SUPPLEMENTAL MATERIAL

WHITE MATTER HYPERINTENSITIES ARE UNDER STRONG GENETIC INFLUENCE

Cover title: Heritability of white matter hyperintensities

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MRI parameters and quantitation of WMH

Both 3D T1-weighted scans and T2-weighted fluid-attenuated inversion recovery (FLAIR) sequence scans were used for data analysis. The following protocol was used for T1-weighted MRI scans on the 1.5T scanners in all three centres: in-plane resolution 1×1 mm with slice thickness of 1.5 mm, contiguous slices, TR/TE/TI = 1530/3.24/780 ms, and flip angle = 8. FLAIR scans were acquired axially with the same acquisition parameters on the 1.5T scanners in all three centres, i.e. TR/TE/TI = 10000/120/2800 ms, with slice thickness 3.5 mm and in-plane resolution 0.898×0.898 mm². On the 3T scanner in centre 1, we had spatial resolution of 1×1×1 mm³, TR/TE = 6.39/2.9 ms for T1-weighted scans, and TR/TE/TI = 10000/110/2800 ms, with slice thickness 3.5 mm and in-plane resolution 0.898×0.898 mm² for FLAIR scans. Intracranial volume (ICV), the sum of grey matter, white matter and cerebrospinal fluid was calculated using SPM8 (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK. http://www.fil.ion.ucl.ac.uk/spm/software/spm8/).

The contrast properties of FLAIR facilitate the possibility of automated segmentation and classification of WMH. The method has been previously described1. A parametric method1 was adapted and applied to the initial WMH detection. The extracted candidate WMH clusters were further investigated using a non-parametric kNN rule and then classified into different brain regions and deep (DWMH), periventricular (PWMH), and false WMH clusters.

The automated classification of WMHs employed in this study was carried out in the native space of the T1-weighted images. Five pre-processing steps were taken to prepare the images for the analysis, as described previously 1: (i) the FLAIR and T1 images of the same subject were coregistered using mutual information method2; (ii) segmentation3 of T1-weighted images into three separate tissue components; (iii) removal of non-brain tissue from both T1-weighted and co-registered FLAIR images using the brain mask transformed from the average mask originally defined in the standard space by inverting the deformation matrix4; (iv) inverting the spatial normalization transformation to produce the brain masks and white matter probability maps in the native space for the WMH detection and non-brain tissue removal; (v) intensity correction5 of both FLAIR and T1-weighted images after the removal of non-brain tissues. Some other smaller steps such as removal of the bright areas observed in the FLAIR sequence ventricles caused by choroid plexus and partial voluming were also carried out. SPM8 was used with Matlab R2013b (MathWorks, Natick, MA, U.S.A.) for these pre-processing steps.

References
Figure I. Path diagram for the age and sex moderated ACE twin model. WMH of twin 1 (WMH1) and 2 (WMH2) are modelled as the function of the mean parameter (M) and the latent additive (A), shared environment (C) and environment (E) factors. The mean is further modelled as a function of the k covariates $M = \mu + \beta_1 X_1 + \cdots + \beta_k X_k$, where $\mu$ is the overall mean of the phenotypes and $X_1, X_2, \ldots, X_k$ are the k covariates (such as age, sex, scanners and ICV) and $\beta_1, \beta_2, \ldots, \beta_k$ are the regression parameters of the model. The path coefficients a, c and e are the estimated loadings of the latent factors, which are further decomposed as $a = a_0 + a_{\text{age}} + a_{\text{sex}}$; $c = c_0 + c_{\text{age}} + c_{\text{sex}}$; $e = e_0 + e_{\text{age}} + e_{\text{sex}}$ to accommodate the moderating effects of age and sex. The parameter $r_a$ ($r_a=1$ for MZ twin pairs and $r_a=0.5$ for DZ twin pairs) and $r_c$ ($r_c=1$ for both MZ and DZ twin pairs) respectively denote the additive genetic and shared environmental correlations between the twin pairs.
Figure II. The path diagram for the opposite sex DZ twin pairs in the general sex heterogeneity model. For opposite DZ twin pairs, the path coefficients for the male samples $a_m$, $c_m$, $e_m$ are same as the path coefficients for the male MZ and DZ pairs. Similarly the path coefficients for the female samples $a_f$, $c_f$ and $e_f$ are also the same as the path coefficients for female MZ and DZ pairs. The correlation between the additive genetic components in opposite sex pairs is half of the genetic correlation between male-female genetic correlation $r_g$. 
<table>
<thead>
<tr>
<th>Covariate</th>
<th>Female (N=213)</th>
<th>Male (N=107)</th>
<th>Stat</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>69.54 (4.75)</td>
<td>71.14 (5.08)</td>
<td>-2.72</td>
<td>0.005</td>
</tr>
<tr>
<td>Hypertension</td>
<td>136 (63.84%)</td>
<td>79 (73.83%)</td>
<td>2.78</td>
<td>0.017</td>
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<tr>
<td>BP systolic (mmHg)</td>
<td>135.66 (17.11)</td>
<td>142.40 (17.55)</td>
<td>-3.27</td>
<td>0.001</td>
</tr>
<tr>
<td>BP diastolic (mm Hg)</td>
<td>79.97 (9.77)</td>
<td>81.61 (10.26)</td>
<td>-1.37</td>
<td>0.174</td>
</tr>
<tr>
<td>BMI</td>
<td>27.33 (4.5)</td>
<td>27.69 (3.6)</td>
<td>-0.79</td>
<td>0.436</td>
</tr>
<tr>
<td>Homocysteine (µmol/L)</td>
<td>12.84 (3.52)</td>
<td>13.41 (3.16)</td>
<td>-1.48</td>
<td>0.141</td>
</tr>
<tr>
<td>Heart attack</td>
<td>8 (3.76%)</td>
<td>7 (6.54%)</td>
<td>0.69</td>
<td>0.131</td>
</tr>
<tr>
<td>Artrial fibrillation</td>
<td>7 (3.29%)</td>
<td>5 (4.67%)</td>
<td>0.09</td>
<td>0.416</td>
</tr>
<tr>
<td>Stroke</td>
<td>6 (2.81%)</td>
<td>5 (4.67%)</td>
<td>0.29</td>
<td>0.247</td>
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</tbody>
</table>

For continuous measures, means (SD) are presented. For categorical measures, N (%) is presented. T-tests for continuous variables and chi-square tests for all other measures were used to compare between the two sexes. All the p-values were obtained using 10000 permutations.
<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Periventricular</th>
<th>Deep</th>
<th>Frontal</th>
<th>Temporal</th>
<th>Parietal</th>
<th>Occipital</th>
<th>Cerebellum</th>
<th>Brainstem</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>1.00</td>
<td>0.96</td>
<td>0.94</td>
<td>0.83</td>
<td>0.72</td>
<td>0.92</td>
<td>0.69</td>
<td>0.40</td>
<td>0.39</td>
</tr>
<tr>
<td><strong>Periventricular</strong></td>
<td>0.96</td>
<td>1.00</td>
<td>0.85</td>
<td>0.76</td>
<td>0.64</td>
<td>0.85</td>
<td>0.58</td>
<td>0.30</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>Deep</strong></td>
<td>0.94</td>
<td>0.85</td>
<td>1.00</td>
<td>0.85</td>
<td>0.76</td>
<td>0.95</td>
<td>0.76</td>
<td>0.43</td>
<td>0.42</td>
</tr>
<tr>
<td><strong>Frontal</strong></td>
<td>0.83</td>
<td>0.76</td>
<td>0.85</td>
<td>1.00</td>
<td>0.65</td>
<td>0.77</td>
<td>0.51</td>
<td>0.34</td>
<td>0.33</td>
</tr>
<tr>
<td><strong>Temporal</strong></td>
<td>0.72</td>
<td>0.64</td>
<td>0.76</td>
<td>0.65</td>
<td>1.00</td>
<td>0.68</td>
<td>0.57</td>
<td>0.41</td>
<td>0.43</td>
</tr>
<tr>
<td><strong>Parietal</strong></td>
<td>0.92</td>
<td>0.85</td>
<td>0.95</td>
<td>0.77</td>
<td>0.68</td>
<td>1.00</td>
<td>0.67</td>
<td>0.39</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>Occipital</strong></td>
<td>0.69</td>
<td>0.58</td>
<td>0.76</td>
<td>0.51</td>
<td>0.57</td>
<td>0.67</td>
<td>1.00</td>
<td>0.48</td>
<td>0.53</td>
</tr>
<tr>
<td><strong>Cerebellum</strong></td>
<td>0.40</td>
<td>0.30</td>
<td>0.43</td>
<td>0.34</td>
<td>0.41</td>
<td>0.39</td>
<td>0.48</td>
<td>1.00</td>
<td>0.58</td>
</tr>
<tr>
<td><strong>Brainstem</strong></td>
<td>0.39</td>
<td>0.25</td>
<td>0.42</td>
<td>0.33</td>
<td>0.43</td>
<td>0.32</td>
<td>0.53</td>
<td>0.58</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Pearson correlation coefficients are presented ignoring the relationship between the zygotic twin pairs.
### TABLE III. Heritability of white matter hyperintensities (WMH) volumes in whole brain (total) and different brain regions: estimates and model summary

<table>
<thead>
<tr>
<th>WMH ROI</th>
<th>ICC MZ (95% CI)</th>
<th>ICC DZ (95% CI)</th>
<th>A (95% CI)</th>
<th>C (95% CI)</th>
<th>E (95% CI)</th>
<th>P-AE</th>
<th>P-CE</th>
<th>P-E</th>
<th>Covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>0.78 (0.68,0.84) 0.39 (0.34,0.56)</td>
<td>0.77 (0.42,0.84) 0.09 (0.00,0.33)</td>
<td>0.01 (0.16,0.32) 0.22 (0.00,0.16)</td>
<td>0.97 &lt;1E-04 &lt;1E-16 111000000000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Periventricular</td>
<td>0.76 (0.66,0.83) 0.44 (0.34,0.60)</td>
<td>0.63 (0.29,0.83) 0.13 (0.00,0.43)</td>
<td>0.24 (0.17,0.34) 0.49 &lt;1E-06 &lt;1E-16 111000001100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep</td>
<td>0.78 (0.69,0.85) 0.39 (0.34,0.49)</td>
<td>0.78 (0.57,0.85) 0.00 (0.00,0.15)</td>
<td>0.22 (0.15,0.31) 1 0.014 &lt;1E-16 111000000000</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal</td>
<td>0.63 (0.48,0.74) 0.36 (0.25,0.53)</td>
<td>0.53 (0.11,0.74) 0.10 (0.00,0.26)</td>
<td>0.37 (0.26,0.52) 0.63 0.026 &lt;1E-10 111101000000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temporal</td>
<td>0.66 (0.52,0.75) 0.44 (0.29,0.60)</td>
<td>0.44 (0.05,0.74) 0.00 (0.00,0.45)</td>
<td>0.22 (0.26,0.48) 0.27 &lt;1E-04 &lt;1E-12 111000001100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parietal</td>
<td>0.71 (0.59,0.80) 0.35 (0.29,0.47)</td>
<td>0.71 (0.43,0.80) 0.00 (0.00,0.24)</td>
<td>0.29 (0.20,0.41) 1 &lt;1E-07 &lt;1E-13 111000000000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occipital</td>
<td>0.79 (0.68,0.86) 0.39 (0.34,0.47)</td>
<td>0.79 (0.63,0.86) 0.00 (0.00,0.13)</td>
<td>0.21 (0.14,0.32) 1 &lt;1E-07 &lt;1E-16 101000000001</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Cerebellum</td>
<td>0.51 (0.36,0.64) 0.47 (0.27,0.60)</td>
<td>0.07 (0.00,0.55) 0.43 (0.01,0.60)</td>
<td>0.49 (0.36,0.64) 0.04 0.738 &lt;1E-9 101010010000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brainstem</td>
<td>0.71 (0.60,0.80) 0.45 (0.31,0.62)</td>
<td>0.53 (0.16,0.79) 0.00 (0.00,0.52)</td>
<td>0.29 (0.20,0.40) 0.41 0.004 &lt;1E-16 001000000000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Standardised additive genetic (A=heritability), shared environment (C) and unique environment (E) variance components (95% confidence intervals) of WMH for different ROIs obtained using ACE model. Missing values for the covariates were imputed using the multiple imputation procedure as implemented in the R-package “mice” (van Buuren S, Groothuis-Oudshoorn K: Mice: Multivariate Imputation by Chained Equations in R. J Stat Softw 2011;45:1-67).The columns P-AE, P-CE and P-E respectively denote the p-values from the likelihood ratio test comparing ACE model vs AE, CE and E models. P-CE is also the p-value for heritability because testing the component A=0 is equivalent to testing heritability is zero. Last column indicates the significance of covariates. Significance of the p-value (p<0.05) for any of the covariates age, sex, scanners, ICV, hypertension, systolic BP, diastolic BP, BMI, homocysteine, heart attack, atrial fibrillation and stroke in that order is indicated as a string; 1=significant; 0=not-significant.
<table>
<thead>
<tr>
<th>WMH region</th>
<th>Female ICC MZ (95% CI)</th>
<th>Female ICC DZ (95% CI)</th>
<th>Male ICC MZ (95% CI)</th>
<th>Male ICC DZ (95% CI)</th>
<th>Male-Female ICC DZ (95% CI)</th>
<th>Female $h^2$ (95% CI)</th>
<th>Male $h^2$ (95% CI)</th>
<th>Test of Homogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (whole brain)</td>
<td>0.78 (0.66,0.86)</td>
<td>0.41 (0.34,0.54)</td>
<td>0.72 (0.52,0.83)</td>
<td>0.64 (0.28,0.81)</td>
<td>0.22 (0.00,0.40)</td>
<td>0.74 (0.46,0.85)</td>
<td>0.15 (0.00,0.81)</td>
<td>0.646</td>
</tr>
<tr>
<td>Periventricular</td>
<td>0.78 (0.65,0.85)</td>
<td>0.44 (0.35,0.58)</td>
<td>0.67 (0.46,0.81)</td>
<td>0.66 (0.28,0.80)</td>
<td>0.23 (0.00,0.43)</td>
<td>0.67 (0.37,0.84)</td>
<td>0.03 (0.00,0.72)</td>
<td>0.282</td>
</tr>
<tr>
<td>Deep</td>
<td>0.78 (0.66,0.86)</td>
<td>0.39 (0.33,0.48)</td>
<td>0.75 (0.54,0.86)</td>
<td>0.40 (0.27,0.72)</td>
<td>0.26 (0.00,0.39)</td>
<td>0.78 (0.59,0.86)</td>
<td>0.69 (0.04,0.86)</td>
<td>0.985</td>
</tr>
<tr>
<td>Frontal</td>
<td>0.66 (0.49,0.78)</td>
<td>0.35 (0.25,0.51)</td>
<td>0.56 (0.30,0.73)</td>
<td>0.50 (0.16,0.72)</td>
<td>0.18 (0.00,0.39)</td>
<td>0.62 (0.22,0.77)</td>
<td>0.11 (0.00,0.72)</td>
<td>0.468</td>
</tr>
<tr>
<td>Temporal</td>
<td>0.74 (0.60,0.82)</td>
<td>0.41 (0.31,0.59)</td>
<td>0.41 (0.12,0.64)</td>
<td>0.50 (0.07,0.55)</td>
<td>0.27 (0.00,0.38)</td>
<td>0.65 (0.24,0.82)</td>
<td>0.11 (0.00,0.64)</td>
<td>0.178</td>
</tr>
<tr>
<td>Parietal</td>
<td>0.72 (0.56,0.82)</td>
<td>0.36 (0.28,0.47)</td>
<td>0.66 (0.41,0.81)</td>
<td>0.41 (0.21,0.71)</td>
<td>0.24 (0.00,0.40)</td>
<td>0.62 (0.47,0.82)</td>
<td>0.50 (0.00,0.81)</td>
<td>0.975</td>
</tr>
<tr>
<td>Occipital</td>
<td>0.83 (0.72,0.89)</td>
<td>0.41 (0.36,0.50)</td>
<td>0.62 (0.37,0.77)</td>
<td>0.31 (0.19,0.49)</td>
<td>0.21 (0.08,0.29)</td>
<td>0.62 (0.65,0.89)</td>
<td>0.83 (0.22,0.77)</td>
<td>0.243</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>0.54 (0.37,0.68)</td>
<td>0.53 (0.27,0.67)</td>
<td>0.47 (0.17,0.68)</td>
<td>0.35 (0.13,0.63)</td>
<td>0.19 (0.00,0.35)</td>
<td>0.01 (0.00,0.56)</td>
<td>0.24 (0.00,0.64)</td>
<td>0.059</td>
</tr>
<tr>
<td>Brainstem</td>
<td>0.75 (0.63,0.83)</td>
<td>0.47 (0.32,0.67)</td>
<td>0.52 (0.23,0.72)</td>
<td>0.29 (0.13,0.61)</td>
<td>0.17 (0.01,0.30)</td>
<td>0.56 (0.13,0.83)</td>
<td>0.46 (0.00,0.71)</td>
<td>0.156</td>
</tr>
</tbody>
</table>

Intra-class correlations (ICC), heritability ($h^2$) and 95% confidence intervals for WMH in different ROIs obtained using heterogeneity ACE model (age, scanner and ICV adjusted). The p-value from the likelihood ratio test of homogeneity (common variances and co-variances versus separate parameters for male and female samples) is also presented.
TABLE V. Heritability of white matter hyperintensities (WMH) as a function of age and sex

<table>
<thead>
<tr>
<th>ROI</th>
<th>Age</th>
<th>Parameter Label</th>
<th>Lower Limit</th>
<th>Estimate</th>
<th>Upper Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total volume</td>
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<td>Female_H2</td>
<td>0.46</td>
<td>0.76</td>
<td>0.88</td>
</tr>
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<td>70</td>
<td>Female_H2</td>
<td>0.49</td>
<td>0.78</td>
<td>0.86</td>
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<td></td>
<td>73</td>
<td>Female_H2</td>
<td>0.08</td>
<td>0.78</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>Female_H2</td>
<td>0.01</td>
<td>0.78</td>
<td>0.88</td>
</tr>
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<td>80</td>
<td>Female_H2</td>
<td>0.00</td>
<td>0.76</td>
<td>0.91</td>
</tr>
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<td></td>
<td>83</td>
<td>Female_H2</td>
<td>0.00</td>
<td>0.74</td>
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<td>0.72</td>
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<td>0.16</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>Male_H2</td>
<td>0.00</td>
<td>0.16</td>
<td>0.81</td>
</tr>
<tr>
<td></td>
<td>73</td>
<td>Male_H2</td>
<td>0.00</td>
<td>0.16</td>
<td>0.79</td>
</tr>
<tr>
<td></td>
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Heritability estimates of WMH and their 95% confidence intervals for male (Male_H2) and female (Female_H2) at different ages under the age and sex moderated ACE model (Figure 1).

**Supplemental Video I.** A 3D movie of voxel-wise heritability of white matter hyperintensities using the binary AE model has been provided.