Mapping Genetic Influences on Brain Activation during the N-Back Working Memory Task: An fMRI Study of 315 Twins

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Introduction: Twin studies can disentangle the genetic and environmental influences on brain function. Here we report the first maps of genetic effects on brain function. We assessed the heritability of task-related brain activation on a voxel-by-voxel basis, using functional MRI (fMRI) during a working memory task in healthy twin pairs.

Methods: BOLD fMRI data were acquired during the 0-back and 2-back conditions of a spatial N-back working memory task (see Fig. 1 in [1]) in 366 twins on a 4T Bruker Medspec MRI scanner. Echo Planar Images of all twins were realigned, coregistered with the twin's 3D T1-weighted scan, spatially normalised in MNI atlas space, smoothed with an 8 mm FWHM Gaussian kernel, and detrended, using SPM5. We excluded 41 twins with <30% accuracy on either N-back condition; and ten twins due to insufficient scan quality. The final sample consisted of 315 twins (aged 23.5±1.8 years); 74 monozygotic (MZ) pairs (29M/45F), 63 dizygotic (DZ) pairs (11M/27F/25MF), and 41 unpaired subjects (contributing to means model). Z-scores were extracted on a voxel-by-voxel-basis from 2>0-back contrast images generated at the single-subject level in each of 40,136 voxels comprising a brain mask created from a group random effects analysis irrespective of zygosity. We calculated voxel-by-voxel intra-class correlations (ICCs) and corresponding significance values for MZ and DZ groups. In addition, we computed Falconer's heritability estimate ($h^2 = 2(r_{MZ} - r_{DZ})$; [2]). Finally, we assessed fMRI reproducibility, using a paired-samples *t*-test, in a sub-sample of 20 twin pairs (5 MZF, 5 MZM, 5 DZF, 5 DZM) rescanned 120±55 (M±SD) days after their initial scan.

Results: Colour-coded maps show ICCs for MZ (Fig. 1a) and DZ twins (Fig. 1b), as well as Falconer's heritability estimates (Fig. 1c) for task-related brain activation. Results are overlaid on the average T1-weighted image in MNI atlas space. Red colours indicate regions with high correlations between twins and high heritability, respectively. These preliminary results show that ICCs for task-related brain activation were greater between MZ twins than between DZ twins, especially in frontal and parietal areas, suggesting genetic control of brain function is greatest in those regions.
The paired-samples *t*-test showed that phenotypic variance due to unique environmental factors is unlikely to be due to a lack of BOLD signal reproducibility, as there was little test-retest difference in activation patterns across the group of 40 twins. At a significance level of $p < .001$ (FWE-corrected) there was merely one cluster of 6 voxels (location: x=-51, y=12, z=-3) significantly different between time points 1 and 2.

Conclusions: This work will serve as the basis for mapping heritable aspects of brain function, and computing maps of genetic parameters from a large twin database. Consistent with earlier work using regions of interest [1], these genetic brain maps demonstrate a significant (moderate to high) influence of genetic factors on working-memory-related brain activation, especially in frontal and parietal brain regions. Although there are also sizeable environmental effects on brain activation, the genetic determination may be sufficiently strong for future studies to detect individual genes contributing to task-related brain activation.

References:

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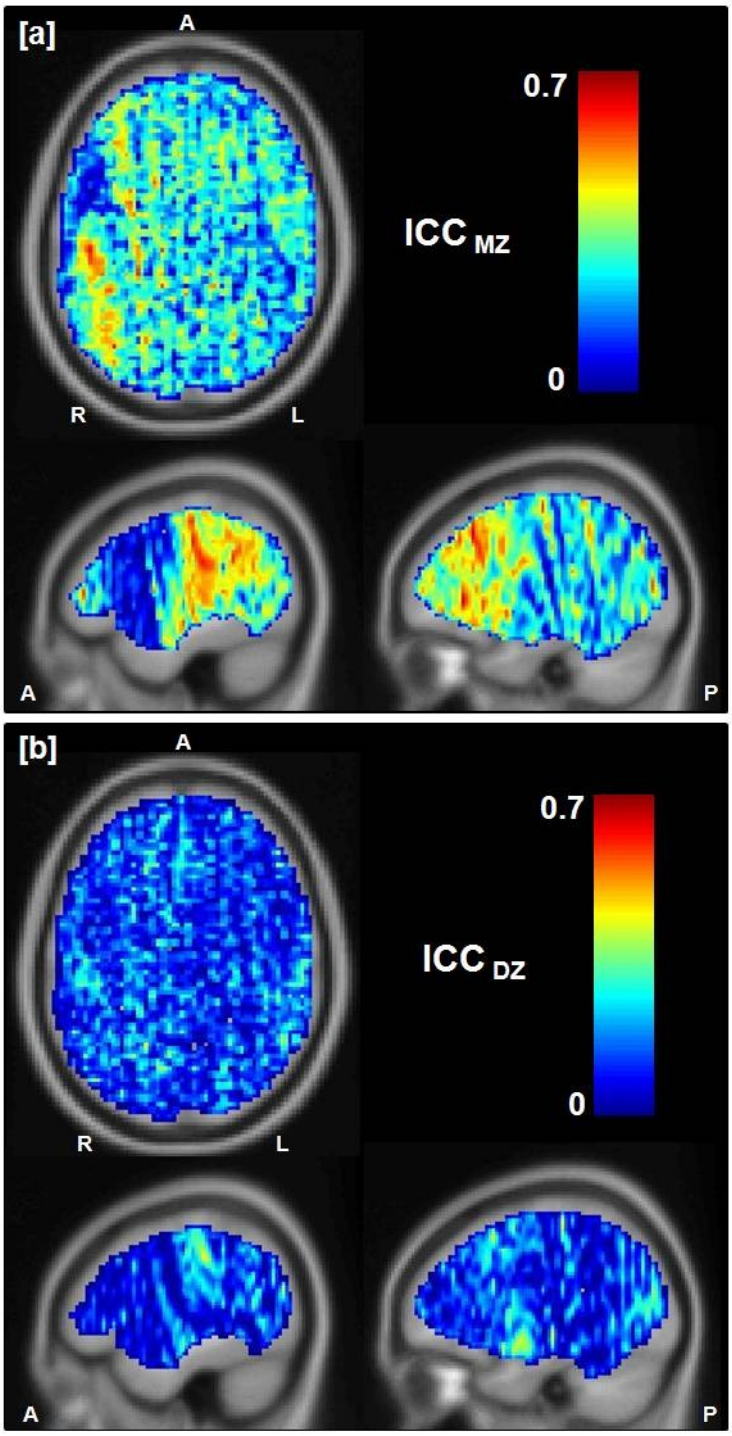
2. Falconer, D. S. & MacKay, T. F. C. (1996), *Introduction to Quantitative Genetics*, 4th edn, Longmans Green, Harlow, Essex, UK.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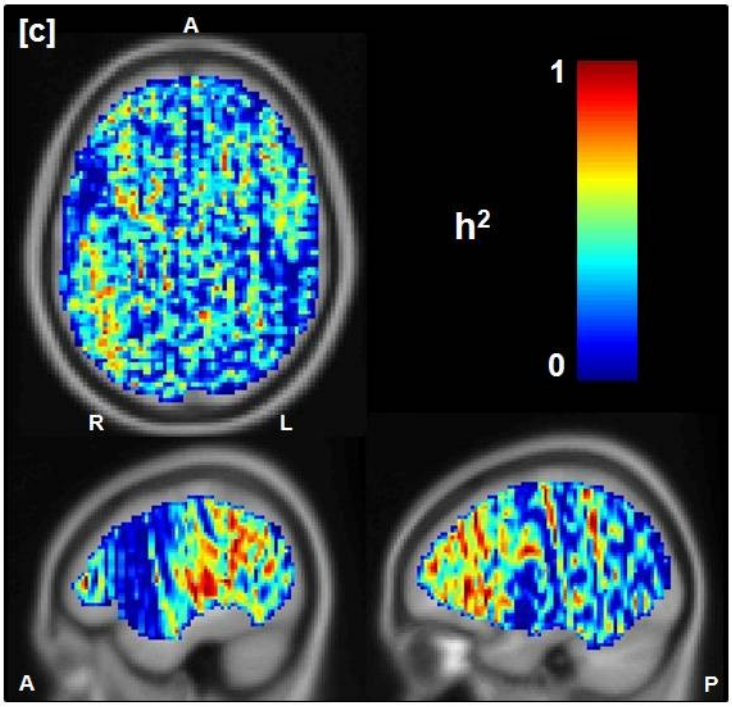
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