Mapping Genetic Influences on Brain Activation during the N-Back Working Memory Task: An fMRI Study of 319 Twins

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Background
- Although genetic effects on brain structure have been reported fairly consistently, only a handful of neuroimaging studies have examined the heritability of task-related brain activation, with very mixed findings.

Objective
- We assessed the relative contributions of genetic (heritability) and environmental influences on task-related brain activation on a voxel-by-voxel basis, using functional MRI (fMRI) during a working memory task in a large twin sample.

Significance
- Determining heritability of fMRI parameters may provide endophenotypes in the search for genes that could be of diagnostic or therapeutic importance in neurological and psychiatric disorders.

Experimental Design
- 127 GE-EPI whole brain volumes sensitive to BOLD contrast were acquired during the 0-back and 2-back conditions of a spatial N-back working memory task (see Fig. 1) on a 4T Bruker Medspec MRI scanner in a sample of 366 healthy twins.

Method
- 120 ± 55 (M ± SD) days after their initial scan.
- 75 monozygotic (MZ) pairs (29M/46F)
- 37 unpaired subjects (15M/22F)
- 75 dizygotic (DZ) pairs (11M/30F/25MF)

Results
- 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 influence of additive 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, which are largely due to unique environmental factors rather than measurement error, the genetic determination may be sufficiently strong for future studies to detect individual genes contributing to task-related brain activation.

Conclusions
- We excluded 37 twins with <30% accuracy on either N-back condition; and 10 twins due to insufficient scan quality. The final sample consisted of 319 twins, aged 23.5±1.8 years:
  - 75 monozygotic (MZ) pairs (29M/46F)
  - 66 dizygotic (DZ) pairs (11M/30F/25MF)
  - 37 unpaired subjects (15M/22F)

Image Processing
- fMRI data were processed with SPM5 using standardised procedures (see [1]).
- T-scores were extracted from 2>0-back contrast images generated at the single-subject level in each of 15,804 voxels comprising a brain mask created from a group random effects analysis, irrespective of zygosity (p<.05, FWE-corrected).

Genetic Analysis
- We calculated voxel-by-voxel intra-class correlations (ICCs) for MZ and DZ groups.
- Structural equation modelling with Mx was applied next. Since the MZ ICCs were generally more than 2x the size of the DZ ICCs we opted for a model that includes additive genetic factors (A), dominance genetic factors (D), and unique environmental factors (E). MZ twins are correlated 1 for A and D; DZ twins are correlated .5 for A and .25 for D. By definition E is left uncorrelated with both MZ and DZ twins. Age, sex, IQ, and 2-back accuracy % were entered as covariates by a model that includes additive genetic factors (A), dominance genetic factors (D), and unique environmental factors (E).
- At 10,000 iterations, a voxel level threshold for significance of A and D of p<.05, using the mask image of 15,804 voxels, and an 8 mm smoothing kernel, Monte Carlo simulation (AFNI AlphaSim) determined that the minimum cluster size was 147 voxels for cluster significance at p<.05.

Reproducibility
- We assessed fMRI reproducibility, using a paired-samples t-test and ICCs, in a sub-sample of 20 pairs (5 MZM, 5 M2M, 5 DZF, 5 D2M) rescanned 120±55 (M±SD) days after their initial scan.