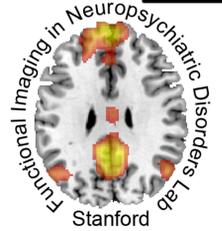




# Genome-Wide Analysis Reveals a Polymorphism Linked to Cost-Efficient Wiring of Functional Brain Networks

Andre Altmann<sup>1</sup>, Anna-Claire Milazzo<sup>1</sup>, Jean-Baptiste Poline<sup>2,3</sup>, Michael D Greicius<sup>1</sup>  
and the IMAGEN consortium

**1.** Functional Imaging in Neuropsychiatric Disorders Lab, Department of Neurology and Neurological Sciences, Stanford University, Stanford, CA, USA **2.** Helen Wills Neuroscience Institute, Brain Imaging Center, University of California at Berkeley, Berkeley, CA, USA **3.** Neurospin, I2BM, CEA2, France



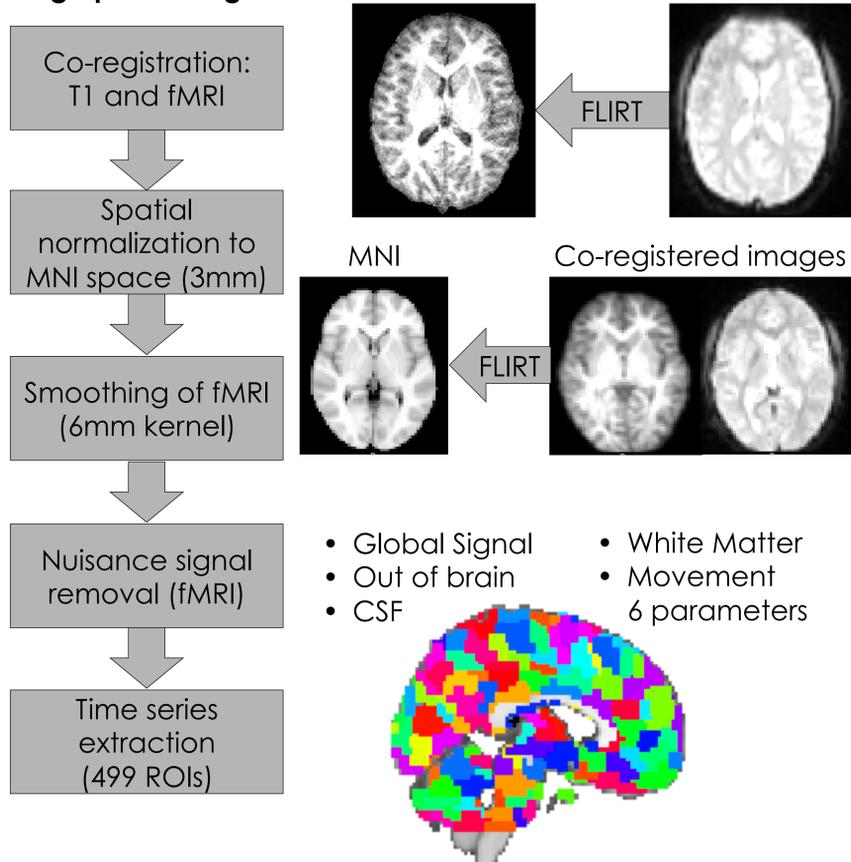
## Introduction

Studying functional connectivity with resting-state functional magnetic resonance imaging (rs-fMRI) is an important experimental paradigm for understanding the brain's functional network organization. Previous twin studies showed that features of functional networks derived from rs-fMRI are under genetic control (e.g., [1]). However, it is still unknown which genes or genetic variants help shape and support functional brain networks. In this work we used rs-fMRI data, in conjunction with matched, genome-wide genotype data collected by the IMAGEN consortium, to elucidate the genetic background of functional brain networks.

## Methods

**Data:** N=259 14-year old adolescents collected by the IMAGEN consortium who have a **structural T1-weighted image**, a **T2\*-weighted functional resting state scan (~6.5 min; TR=2.2s)** and **genome-wide genotyping data (~550K SNPs)**.

### Image processing:



The time series for each ROI was filtered using a band pass filter (0.007Hz – 0.18Hz).

### Compute Cost-efficiency:

- Compute pairwise partial correlation between ROIs using L2-shrinkage
- Threshold the graph to reach edge densities of 5%, 10%, ..., 35%, 40%
- **Efficiency** of the graph  $G$ :  $E_{\text{global}} = \frac{1}{N(N-1)} \sum_{i \neq j \in G} L_{ij}$   
 $N$ : # of ROIs in thresholded graph  
 $L_{ij}$ : length of shortest path between nodes (i.e., ROIs)  $i$  and  $j$
- Compute wiring **cost**:  $D_{\text{global}} = \sum_{i \neq j \in G} d_{ij}$   
 $d_{ij}$ : Euclidian distance between nodes  $i$  and  $j$
- Cost-efficiency (**CE**):  $CE = E_{\text{global}} - D_{\text{global}}$   
 $CE_{15}$  refers to CE at the edge density of 15%

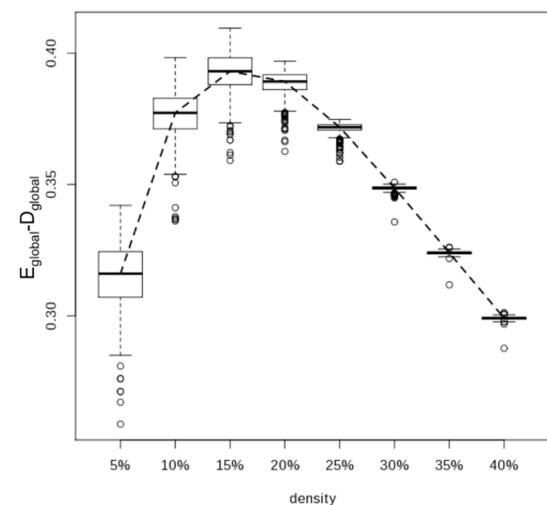
**Genotype Data:** 550K SNPs were genotyped. SNPs were filtered based on minor allele frequency (MAF < 5%), genotyping rate (missing >5%) and Hardy-Weinberg-Equilibrium (HWE  $P$ -value <  $6e-7$ ). After filtering 492,856 remained.

**Statistical Analysis:** CE is used as an imaging Quantitative Trait (iQT) in a genome-wide association study (GWAS). A linear model was fitted for each SNP using PLINK and corrected for sex, scan site (5 sites), and population structure (1<sup>st</sup> 4 PCs).

## Results

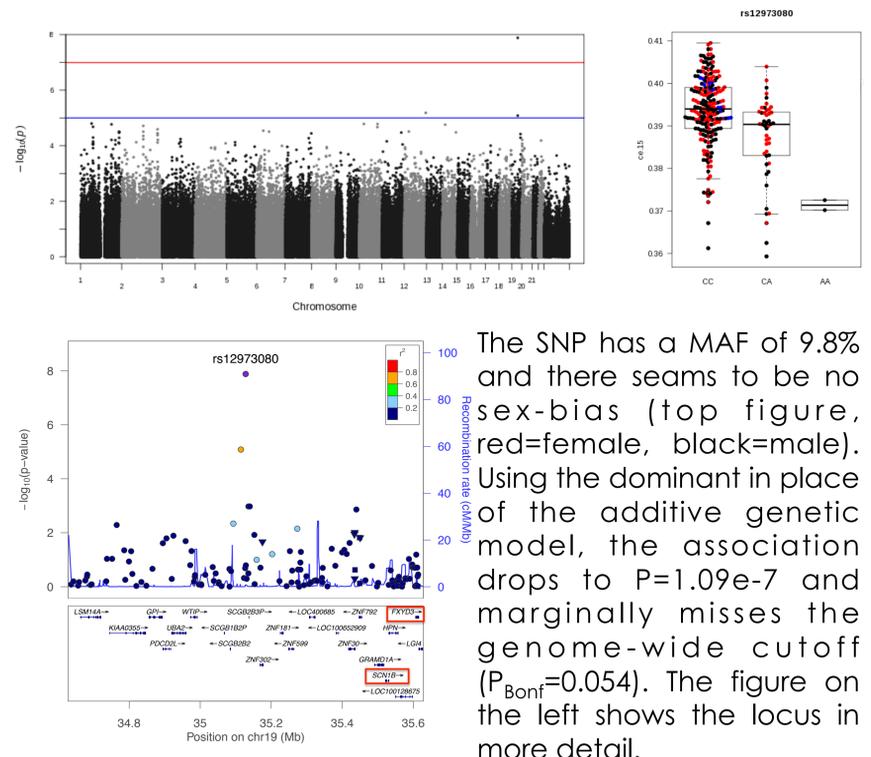
### Cost-efficiency (Y-axis) in dependence of graph's edge density (X-axis).

The figure depicts the distribution of the CE (=  $E_{\text{global}} - D_{\text{global}}$ ) scores for all considered graph densities. There is a clear peak at a density of 15%.



### GWAS results: Manhattan plot for CE<sub>15</sub>.

$CE_{15}$  was selected as iQT since it achieved the maximum CE for most subjects (224 of 259). Results are based on an additive genetic model. Genomic inflation factor ( $\lambda$ ) was 1.01. One SNP reached genome-wide significance ( $P < 1.01e-7$ ): rs12973080 with  $P = 1.288e-08$  ( $P_{\text{Bonf}} = 0.0063$ ).



## Conclusions

One locus was significantly associated with cost-efficient wiring. The SNP is located in an intergenic region, thus no direct association to a single gene is possible without further analysis. However, the genetic neighborhood ( $\pm 0.5\text{Mb}$ ) of rs12973080 contains interesting candidates such as subunits of sodium channels (SCN1B). While preliminary, these results point to the potential utility of using global, graph theory-based measures of connectivity as quantitative traits in genome-wide analyses of functional connectivity. Larger datasets are required to follow up on these preliminary finding.

## References

1. Fornito, A. et al. (2011) Genetic influences on cost-efficient organization of human cortical functional networks. *J. Neurosci.* 31, 3261–3270.