# Editorial

## Towards "Systems Psychiatry"

## Rumo a sistemas de Psiquiatria

The dramatic genetics and omics revolution of recent years has pushed systems biology approaches to the forefront of finding prognostic and predictive biomarkers for psychiatric disorders. Systems psychiatry is emerging as a discipline in its own right via combination of conventional systems biology approaches with state-of-the-art neuroimaging techniques. It will be key for the growth of translational medicine in psychiatry. Below we review some the recent advances in neuroimaging and –omics that are making systems psychiatry an achievable goal.

### Genetics and genomics

The recently completed phase II of the HapMap project genotyped ~3.9 million variations called single nucleotide polymorphisms (SNPs) on each of the major human population groupings and currently represents the gold standard for genetic studies of human populations (www.hapmap.org). While this scale of project remains unachievable for disease studies, the fact that alleles of polymorphisms in close proximity exhibit association with each other (linkage disequilibrium or LD) means that using a microarray 'chip' to genotype hundreds of thousands up to 1 million SNPs is efficient at detecting whole genome variation. It is estimated that the ~500K SNPs has the ability to capture information from 80-86% of common for Asians and Europeans (www.hapmap.org, www.illumina.com, www.affymetrix.com).

Multiple large scale Genome Wide Association Studies (GWAS) have now been carried out or are in the process of being published, including psychiatric disorders such as bipolar disorder in the WTCCC study (www.wtccc.org.uk). Published results have, as yet, been modest, however, more in-depth analysis of the data (Breen, McGuffin et al.; unpublished data), has revealed approximately 5 new gene regions with genome wide significant association with bipolar disorder. The next generation of GWAS will in part be driven by increasingly dense SNP microarray and next generation sequencing approaches such as exon resequencing (www.solexa.com, www.454.com, www.nimblegen.com). Discussion with suppliers and large scale customers indicate that the likely base level cost, in the medium term, of a state-of-the-art method on thousands of samples is US$200 per sample, perhaps eventually including a combined array and large scale sequencing approach, which seems likely to become the new standard in a few years time.

With the rapid advancement of technology and the accompanying rapidly changing commercial scene, it is hard to predict the technological platform of choice in even 3 years time. Given the immature state of technologies and the rapid obsolescing of equipment once purchased, money spent on equipment may be better spent on generating data through an outside contractor. Hard choices between capital investment, which may be desirable for strategic reasons, and outsourcing of genotyping and microarray analysis must be made with knowledge of the true costs and difficulties of purchasing, maintenance and reagent supplies. However, whatever the platform, there is a definite need for national

or in-house capabilities for data warehousing for the many terabytes (or even petabytes) of data generated by genomics and the other approaches outlines below, and for in-house maintenance and development of expertise in data cleaning and analysis.

### Proteomics

Many studies are collecting plasma and buffy coat on large cohorts of subjects. Recent studies have successfully used two dimensional gel electrophoresis combined with mass spectrometry and also candidate proteins to identify biomarker panels in dementia (www.innomed-addneuromed.com). This well established approach can be combined with multivariate and class prediction models and the development of isobaric tagging mass spectrometry technology will allow simultaneous assessment of large numbers of proteins without gel-based separation. Validation to date has been by immunodetection by both ELISA and western blotting.

### Transcriptomics

RNA can now be easily collected from whole blood, saliva and fibroblasts stored in tubes containing stabilisation buffers that prevent the rapid degradation of mRNA. Exon arrays and digital gene expression profiling using modified massively parallel sequencing strategies represent the current state-of-the-art with whole transcriptome sequencing strategies currently being developed. Whatever the platform, expressed transcripts are ranked according to false discovery rate, fold change and p-value. As expected in whole genome arrays a large number of genes differ between groups of subjects. In order to analyse group-wide changes further it is possible to use methods such as Gene Set Enrichment Analysis (www.broad.mit.edu/gsea/). This bioinformatics-driven analysis compares experimental changes to those previously identified in both disease states and in biological pathways.

### Imaging

Modern strategies for psychiatric neuroimaging are based on the use of imaging as both a scientific instrument for the study of the brain in translational research and as a clinical diagnostic tool. The ability to image both structure and function in a wide range of psychiatric populations from the infant to old age has expanded our horizons dramatically in the last two decades. Standardised imaging protocols are required for sharing subjects between different translational research studies and across centres, as well as for major imaging-omics studies. Large scale projects and replication of studies necessitate the adoption of such protocols for volumetric MRI, functional magnetic resonance imaging (fMRI), diffusion tensor MR imaging, perfusion imaging (PET and MR arterial spin labelling), receptor binding and magnetic resonance spectroscopy. Standardising imaging protocols across both clinical and research work offers the potential to use routine clinical scans as a key resource for translational research and add value to clinical work. Once data have been acquired there are both challenges and opportunities when analysing large datasets. Analysis methodologies have improved continuously in recent years, but most current studies are still measured in the tens of subjects rather than the thousands and there are ever-expanding demands on computational infrastructure for both processing and storing the terabytes of processed data generated by large scale imaging studies. Although MR is probably the most powerful and flexible modern cross sectional imaging modality that is available to clinicians and researchers there are also clear key strengths in PET, EEG, MEG and near infra-red spectroscopy. Integrating information from different imaging modalities, such as functional MRI and diffusion tensor imaging, offers exciting possibilities for enhancing our understanding of the brain in sickness and in health.

### Conclusions

A key strength of systems psychiatry, but also its main challenge is the breadth of our analysis methodologies. This needs both a unified and unifying analytical strategy for coordinated neuroimaging, proteomic, transcriptomic and genetic analysis. It also implies the need for recruitment and core characterization using detailed psychometric and neuroimaging instruments of large patient groups to perform a coherent – omics strategy, i.e. a whole genome analysis (WGA) followed by transcriptomics and targeted proteomics. These methods have traditionally been quite separate studies but recent studies have shown how at least transcriptomics and genomics may be successfully integrated in the study of disease (data and background may be found at www.sph.umich.edu/csg/liang/asthma/). To conclude the application of systems psychiatry will yield biomarkers and identify clearly aetiopathological factors for common mental disorders.

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