with

vocabulary performance (Schottenbauer *et al.* 2007), and with semantic memory, executive function and spatial ability when adjusting for current brain pathology in older people (Farias *et al.* 2012). HV has largely been investigated in relation to memory abilities. A meta-analysis of 33 studies reporting correlations between HV and memory performance showed a negative correlation of 0.25 for children and young adult samples, and a positive correlation (0.10) in older samples (Van Petten 2004). Heterogeneity within older sample estimates indicated a variable association dependent on age-related changes, possibly influenced more by environmental factors, which have a greater effect on HV in old age than do genes (Sullivan *et al.* 2001).

Other brain MRI traits have shown significant associations with particular cognitive domains or in specific demographic groups. WMH, for example, are mainly associated with impaired executive functioning, particularly in ageing populations where WMH are more prevalent (Farias *et al.* 2012; Gunning-Dixon & Raz 2000; Hedden *et al.* 2012). A twin study of older men showed that 70-100% of the correlation between WMH and cognitive traits was due to common genes (Carmelli *et al.* 2002). BIs are also related to cognitive dysfunction and decline in the elderly, with rates being increased even in persons with covert BI in the absence of clinical stroke events (Vermeer *et al.* 2003). The genetic underpinning of this relationship is unknown.

The genetic covariance between brain MRI and cognitive traits provides the rationale for our investigation which aims to establish whether the variability in cognition can be partly explained by structural brain differences. No common genes of large effect (e.g., >5% variance) have been reported for brain MRI traits. Therefore, we create brain MRI polygenic scores based on the summative influence of SNPs with differing levels of effect size (i.e.,

from significant to non-significant effects) from recent GWA meta-analysis studies (Bis *et al.* 2012; Debette *et al.* 2010; Fornage *et al.* 2011; Ikram *et al.* 2012). We test whether these polygenic scores are predictive of 1) their respective MRI trait, and 2) of cognitive variation.

Material and Methods

Cohorts

Brain MRI polygenic profile scores were calculated in three independent Scottish cohorts: Generation Scotland: Scottish Family Health Study (GS:SFHS), the Lothian Birth Cohort 1936 (LBC1936), and the Lothian Birth Cohort 1921 (LBC1921). GS:SFHS is a large population family-based study of around 24,000 Scottish participants sampled between the years 2006 and 2011 (www.generationscotland.org/); 10,000 participants were selected for genome-wide analysis based on: Caucasian ethnicity, being born in the UK, and full phenotype data (Kerr *et al.* 2013). In the current analysis only unrelated subjects were included, leaving an analysis sample of 6,814. The mean age of the sample was 55.5 years (SD=11.4) at testing (59% women). The LBC samples comprise relatively healthy individuals born in 1921 or 1936 in the Edinburgh area, most of whom had completed the Moray House Test No. 12 (MHT) assessment of general intelligence in the Scottish Mental Surveys of 1932 or 1947 at a mean age of 11 years (Deary *et al.* 2012). The LBC1936 (n=1091; 49.8% women) were tested on the MHT and other cognitive measures in adulthood at a mean age of 69.5 years (SD=0.8). At age 73, a subset of these individuals (n=724) underwent structural MRI. The LBC1921 (n=550; 57.4% women) completed the MHT plus additional cognitive tests at a mean age of 79.1 years (SD=0.6) and later at 83.3 years (SD=0.54). Following informed consent, venesected whole blood was collected for DNA extraction for the LBC samples with both

saliva and blood being used for DNA extraction in the GS:SFHS. Ethical approval for the LBCs was obtained from Scotland's Multicentre Research Ethics Committee and local research ethics committee. GS:SFHS ethical approval was granted by the NHS Tayside Committee on Medical Research Ethics (REC Reference Number: 05/S1401/89). Research Tissue Bank status was approved by the Tayside Committee on Medical Research Ethics (REC Reference Number: 10/S1402/20), enabling generic ethical approval for medical research purposes.

MRI measures in LBC1936

Structural T2-, T2*-, FLAIR- and T1-weight brain MRI data were collected using a GE Signa 1.5 T HDXT clinical scanner. BIs were coded for size and location based on vascular territory and typical signal characteristics by consultant neuroradiologists using a validated stroke lesion rating scale (Wardlaw *et al.* 2011; Wardlaw & Sellar 1994) which differentiates infarcts into cortical, lacunar, borderzone and brainstem/cerebellar. Lacunar infarcts were coded as being cavitated or not (Wardlaw *et al.* 2013). BI of any size and location were present in 93 individuals and absent in 537. WMH measured in the white matter, subcortical grey matter including cerebellum and brainstem were quantified semi-automatically with MCMxxxVI (Hernandez Mdel *et al.* 2010). Images were inspected and false positive and negative lesions manually corrected (http://www.bric.ed.ac.uk/research/imageanalysis.html). Focal stroke lesions were masked manually to distinguish them from other structures. The dependent measure was the natural logarithm(WMH burden in mL +1). ICV includes the contents within the inner skull table including venous sinuses and has its inferior limit in the axial slice just superior to the tip of the odontoid peg at the foramen magnum and superior to the inferior limits of the cerebellar tonsils. The ICV was obtained semi-automatically using the T2*W sequence. The

first approximation of the ICV was obtained automatically using the Object Extraction Tool in Analyze 9.0. Then, the cervical spinal cord inferior to the inferior boundary was removed manually, along with the pituitary gland (in cases where this latter structure was included). HV was obtained after an automatic segmentation of left and right hippocampi using FSL tools (www.fmrib.ox.ac.uk/fsl) and an ageing template. The resulting automatically segmented masks were visually assessed for accuracy, and manually edited using Analyze 9.0 (Mayo Clinic, AnalyzeDirect, Inc. Mayo Clinic) if required. Mean of left and right hippocampal volumes was used. TBV (mm^3) was defined by the volume of the cerebrospinal fluid, venous sinuses and meninges subtracted from the ICV. To correct for variation in head size between individuals, HV and TBV were expressed as percentages of ICV.

Cognitive measures collected in all cohorts

In GS:SFHS, four cognitive ability tests were administered: the Wechsler Digit Symbol Substitution Test (DS), Wechsler Memory Scale Logical Memory Test (sum of immediate and delayed recall of one paragraph) (LM), the phonemic Verbal Fluency Test using the letters C, F, and L, each for one minute (VF), and the Mill Hill Vocabulary Scale combining junior and senior synonyms (MHV) (Smith *et al.* 2006). In the LBC samples, DS, LM and VF tests were administered, but instead of the MHV, the National Adult Reading Test (NART) (Nelson 1982) was used to index vocabulary ability. For the LBC1921, DS was only measured at age 83 years, where the sample size was reduced (n=302). A composite score of these four measures (or 3 age 79 measures for the LBC1921) was formed by deriving regression-based factor scores from an unrotated principal components analysis which explained 45%-55.3% of variance across cohorts. In addition to these four overlapping tests across the three

cohorts, LBC samples had overlapping MHT scores from childhood (MHT11) and old-age (MHT).

Genotyping

Genotyping in the GS:SFHS and LBC samples was performed at the Wellcome Trust Clinical Research Facility Genetics Core, Edinburgh (www.wtcrf.ed.ac.uk). GS:SFHS samples were genotyped on the Illumina HumanOmniExpressExome-8 v1.0 DNA Analysis BeadChip using Infinium chemistry (Marioni *et al.* 2014). In the LBC samples, Illumina Human610-Quadv1 Chip whole genome genotyping was available. Genotype quality control procedures are described elsewhere (Davies, 2011), but briefly, necessary exclusion were made for gender discrepancies, individual relatedness, and non-Caucasian descent. Good quality genotyping information was available for 509 (LBC1921) and 1005 (LBC1936) Caucasian individuals.

Statistical Analysis

Five sets of brain MRI polygenic scores—BI, WMH, ICV, TBV, and HV—were estimated using SNP association results from GWA meta-analyses of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium (Bis *et al.* 2012; Debette *et al.* 2010; Fornage *et al.* 2011; Ikram *et al.* 2012). In these studies, GWA was performed using HapMap release 22, Build 36 imputed data in Caucasian samples ranging in size from 8175 (mean age 67.5 ±7.7 years) to 9401 (the mean age of each of the contributing cohorts was as follows: 76.2 ±5.4, 63.2 ±4.4, 65.3 ±8, 71.7 ±4.8, 63.9 ±11.3, 72.9 ±7.9, and 67.2 ±5.3). See Supplementary Table 1 (available on the Cambridge Journals Online website) for a comparison of age characteristics with the prediction cohorts.

A series of brain MRI polygenic scores were estimated in the GS:SFHS and LBC samples by inclusion of SNPs with varying association p-values—$p<0.01$, $p<0.05$, $p<0.1$, $p<0.5$, $p<1$—from the GWA meta-analyses. These scores were calculated on observed genotype data using the profile scoring function in PLINK software (Purcell *et al.* 2007) and represented the sum of individual SNP effects whereby the meta-analytic effect size (Z-score/beta) was weighted by the number of copies (0/1/2) of the effect allele carried by the individual. Prior to calculating these scores, exclusions of SNP data were made in the three cohorts for: minor allele frequency <0.05, Hardy-Weinberg Equilibrium test $<px10^{-7}$, and strand ambiguity (AT and GC SNPS). To minimise any bias caused by correlated SNPs entering the polygenic score, remaining SNPs were pruned for linkage disequilibrium based on r^2 being less than 0.25 within a 200-SNP sliding window. As part of profile scoring, the remaining SNPs were then matched with those from the GWA meta-analysis results. Whereas the GWA results were for ~2.5 million SNPs, only a subset of these (at most ~112,000) were used in polygenic score estimation. Supplementary Table 2 shows the number of SNPs included in the calculation of the polygenic scores. In the polygenic score calculation, missing genotypes for any individual were imputed based on the observed SNP allele frequency in the cohort.

Multiple regression was used to test the association between brain MRI polygenic scores and brain MRI traits in the LBC1936. Predictors included: brain MRI polygenic score, age at MRI scan, sex, three population stratification principal components (seeDavies *et al.* 2011), and the number of non-missing SNPs forming the score for each individual (less reliable polygenic scores will be formed for individuals with a greater amount of missing data). The dependent measure was the MRI trait corresponding with the MRI polygenic score in the

prediction model. ICV was additionally entered as a covariate in the analysis of WMH in line with the GWA study of WMH (Fornage *et al.* 2011). Sensitivity analyses for all MRI dependent measures were performed by excluding 43 individuals with self-reported stroke. The LBC1936 was a relatively healthy sample (no self-reported dementia) and consistent with the previous GWA studies we do not adjust for other genotypes such as APOE. Regression analyses were performed for polygenic scores at each SNP inclusion criterion ($p<0.01$, $p<0.05$, $p<0.1$, $p<0.5$, $p<1$). Because the polygenic scores at different SNP inclusion are non-independent, we made a Bonferroni correction to our alpha level of .05 for the five polygenic MRI traits, which gave an adjusted significance level of .01.

For the cognitive measures, similar regression models were tested, but with age at MRI scanning replaced by age at cognitive test. Standardised betas from the regression models for the cognitive traits were meta-analysed under a random effects model in R (MAc package) (R Development Core Team 2008) giving an overall effect size and standard error. Given the inter-correlations among the four cognitive tests and among the five MRI polygenic traits we made an alpha-level adjustment based on a matrix spectral decomposition (Nyholt, 2005) of these traits (g was not included because it is a composite measure of the cognitive tests, and we chose one polygenic score ($p<1$ inclusion threshold) to avoid dependency among polygenic scores at differing SNP p-value inclusion levels). Using the largest cohort, GS:SFHS, we identified 8.86 effective traits to give an adjusted alpha level of .006. Heterogeneity between sample estimates was tested via Cochran's Q statistic.

Results

Polygenic prediction of MRI traits in the LBC1936

The sample size varied between 573 (WMH) and 629 (BI). ICV was the only variable to show significant associations at the corrected alpha level ($p<0.01$); correlations ranged 0.08-0.10 across all p-value polygenic inclusion criteria (Supplementary Table 4). The HV polygenic score was most strongly correlated with HV at the polygenic $p<0.50$ inclusion ($r=0.08$, $p=0.04$) and polygenic $p<1$ inclusion ($r=0.07$, $p=0.05$). Polygenic scores for TBV at the polygenic $p<0.01$ inclusion was correlated .08 with TBV ($p=0.02$). For WMH, correlations of 0.08 and 0.09 ($p<0.05$) were observed at $p<0.05$, $p<0.50$ and $p<1$ polygenic inclusion thresholds. All BI polygenic score correlations showed correlational p-values greater than 0.05 with BI. Exclusion of stroke cases did not alter the polygenic score effects, thus, subsequent results are reported for the larger sample to reduce the standard error of the estimates.

Correlation between MRI and cognitive traits in LBC1936

Phenotypic correlations between MRI traits and the main cognitive traits of interest in the LBC1936 (n ranged 570 to 629) are shown in Supplementary Table 3. With the exception of HV, all brain MRI traits were significantly correlated with at least one cognitive trait. BI correlated significantly (negatively) with all cognitive traits (n ranged 625 to 629) and TBV correlated significantly (positively) with all traits except NART (n ranged 619 to 623).

Polygenic prediction of cognitive traits in all cohorts

Meta-analysis results of the correlations between the brain MRI polygenic scores (at differing polygenic p-value inclusion intervals) and cognitive measures are shown in Table 1.

The only significant correlations (at the corrected alpha level) to demonstrate consistency across differing polygenic p-value threshold scores were for HV with MHT11 and MHT in old age (at polygenic $p<0.50$ and 1 thresholds). For MHT11, the correlational p-value was .003 and for MHT, it was .003. A negative correlation was observed such that a smaller HV was related to better MHT scores. Forest plots for these variables (only measured in the LBC samples) and for a comparable measure (general cognitive ability) in all three cohorts are shown in Supplementary Figure 1. For TBV, heterogeneity was found between cohort estimates for DS, MHT11, and MHT.

TABLE 1 ABOUT HERE

Discussion

Our study showed that MRI ICV polygenic scores derived from GWA results on around 10,000 individuals (CHARGE) were predictive of variance in ICV in 624 subjects aged 72. On a phenotypic level, BI and WMH were negatively correlated with cognitive measures in this cohort, whereas the cranial and TBV measures were positively correlated. A meta-analysis of this and another elderly cohort showed HV polygenic scores were negatively correlated with the same general cognitive ability test measured in childhood and old age, explaining up to 1% of cognitive score variance. No other brain MRI polygenic scores were significantly associated with any other cognitive traits in the meta-analyses including all three Scottish cohorts.

This is the first study to test whether the SNP effects reported in current GWA studies of brain MRI traits are predictive of variance in these traits in an independent sample. At a significance level corrected for multiple testing, we confirm this for ICV, and for other traits

(WMH, TBV, and HV) at an unadjusted alpha level of .05. The amount of variance explained by these polygenic effects, although small, is consistent with other polygenic prediction studies of psychiatric and disease traits and is argued to increase with increases in size of the genome-wide association samples on which prediction is based (Dudbridge 2013). The lack of polygenic prediction for BI is likely due to the small number of individuals in our sample with BI (14.8%); as a dichotomous variable this analysis was less powered than those of continuous traits.

HV polygenic scores showed the strongest positive correlations with HV at polygenic $p<0.5$ and $p<1$ inclusion thresholds (although not significant at a corrected alpha level). It was at these thresholds that we observed a significant (negative) correlation (at a corrected alpha level) between polygenic variation in HV and phenotypic variation in MHT despite a lack of association between phenotypic variation in HV and MHT. This is an interesting finding given that in young adulthood, HV shows a negative phenotypic correlation at least with measures of memory, an aspect of general cognitive ability. Incomplete synaptic pruning during childhood and adolescence has been offered as an explanation for the negative association between HV and cognition in earlier life (Foster *et al.* 1999); and if genes influence pruning then it might be that this variation is driving the negative correlation between HV polygenic scores and general cognitive ability in our sample.

Alternatively, the HV polygenic score derived in our study might not be a valid measure of variation in HV because it did not significantly predict HV, therefore, any correlation with cognition could be a false positive finding. That a similar measure of general cognitive ability was not found to be associated with HV polygenic scores in the meta-analysis of all cohorts further supports this finding representing type 1 error. If it is important for the independent

prediction samples to closely match the samples used in the GWA study on which polygenic scores are based, then the LBC samples more closely matched the brain MRI GWAS samples in age (being elderly), whereas GS:SFHS was predominantly comprised of individuals under the age of 60 years (62%). The polygenic scores would therefore represent genetic effects that are important in old age, so it follows that prediction is going to be more reliable in older adults. However, the observation in the LBC samples that HV polygenic scores did not predict vocabulary or the general cognitive factor (results not shown), which are strongly correlated with MHT scores again points to type 1 error.

In conclusion, polygenic effects on MRI ICV, determined in a relatively small GWA study, were predictive of phenotypic trait variation in ICV in an independent sample. The lack of association between ICV polygenic scores and cognitive ability in the larger meta-analysis sample might suggest that other types of genetic variants (e.g., rare, structural) explain their genetic covariance. Larger GWA studies of WMH, TBV, HV and BI will likely improve the polygenic prediction of these traits in independent samples. Polygenic scores based on these larger studies should then be investigated in relation to cognition. Improvements in the harmonization of imaging measures across studies will also enable GWA results for other brain MRI measures such as laterality to be included.

Acknowledgements

We thank all participants and research assistants, including the general practitioners and the Scottish School of Primary Care.

Financial support

GS:SFHS has received core funding from the Chief Scientist Office (CSO) of the Scottish Government Health Directorates CZD/16/6 and the Scottish Funding Council HR03006. Phenotype collection in the LBC1921 was supported by the BBSRC, The Royal Society, and the CSO of the Scottish Government. LBC1936 phenotype collection was supported by Research Into Ageing (now part of Age UK's The Disconnected Mind project). LBC genotyping was supported by the UK's Biotechnology and Biological Sciences Research Council (BBSRC). The work was undertaken by The University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology, part of the cross council Lifelong Health and Wellbeing Initiative (MR/K026992/1), with funding from the BBSRC and Medical Research Council. Imaging was performed in the Brain Research Imaging Centre, Edinburgh, supported by the Scottish Funding Council SINAPSE Collaboration.

Infrastructure for the CHARGE Consortium is supported in part by the National Heart, Lung, and Blood Institute (NHLBI) grant HL105756 and for the neurology working group of CHARGE (neuroCHARGE) through a grant from the National Institute on Aging (NIA), AG 033193. CDC acknowledges support from ADCC grant P30 010129. **AGES:** Age, Gene, Environment Susceptibility Reykjavik Study: This study has been funded by NIA contract N01-AG-12100 with contributions from NEI, NIDCD and NHLBI, the NIA Intramural Research Program, Hjartavernd (the Icelandic Heart Association), and the Althingi (the Icelandic Parliament). ARIC: The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by NHLBI contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C), R01HL087641, R01HL59367 and R01HL086694; National Human Genome Research Institute contract

U01HG004402; NIH contract HHSN268200625226C, NHLBI contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, N01-HC-55022, and grants R01-HL087641, U01 HL096917 and R01-HL093029 (Fornage). Infrastructure was partly supported by Grant Number UL1RR025005, a component of the National Institutes of Health and NIH Roadmap for Medical Research. **ASPS:** The Austrian Science Fond (FWF) grant number P20545-P05 and P13180. The Medical University of Graz. **CHS:** Cardiovascular Health Study: This CHS research was supported by NHLBI contracts HHSN268201200036C, HHSN268200800007C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086; and NHLBI grants HL080295, HL087652, HL105756, HL103612, HL068986, and HL120393 with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided through AG023629, R01AG15928, and R01AG20098 from NIA. A full list of principal CHS investigators and institutions can be found at CHS-NHLBI.org/. The provision of genotyping data was supported in part by the National Center for Advancing Translational Sciences, CTSI grant UL1TR000124, and the National Institute of Diabetes and Digestive and Kidney Disease Diabetes Research Center (DRC) grant DK063491 to the Southern California Diabetes Endocrinology Research Center. **FHS:** Framingham Heart Study: This work was supported by the NHLBI's Framingham Heart Study (Contract No. N01-HC-25195) and its contract with Affymetrix, Inc for genotyping services (Contract No. N02-HL-6-4278). This study as also supported by grants from the NIA: AG008122 and AG033193, the NINDS (R01 NS17950), and the NHLBI (HL093029, HL096917, NS087541). **Three City Study (3C):** The 3C Study is conducted under a partnership agreement between the Institut National de la Santé et de la Recherche Médicale (INSERM), the Victor Segalen–Bordeaux II University, and Sanofi-Aventis. The Fondation pour la Recherche Médicale funded the preparation and

initiation of the study. The 3C Study is also supported by the Caisse Nationale Maladie des Travailleurs Salariés, Direction Générale de la Santé, Mutuelle Générale de l'Education Nationale (MGEN), Institut de la Longévité, Conseils Régionaux of Aquitaine and Bourgogne, Fondation de France, and Ministry of Research–INSERM Programme "Cohortes et collections de données biologiques." Lille Génopôle received an unconditional grant from Eisai. This work was supported by the National Foundation for Alzheimer's Disease and Related Disorders, the Institut Pasteur de Lille and the Centre National de Génotypage. Ganesh Chauhan is supported by a grant from the Fondation Leducq. **RS:** The Rotterdam Study is funded by Erasmus Medical Center and Erasmus University, Rotterdam, Netherlands Organization for the Health Research and Development (ZonMw), the Research Institute for Diseases in the Elderly (RIDE), the Ministry of Education, Culture and Science, the Ministry for Health, Welfare and Sports, the European Commission (DG XII), and the Municipality of Rotterdam.

Conflict of interest

None.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

References

Andreasen, N.C., Flaum, M., Swayze, V., 2nd, O'Leary, D.S., Alliger, R., Cohen, G., Ehrhardt, J. & Yuh, W.T. (1993) Intelligence and brain structure in normal individuals. *Am J Psychiatry* **150** 130-134.

Betjemann, R.S., Johnson, E.P., Barnard, H., Boada, R., Filley, C.M., Filipek, P.A., Willcutt, E.G., DeFries, J.C. & Pennington, B.F. (2010) Genetic covariation between brain volumes and IQ, reading performance, and processing speed. *Behav Genet* **40** 135-145.

Bis, J.C., DeCarli, C., Smith, A.V., van der Lijn, F., Crivello, F., Fornage, M., Debette, S., Shulman, J.M., Schmidt, H., Srikanth, V., Schuur, M., Yu, L., Choi, S.H., Sigurdsson, S., Verhaaren, B.F., DeStefano, A.L., Lambert, J.C., Jack, C.R., Jr., Struchalin, M.*, et al* (2012) Common variants at 12q14 and 12q24 are associated with hippocampal volume. *Nat Genet* **44** 545-551.

Bohlken, M.M., Brouwer, R.M., Mandl, R.C., van Haren, N.E., Brans, R.G., van Baal, G.C., de Geus, E.J., Boomsma, D.I., Kahn, R.S. & Hulshoff Pol, H.E. (2014) Genes contributing to subcortical volumes and intellectual ability implicate the thalamus. *Hum Brain Mapp* **35** 2632-2642.

Carmelli, D., Reed, T. & DeCarli, C. (2002) A bivariate genetic analysis of cerebral white matter hyperintensities and cognitive performance in elderly male twins. *Neurobiol Aging* **23** 413-420.

Davies, G., Tenesa, A., Payton, A., Yang, J., Harris, S.E., Liewald, D., Ke, X., Le Hellard, S., Christoforou, A., Luciano, M., McGhee, K., Lopez, L., Gow, A.J., Corley, J., Redmond, P., Fox, H.C., Haggarty, P., Whalley, L.J., McNeill, G.*, et al* (2011) Genome-wide

association studies establish that human intelligence is highly heritable and polygenic. *Mol Psychiatry* **16** 996-1005.

Deary, I.J., Gow, A.J., Pattie, A. & Starr, J.M. (2012) Cohort profile: the Lothian Birth Cohorts of 1921 and 1936. *Int J Epidemiol* **41** 1576-1584.

Deary, I.J., Johnson, W. & Houlihan, L.M. (2009) Genetic foundations of human intelligence. *Hum Genet* **126** 215-232.

Debette, S., Bis, J.C., Fornage, M., Schmidt, H., Ikram, M.A., Sigurdsson, S., Heiss, G., Struchalin, M., Smith, A.V., van der Lugt, A., DeCarli, C., Lumley, T., Knopman, D.S., Enzinger, C., Eiriksdottir, G., Koudstaal, P.J., DeStefano, A.L., Psaty, B.M., Dufouil, C.*, et al* (2010) Genome-wide association studies of MRI-defined brain infarcts: meta-analysis from the CHARGE Consortium. *Stroke* **41** 210-217.

Dudbridge, F. (2013) Power and predictive accuracy of polygenic risk scores. *PLoS Genet* **9** e1003348.

Farias, S.T., Mungas, D., Reed, B., Carmichael, O., Beckett, L., Harvey, D., Olichney, J., Simmons, A. & DeCarli, C. (2012) Maximal brain size remains an important predictor of cognition in old age, independent of current brain pathology. *Neurobiology of Aging* **33** 1758-1768.

Fornage, M., Debette, S., Bis, J.C., Schmidt, H., Ikram, M.A., Dufouil, C., Sigurdsson, S., Lumley, T., DeStefano, A.L., Fazekas, F., Vrooman, H.A., Shibata, D.K., Maillard, P., Zijdenbos, A., Smith, A.V., Gudnason, H., de Boer, R., Cushman, M., Mazoyer, B.*, et al* (2011) Genome-wide association studies of cerebral white matter lesion burden: the CHARGE consortium. *Ann Neurol* **69** 928-939.

Foster, J.K., Meikle, A., Goodson, G., Mayes, A.R., Howard, M., Sunram, S.I., Cezayirli, E. & Roberts, N. (1999) The hippocampus and delayed recall: bigger is not necessarily better? *Memory* **7** 715-732.

Gunning-Dixon, F.M. & Raz, N. (2000) The cognitive correlates of white matter abnormalities in normal aging: a quantitative review. *Neuropsychology* **14** 224-232.

Haier, R.J., Jung, R.E., Yeo, R.A., Head, K. & Alkire, M.T. (2004) Structural brain variation and general intelligence. *Neuroimage* **23** 425-433.

Hedden, T., Mormino, E.C., Amariglio, R.E., Younger, A.P., Schultz, A.P., Becker, J.A., Buckner, R.L., Johnson, K.A., Sperling, R.A. & Rentz, D.M. (2012) Cognitive profile of amyloid burden and white matter hyperintensities in cognitively normal older adults. *J Neurosci* **32** 16233-16242.

Hernandez Mdel, C., Ferguson, K.J., Chappell, F.M. & Wardlaw, J.M. (2010) New multispectral MRI data fusion technique for white matter lesion segmentation: method and comparison with thresholding in FLAIR images. *Eur Radiol* **20** 1684-1691.

Ikram, M.A., Fornage, M., Smith, A.V., Seshadri, S., Schmidt, R., Debette, S., Vrooman, H.A., Sigurdsson, S., Ropele, S., Taal, H.R., Mook-Kanamori, D.O., Coker, L.H., Longstreth, W.T., Jr., Niessen, W.J., DeStefano, A.L., Beiser, A., Zijdenbos, A.P., Struchalin, M., Jack, C.R., Jr.*, et al* (2012) Common variants at 6q22 and 17q21 are associated with intracranial volume. *Nat Genet* **44** 539-544.

Kerr, S.M., Campbell, A., Murphy, L., Hayward, C., Jackson, C., Wain, L.V., Tobin, M.D., Dominiczak, A., Morris, A., Smith, B.H. & Porteous, D.J. (2013) Pedigree and genotyping quality analyses of over 10,000 DNA samples from the Generation Scotland: Scottish Family Health Study. *BMC Med Genet* **14** 38.

Marioni, R.E., Davies, G., Hayward, C., Liewald, D., Kerr, S.M., Campbell, A., Luciano, M., Smith, B.H., Padmanabhan, S., Hocking, L.J., Hastie, N.D., Wright, A.F., Porteous, D.J., Visscher, P.M. & Deary, I.J. (2014) Molecular genetic contributions to socioeconomic status and intelligence. *Intelligence* **44** 26-32.

McDaniel, M.A. (2005) Big-brained people are smarter: A meta-analysis of the relationship between in vivo brain volume and intelligence. *Intelligence* **33** 337-346.

Nelson, H.E. (1982) *National Adult Reading Test (NART):Test Manual*

NFER-NELSON, Windsor

Nyholt, D. (2005, August 10). Index. Retrieved September 1, 2015, from http://neurogenetics.qimrberghofer.edu.au/matSpD/ Peper, J.S., Brouwer, R.M., Boomsma, D.I., Kahn, R.S. & Hulshoff Pol, H.E. (2007) Genetic influences on human brain structure: a review of brain imaging studies in twins. *Hum Brain Mapp* **28** 464-473.

Posthuma, D., De Geus, E.J., Baare, W.F., Hulshoff Pol, H.E., Kahn, R.S. & Boomsma, D.I. (2002) The association between brain volume and intelligence is of genetic origin. *Nat Neurosci* **5** 83-84.

Purcell, S., Neale, B., Todd-Brown, K., Thomas, L., Ferreira, M.A., Bender, D., Maller, J., Sklar, P., de Bakker, P.I., Daly, M.J. & Sham, P.C. (2007) PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet* **81** 559-575.

R Development Core Team (2008) R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing.

Schottenbauer, M.A., Momenan, R., Kerick, M. & Hommer, D.W. (2007) Relationships among aging, IQ, and intracranial volume in alcoholics and control subjects. *Neuropsychology* **21** 337-345.

Smith, B.H., Campbell, H., Blackwood, D., Connell, J., Connor, M., Deary, I.J., Dominiczak, A.F., Fitzpatrick, B., Ford, I., Jackson, C., Haddow, G., Kerr, S., Lindsay, R., McGilchrist, M., Morton, R., Murray, G., Palmer, C.N., Pell, J.P., Ralston, S.H.*, et al* (2006) Generation Scotland: the Scottish Family Health Study; a new resource for researching genes and heritability. *BMC Med Genet* **7** 74.

Sullivan, E.V., Pfefferbaum, A., Swan, G.E. & Carmelli, D. (2001) Heritability of hippocampal size in elderly twin men: equivalent influence from genes and environment. *Hippocampus* **11** 754-762.

Van Petten, C. (2004) Relationship between hippocampal volume and memory ability in healthy individuals across the lifespan: review and meta-analysis. *Neuropsychologia* **42** 1394-1413.

Vermeer, S.E., Prins, N.D., den Heijer, T., Hofman, A., Koudstaal, P.J. & Breteler, M.M. (2003) Silent brain infarcts and the risk of dementia and cognitive decline. *N Engl J Med* **348** 1215-1222.

Wardlaw, J.M., Bastin, M.E., Valdes Hernandez, M.C., Maniega, S.M., Royle, N.A., Morris, Z., Clayden, J.D., Sandeman, E.M., Eadie, E., Murray, C., Starr, J.M. & Deary, I.J. (2011) Brain aging, cognition in youth and old age and vascular disease in the Lothian Birth Cohort 1936: rationale, design and methodology of the imaging protocol. *Int J Stroke* **6** 547-559.

Wardlaw, J.M. & Sellar, R. (1994) A simple practical classification of cerebral infarcts on CT and its interobserver reliability. *AJNR Am J Neuroradiol* **15** 1933-1939.

Wardlaw, J.M., Smith, E.E., Biessels, G.J., Cordonnier, C., Fazekas, F., Frayne, R., Lindley, R.I., O'Brien, J.T., Barkhof, F., Benavente, O.R., Black, S.E., Brayne, C., Breteler, M., Chabriat, H., Decarli, C., de Leeuw, F.E., Doubal, F., Duering, M., Fox, N.C.*, et al*

(2013) Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol* **12** 822-838.

Table 1. Meta-analysis Standardised Betas (SE) between MRI Trait Polygenic Scores and Cognitive Traits. Bolded Rows Indicate Polygenic Scores that Significantly Predicted the Accompanying MRI Phenotype and for which we would expect significant correlations.

p<	Digit Symbol (N= 8020)	Verbal Fluency (N= 8250)	Logical Memory (N= 8249)	Vocabul-ary (N= 8212)	General Factor (N= 8115)	MHT11 (N= 1411)	MHT (N= 1498)
BI							
.01	0(.01)	0(.01)	0(.01)	0(.01)	0(.01)	-.06(.06)ʕ	-.04(.03)
.05	0(.01)	.03(.02)	0(.01)	-.01(.01)	.01(.01)	-.02(.03)	.03(.03)
.10	-.01(.01)	.03(.03)ʕ	-.01(.01)	-.02(.01)	0(.02)	-.05(.05)	0(.03)
.50	-.02(.01)	.01(.02)	-.01(.01)	-.03(.01)	-.02(.01)	-.04(.03)	-.02(.03)
1	-.01(.01)	.02(.02)	-.01(.01)	-.02(.01)	-.01(.02)	-.04(.03)	0(.03)
WMH							
.01	-.01(.01)	.01(.01)	0(.01)	0(.01)	0(.01)	-.01(.03)	0(.03)
.05	.01(.01)	.01(.01)	0(.01)	.01(.01)	.01(.01)	-.01(.04)	0(.05)
.10	0(.01)	0(.01)	-.02(.01)	-.01(.01)	-.01(.01)	-.05(.05)	-.03(.03)
.50	-.01(.01)	0(.01)	-.02(.01)	-.01(.01)	-.02(.01)	-.03(.04)	-.03(.04)
1	-.01(.01)	0(.01)	-.02(.01)	-.01(.01)	-.02(.01)	-.02(.04)	-.02(.03)
ICV							
.01	**-.01(.01)**	**0(.01)**	**-.02(.01)**	**0(.01)**	**-.01(.01)**	**.02(.03)**	**-.03(.03)**
.05	**0(.01)**	**.01(.02)**	**-.01(.01)**	**0(.01)**	**0(.01)**	**.03(.03)**	**-.03(.03)**
.10	**0(.02)**	**0(.01)**	**0(.01)**	**.01(.01)**	**.01(.01)**	**.04(.03)**	**-.01(.03)**
.50	**0(.02)**	**.01(.01)**	**0(.01)**	**.01(.01)**	**.01(.01)**	**.02(.03)**	**-.02(.03)**
1	**.01(.02)**	**.01(.01)**	**0(.01)**	**.01(.01)**	**.01(.01)**	**.01(.03)**	**-.02(.03)**
HV							
.01	-.02(.02)	0(.02)	-.01(.01)	-.01(.04)	-.01(.02)	-.04(.03)	-.07(.03)*
.05	0(.01)	0(.01)	-.02(.02)	-.01(.01)	-.01(.01)	-.04(.03)	-.05(.03)*
.10	-.01(.02)	0(.01)	-.01(.01)	-.01(.01)	0(.01)	-.05(.03)	-.05(.03)*
.50	-.02(.03)	0(.01)	-.02(.02)	-.03(.03)	-.02(.02)	-.08(.03)**	-.08(.03)**

1	-.03(.03)[ς]	0(.01)	-.02(.02)	-.02(.02)	-.02(.03)	-.08(.03)**	-.08(.03)**
TBV							
.01	.05(.03)[ς]	.02(.01)	0(.01)	.01(.02)	.02(.03)	-0.01(.09)[ς]	0(.05)
.05	.04(.03)	.02(.01)*	0(.01)	.01(.01)	.03(.01)*	-0.02(.08)[ς]	-0.04(.07)[ς]
.10	.04(.03)[ς]	0(.01)	-.01(.01)	-.03(.03)	.01(.01)	-0.02(.08)[ς]	-0.03(.07)[ς]
.50	.05(.03)[ς]	0(.01)	0(.01)	.02(.01)	.03(.02)	0(.07)[ς]	-0.01(.07)[ς]
1	.04(.03)[ς]	.01(.01)	0(.01)	.03(.02)	.03(.03)	0(.08)[ς]	-0.02(.08)[ς]

*p<.05; **p<.01

[ς] sample heterogeneity (p<.05):

BI: MHT11 (p<.01 inclusion), LBC1936 (r=-.01), LBC1921 (r=-.13*); Verbal Fluency (p<.1 inclusion) GS (r=0), LBC1936 (r=.07*), LBC1921 (r=.02)

HV: Digit Symbol (p<1 inclusion), GS (r=.01), LBC1936 (r=-.09*), LBC1921 (r=-.01)

TBV: Digit Symbol (p<.01, .1, .5, 1), GS (r=.01, 0, .01, .01), LBC1936 (r=.11*, .09*, .10*, .09*), LBC1921 (r=.04, .03, .05, .05); MHT11 (p<.01, .05, .1, .5, 1), LBC1936 (r=.07*, .05, .06, .07*, .07*), LBC1921 (r=-.10*, -.11*, -.11, -.08, -.08); MHT (p<.05, .1, .5, 1), LBC1936 (r=.02, .03, 06, .06), LBC1921 (r=-.11*, -.11*, -.09*, -.10*)