**Project Description**

**Genomic mapping of neuroimaging endophenotypes of psychiatric disorders**

1. Specific Aims and Significance

It has been recently shown that a substantial proportion (50%) of autism risk is captured by common genetic variants each of small effect (Gaugler et al 2014). This result suggest that in many cases it will not be one or a few genes/mutations that determine the presence of an autistic phenotype, but a genomic, highly diluted, massively polygenic accumulation of frequent variants. We have recently shown that neuroanatomical variability in the IMAGEN cohort is also captured by frequent variants (Toro et al 2014). We could then try to map the ***genetic correlation*** between autism risk and neuroimaging, which would allow us to determine which brain structures are those whose genetic bases are more strongly overlapping with those of autism. Although it may not be possible to obtain biological information about psychiatric disorders through the detection of major genes, genomic mapping of neuroimaging phenotypes could allow us to obtain relevant biological information for psychiatric disorder with massively polygenic architectures.

We propose to estimate ***genetic correlations*** between risk to psychiatric disorders and neuroimaging by combining cohorts of genotyped patients (for example, the Autism Genome Project in the case of autism) and cohorts of MRI scanned, genotyped controls, such as IMAGEN. Our estimations of statistical power show that ~4,000 subjects will be required to detect reliably moderate genetic correlations. We will have to combine the IMAGEN cohort with additional cohorts. This project is a collaboration with ENIGMA consortium which will provide with other cohorts than the IMAGEN cohort.

2. Material and Methods

2.1. IMAGEN and ENIGMA consortium

The data for this project already exist in the IMAGEN (Schumann et al., 2010) and ENIGMA (Thompson et al, 2014) consortia. Both R. Toro and JB Poline are members of these consortia and have access to the data (the project described has been submitted and approved by both IMAGEN and ENIGMA). These consortia give access to either the primary data (IMAGEN) or the subjects genetic relation matrix (ENIGMA). With four thousands subjects or more, these data will provide us with enough power to detect small effects (heritability or genetic correlations) with small confidence interval.

2.2. Genome-wide complex trait analysis

Lexin

2.3. Least squares kernel machine and Wright-Fisher kernel

Lexin

2.4. Other extensions

Lexin

2.5. Previous work and preliminary results

We have recently shown, using the MRI and genetic data collected by IMAGEN, that an important part of the diversity of neuroanatomical phenotypes is captured by thousands of common SNPs, each of small-effect (Toro et al 2014). The strong heritability of phenotypes such as intracranial volume (~50%) or brain volume (~45%) allowed us to obtain statistically significant estimations of the variance captured by SNPs. However, the standard errors were large, ~20%. Power estimations show that a cohort of 4,000 subjects will be required to decrease standard error to ~10%, and 8,000 subjects would be required to further decrease standard error to ~5%. The extra statistical power would not only allow us to have better estimations of the amount of neuroanatomical variance captured by SNPs, but also to detect more subtle effects than those we could detect with 1,765 subjects. We propose here to lead an effort to replicate and extend our previous results. Through the ENIGMA consortium we could potentially have access to a cohort of 20,000 subjects.

Contrary to GWAS analyses, genomic complex trait analysis (GCTA) requires direct access to the genotyping data. The analysis approach is then a mega-analysis, instead of a meta- analysis. Thanks to the expertise that we have acquired with the analysis of the IMAGEN cohort, we have now the knowledge and the infrastructure to perform this mega-analysis. We would also benefit from the work already done in the context of the participation of IMAGEN to the ENIGMA 1 project (ICV, BV, Hipp) and the ENIGMA 2 project (subcortical structures).

Lexin

3. Research Team

Lexin Li is a new faculty in the departement of Biostats at Berkeley. He has experience in both imaging and genetic data.

JB Poline is a researcher at the Brain Imaging Center at Berkeley. He has been the lead of the biostatistics and bioinformatics subproject of the IMAGEN consortium and has collaborated with ENIGMA on several projects.

Roberto Toro is a tenured researcher at Pasteur in a human genetic laboratory specialized in autism research. R. Toro has a wide experience on imaging and imaging genetics. The three individuals gather the necessary experience and expertise for the success of this project.

4. Work Plan

* First kick off meeting at the Pasteur Institute, Paris. Objectives of the meeting:
  + set up the collaboration tools (github account, common repositories, etc)
  + Develop a simulation dataset to validate estimation procedure (R. Toro, JB Poline, L. Li)
  + Bring participants up to date: genetic correlation current estimation procedures,
* During month 1-8, we will accomplish the following tasks.
  + Develop a simple simulation tool for validation
  + Obtain first genetic kindship matrix from IMAGEN and ENIGMA
  + Develop standard and regularized genetic correlation estimation procedures
* During month 9-12:
  + test the regularized estimation procedures on both simulated and actual kinship matrices. Compare results with standard GCTA approach. Publish the results.

5. References

Toro R, Poline JB, Huguet G, Loth E, Frouin V, Banaschewski T, Barker GJ, Bokde A, Büchel C, Carvalho FM, Conrod P, Fauth-Bühler M, Flor H, Gallinat J, Garavan H, Gowland P, Heinz A Ittermann B, Lawrence C, Lemaître H, Mann K, Nees F, Paus T, Pausova Z, Rietschel M, Robbins T, Smolka MN, Ströhle A, Schumann G, Bourgeron T and the IMAGEN consortium (2014) Genomic architecture of human neuroanatomical diversity. Mol Psychiatry, Accepted doi: 10.1038/mp.2014.99

JL Stein, SE Medland, A Arias Vasquez, DP Hibar, RE Senstad, AM Winkler, R Toro, et al (2012) Common genetic polymorphisms are associated with human hippocampal and intracranial volumes. Nature Genetics.

Hibar, D. P., J. L. Stein, M. E. Renteria, A. Arias-Vasquez, S. Desrivières, N. Jahanshad, R. Toro, et al. 2015. “Common Genetic Variants Influence Human Subcortical Brain Structures.” Nature advance online publication (January). doi:10.1038/nature14101.

Gaugler, Trent, Lambertus Klei, Stephan J. Sanders, Corneliu A. Bodea, Arthur P. Goldberg, Ann B. Lee, Milind Mahajan, et al. 2014. “Most Genetic Risk for Autism Resides with Common Variation.” Nature Genetics 46 (8): 881–85. doi:10.1038/ng.3039.

Toro R, Poline JB, Huguet G, Loth E, Frouin V, Banaschewski T, Barker GJ, Bokde A, Büchel C, Carvalho FM, Conrod P, Fauth-Bühler M, Flor H, Gallinat J, Garavan H, Gowland P, Heinz A Ittermann B, Lawrence C, Lemaître H, Mann K, Nees F, Paus T, Pausova Z, Rietschel M, Robbins T, Smolka MN, Ströhle A, Schumann G, Bourgeron T and the IMAGEN consortium (2014) Genomic architecture of human neuroanatomical diversity. Mol Psychiatry, Accepted doi: 10.1038/mp.2014.99

Schumann, G., Loth, E., Banaschewski, T., Barbot, A., Barker, G., Büchel, C., Conrod, P.J., Dalley, J.W., Flor, H., Gallinat, J., et al. (2010). The IMAGEN study: reinforcement-related behaviour in normal brain function and psychopathology. Molecular Psychiatry *15*, 1128–1139.

Thompson, P.M., Stein, J.L., Medland, S.E., Hibar, D.P., Vasquez, A.A., Renteria, M.E., Toro, R., Jahanshad, N., Schumann, G., Franke, B., et al. (2014). The ENIGMA Consortium: large-scale collaborative analyses of neuroimaging and genetic data. Brain Imaging and Behavior 1–30.