

## Genetic influences on economical properties of human functional cortical networks

A. Fornito<sup>1,2</sup>, A. Zalesky<sup>2</sup>, D. Bassett<sup>1</sup>, D. Meunier<sup>1</sup>, M. Yücel<sup>2</sup>, S. J. Wood<sup>2</sup>, D. Nertney<sup>3</sup>, B. Mowry<sup>3</sup>, C. Pantelis<sup>2</sup>, and E. Bullmore<sup>1</sup>

<sup>1</sup>Brain Mapping Unit, Department of Psychiatry, University of Cambridge, Cambridge, Cambridgeshire, United Kingdom, <sup>2</sup>Melbourne Neuropsychiatry Centre, Department of Psychiatry, University of Melbourne, Parkville, Victoria, Australia, <sup>3</sup>Queensland Centre for Mental Health Research, University of Queensland, Brisbane, Queensland, Australia

### Background

The human cerebral cortex is a web of spatially distributed, functionally specialized regions interconnected by axonal fibers. These fibers facilitate efficient information transfer by reducing the mean path length between any two nodes (i.e., the number of connections that must be traversed to transfer information). In principle, one could maximize network efficiency simply by adding more connections, but each connection comes at a metabolic cost that can negatively impact the brain's energy budget<sup>1</sup>. Accordingly, recent evidence suggests that cortical networks have evolved to balance the competing priorities of maximizing efficiency of information transfer while minimizing wiring cost<sup>2,3</sup>. This view predicts that there is a continuum along which individual brains may be more or less cost-efficient, and that such individual differences should have genetic origins. We tested these predictions by applying graph analytic techniques to resting-state fMRI data acquired in healthy monozygotic (MZ) and dizygotic (DZ) twin pairs. Twin designs offer a powerful means for examining genetic influences on a given trait by exploiting differences in the degree of genetic relatedness between MZ and DZ twins. MZ twins have identical genomes while DZ twins share, on average, 50% of their genes. Thus, genetic effects are implied if MZ twins show greater similarity than DZ twins.

### Methods

Fourteen MZ and fifteen DZ twins underwent resting-state fMRI (840 volumes; TR=1.4s). The volumes were motion corrected and spatially normalized, and a custom template was used to parcellate the cortex into 1196 evenly sized and spaced regions. The mean timeseries of each region was then extracted and decomposed using a wavelet transform<sup>4</sup>. Pairwise correlations between wavelet coefficients representing low-frequency oscillations were computed, resulting in an 1196 x 1196 correlation matrix for each subject. These matrices were progressively thresholded to evaluate network cost-efficiency across a range of connection densities. For each node at each threshold, efficiency (E) was calculated as the inverse of its characteristic path length (i.e., the higher the mean path length, the lower the efficiency)<sup>5</sup>. The wiring cost (C) of each node was calculated as the sum of the physical distances of each of its supra-threshold connections, estimated by computing the Euclidean distance between regional centroid coordinates in stereotactic space. Heritability ( $h^2$ ), an estimate of the proportion of variance in a trait attributable to genetic factors, was estimated using a regression approach<sup>6</sup>.

### Results

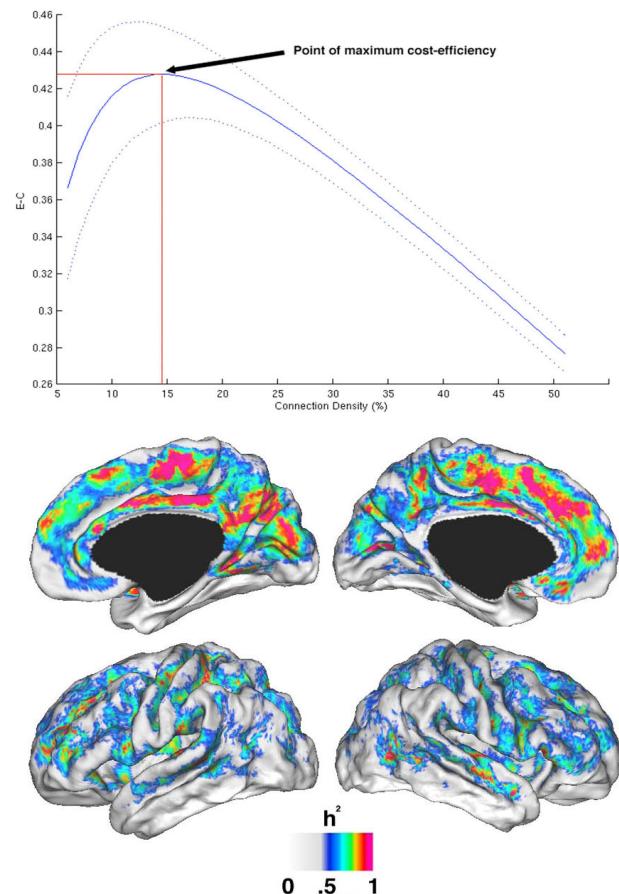
Figure 1 (top) illustrates how global network cost-efficiency (calculated by subtracting C from E; i.e., E-C) varies as a function of network connection density. The E-C measure is concave, revealing a peak beyond which adding more connections does not improve cost-efficiency. Thus, the maximal E-C value represents the optimum cost-efficiency trade-off that can be obtained for each individual. This maximal value (normalized by the connection density at which it occurs), was highly heritable:  $h^2=.91$  ( $p<.01$ ), indicating 91% of the variance is attributable to genetic influences. Regional analysis indicated these influences were not uniformly distributed throughout the brain, with the strongest effects being found in medial cortical regions (figure 1, bottom).

### Discussion

Our findings suggest that individual differences in economical properties of human cortical networks are under strong genetic control. These influences are not uniformly distributed, and appear strongest in regions known to show relatively high metabolic activity in the resting state<sup>7</sup>.

### References

- <sup>1</sup> Laughlin & Sejnowski (2003). *Science*, 301:1870.
- <sup>2</sup> Kaiser & Hilgetag (2006). *PLOS Comp Biol*, 2:e95.
- <sup>3</sup> Cherniak et al. (2004) *Proc Natl Acad Sci: USA*, 101:1085.
- <sup>4</sup> Achard et al. (2006) *J Neurosci*, 26:63.
- <sup>5</sup> Latora & Marchiori (2003) *Eur Phys J B*, 32:249.
- <sup>6</sup> De Fries & Fulker (1985) *Behav Genet*, 15:467.
- <sup>7</sup> Raichle et al. (2001) *Proc Natl Acad Sci: USA*, 98:676.



**Figure 1.**

Top: Mean global network cost-efficiency (E-C) as a function of connection density for all subjects (solid line). Standard deviations (dotted lines) illustrated individual variability in the E-C measure. Bottom: Regional maps displaying heritability estimates for cost-efficiency measures for each node.