Using high-performance computing to explore high-dimensional neuroimaging data

High-dimensional neuroimaging and genetics for clinical applications in neuropsychiatry and cognitive neuroscience

L. Waller, J. D. Kruschwitz, T. A. Lett, S. Mohnke, S. Erk, H. Walter*, Department of Psychiatry and Psychotherapy, Charité Universitätsmedizin Berlin*

In Short

- Recent advances in neuroimaging and genotyping allow the acquisition of measurements for thousands of individuals
- Newly available large-scale datasets allow the application of novel, exploratory statistical methods
- These analyses may reveal important relationships between genetics, anatomy, physiology, and behavior, and psychiatric disorders

In the past years, neuroimaging has developed from an experimental technique used by specialists in isolated studies into a standard technique in human neuroscience that is used to perform large-scale, multicentre neuroimaging studies. In these studies, neuroimaging with magnetic resonance imaging (MRI) allows researchers to obtain anatomical and physiological measurements of the brain in both healthy participants and clinical populations. In psychiatry, a major long-term goal of such investigations is to establish biomarkers for mental processes in clinical populations for classification, diagnosis, and prediction. In basic neuroscience, these investigations can be used to explore the general relationship between genetics, anatomy, physiology, and behavior. This approach has been termed imaging genetics (see Figure 1).

In order to achieve these goals, researchers are conducting an ever increasing number of multicenter studies. In these studies, neuroimaging data are obtained for large cohorts of healthy participants, healthy participants at risk, and patient populations. We are principal investigators in several of these studies, notably MooDS, IntegraMent, IMAGEN and FOR1617, in addition to using large public datasets such as the Human Connectome Project.

In addition to large-scale neuroimaging data, these studies typically acquire genetic information, because genome-wide genotyping has become affordable in the past years, and because genetic factors play a considerable role in the etiology of major psychiatric disorders such as schizophrenia, depression, bipolar disorder, or addiction, on which our research group has focused. Genome wide genotyping delivers genome-wide information on more than 600,000 single nucleotide polymorphisms (SNPs) and is thus high-dimensional.

We have analyzed these datasets using standard methods, which means that our analyses were based on well defined hypotheses. For example, by examining the effect of a specific gene variant on brain activation in a specific task and brain region, we can answer basic research questions about brain development and physiology, and clinical questions such as disease-relevant brain dysfunction in high-risk individuals or relapse prediction in alcoholism [1–7]. However, standard analyses are not suited to exploit the richness of our high-dimensional neuroimaging and genetic datasets. Functional neuroimaging data of one individual typically include time series for 50,000 data points, but can exceed up to 1 million data points with high resolution imaging. In particular, standard analyses employ dimensionality reduction from these tens of thousands of data points acquired using MRI to only a few hundred brain regions of interest. Here, we propose to use the supercomputer to perform analyses with less or without dimensionality reduction, and to perform more exploratory analyses that have less clearly defined hypotheses, but the ability to reveal unexpected but important relationships [8].

WWW

http://mindandbrain.charite.de

More Information

[1] Esslinger, C., Walter, H., Kirsch, P., Erk, S., Schnell, K., Arnold, C., ... & Witt, S. H. (2009). Neural mechanisms of a genome-wide supported psychosis variant. *Science*, 324(5927), 605-605. doi:10.1126/science.1167768

[2] Walter, H., Schnell, K., Erk, S., Arnold, C., Kirsch, P., Esslinger, C., ... & Nöthen, M. M. (2011). Effects of a genome-wide supported psychosis risk variant on neural activation during a theory-of-mind task. *Molecular psychiatry*, 16(4), 462-470. doi:10.1038/mp.2010.18

[3] Erk S., Meyer-Lindenberg A., Schnell K., Opitz von Boberfeld C., Esslinger C., Kirsch P., ... & Cichon, S. (2010). Brain function in carriers

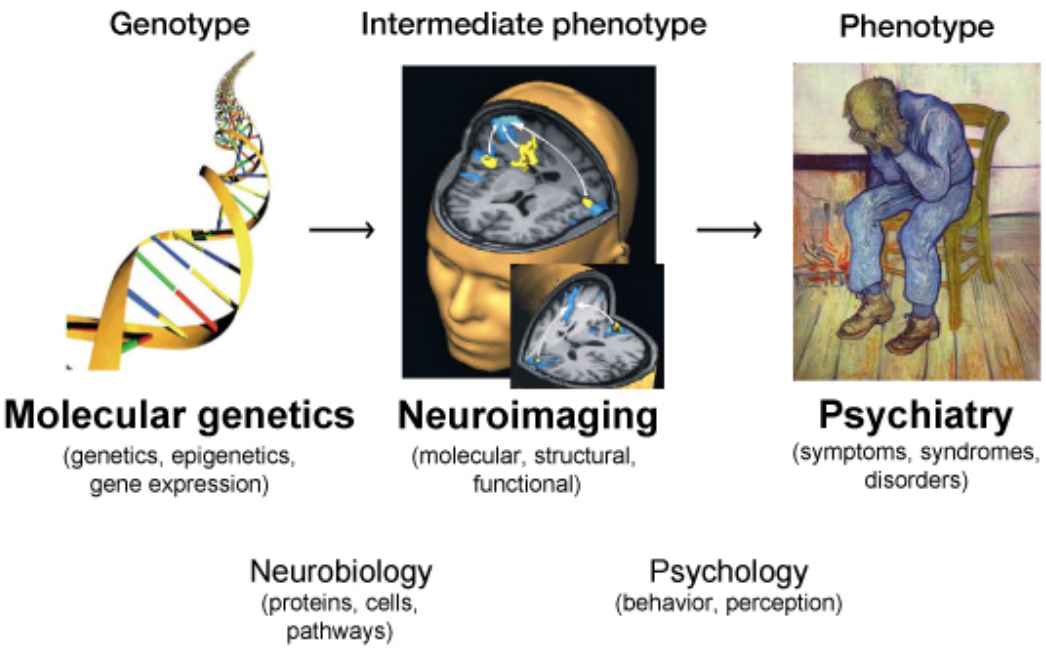

Figure 1: *Imaging genetics focus on finding intermediate phenotypes that arise from the interaction of genetic information, brain function and clinical phenotype [9].*

of a genome-wide supported bipolar disorder variant. *Archives of General Psychiatry*. 67(8):803-11. doi:10.1001/archgenpsychiatry.2010.94

[4] Erk S., Meyer-Lindenberg A., Schmierer P., Mohnke S., Grimm O., Garbusow M., ... & Tost, H. (2014). Hippocampal and frontolimbic function as intermediate phenotype for psychosis: evidence from healthy relatives and a common risk variant in CACNA1C. *Biological Psychiatry*. 76(6):466-75. doi:10.1016/j.biopsych.2013.11.025

[5] Mohnke S., Erk S., Schnell K., Schutz C., Romanczuk-Seiferth N., Grimm O., ... & Kirsch, P. (2014). Further evidence for the impact of a genome-wide-supported psychosis risk variant in ZNF804A on the Theory of Mind Network. *Neuropsychopharmacology*. 39(5):1196-205. doi:10.1038/npp.2013.321

[6] Mohnke S., Erk S., Schnell K., Romanczuk-Seiferth N., Schmierer P., Romund L., ... & Haller, L. (2015). Theory of Mind network activity is altered in subjects with familial liability for schizophrenia. *Social Cognitive and Affective Neuroscience*. doi:10.1093/scan/nsv111

[7] Jorde, A., Bach, P., Witt, S H., Becker, K., Reinhard, I., Vollstädt-Klein, S., ... & Wimmer, L. (2014). Genetic variation in the atrial natriuretic peptide transcription factor GATA4 modulates amygdala responsiveness in alcohol dependence. *Biological psychiatry*, 75(10), 790-797. doi:10.1016/j.biopsych.2013.10.020

[8] Erk, S., Mohnke, S., Ripke, S., Lett, T. A., Veer, I. M., Wackerhagen, C., ... & Mattheisen, M. (2017). Functional neuroimaging effects of recently discovered genetic risk loci for schizophrenia and polygenic risk profile in five RDoC subdomains. *Translational Psychiatry*. 7(1), e997. doi:10.1038/tp.2016.272

[9] Walter H., Meyer-Lindenberg A., Heinz A. (2014) Imaging Genetics. In: Gruber O., Falkai P. (Eds.), *Systemische Neurowissenschaften in der Psychiatrie. Methoden und Anwendungen in der Praxis* (pp. 308-326). Stuttgart: Kohlhammer Verlag.

Funding

MooDS - BMBF 01GS08144
IntegraMent - BMBF 01ZX1314B
FOR1617 - DFG WA1539/7-1