

Summary of the IMpACT Nijmegen Spring Meeting 2009, May 5-6

Formed in 2007, IMpACT, the International Multicenter persistent ADHD CollaboraTion, has the goal of performing and promoting high quality research in adult ADHD. IMpACT consists of research groups from 5 European countries and 2 groups from the US. Together, these groups currently coordinate the largest clinical ADHD sample worldwide, consisting of more than 2700 patients and 3500 controls.

In 2008, IMpACT members have consolidated their collaboration by starting up several collaborative projects, aimed at meta-analysis of existing genetic data, as well as replication of genetic findings of individual group members in the IMpACT sample. These studies will be published from 2009 onwards. The goals for 2009 include the development of a uniform phenotyping protocol for the IMpACT member sites as well as the scientific community working on adult ADHD, setting up a combined database of phenotypic and genotypic information of the IMpACT sample, and, most importantly, obtaining funding for more collaborative studies. For that reason, we had applied for a workshop to prepare a collaborative research proposal. This proposal was held in Nijmegen at May 5-6. In total, 33 people attended the meeting, including students and junior researchers in addition to the IMpACT members. The program of the two-day meeting is attached to this summary.

At the first day of the meeting on May 5th, the IMpACT member sites gave presentations about their earlier work on adult ADHD. The facilities of the groups range from clinical expertise, endophenotyping facilities including expertise regarding neuropsychology, electrophysiology and neuroimaging, via animal models and statistical method development, to genetics, epigenetics, gene expression profiling and metabolite monitoring. This showed the enormous potential of the group for interdisciplinary research and set the stage for the second day of the workshop, a day for of brain storming. The participants discussed their view on future directions in adult ADHD genetics research and potential collaboration projects for IMpACT. The following points were discussed:

Importantly, we achieved consensus on a minimal phenotyping protocol for genetics studies on adult ADHD. This protocol should include a validated clinical interview diagnosing ADHD on the basis of DSM-IV criteria. The group would suggest to use the CAADID or the (non-commercial) DIVA for this purpose. In addition, severity of the disorder should be assessed using a rating scale, preferable the ADHD-RS for childhood symptoms and the ASRS-18 for adult symptoms. Comorbidity should be thoroughly assessed using DSM-IV diagnoses on the basis of a validated instrument (e.g. SCID, OPCRIT, MINI). The comorbidities that were regarded important are: bipolar disorder, depression, anxiety, substance use disorders, psychotic disorder For earlier studies, in which different types of instruments we identified the OPCRIT to extract the important information in a 'validated' format. Also, OPCRIT was suggested to 'homogenize' existing datasets based on different instruments. This protocol will be published on the website of the International ADHD Resource (<http://adhd.curtin.edu.au/index.html>).

Another issue that was discussed was the set-up of a joined database for IMpACT. All of the members felt that setting up the database is very important for IMpACT and should be done as soon as possible. We identified one of the junior researchers who would set up the database in the coming months, the first version including the basic info on patients and controls. After that, additional phenotyping data, like endophenotypes and personality data will be added. We decided to survey/harmonize within IMpACT the available imaging, neuropsychology and pharmacogenetics data in the future. We also decided that an IMpACT website should be launched, both to place our database in, but also to ensure the visibility of IMpACT.

For junior researchers and students it was discussed to set up possibilities for exchange between the member sites of IMpACT. Young researchers will be encouraged to take advantage of the different research infrastructure at the different sites.

Apart from these more general issues, the discussion went to immediate, intermediate and longer term projects.

- For the immediate projects, each group defined a number of genes that will be genotyped in the IMpACT sample for meta-analysis purposes. These genes include genes from former research in children, but also those appearing sufficiently interesting in the studies of individual IMpACT members. In addition, a number of pathways were identified that would be analysed. Notably, investigations of copy number variants as well as microRNAs in ADHD were felt to be important ways forward in ADHD research.
- Also for immediate application, it was decided to participate in a number of US proposals and an application at the German DFG to obtain funding for genome-wide association. For the German project we decided that it would be best to go for the patients with combined subtype ADHD, for the following reasons: (1) This strategy will pick up genes for each of the domains, as well as genes for both domains. (2) It is the most severe form of the disorder. (3) This approach makes the study sample most homogeneous.
- For the statistical analysis of GWAS data, which is using rather ‘simplistic’ models at the current time, not taking into account the complexity of the data, Bayesian Modelling will be developed to improve this.
- Interdisciplinary projects that included participants of IMpACT were discussed, for application in the Brain & Cognition program. It was decided that a combination of endophenotyping (neuroimaging) and animal model work would be prioritized.
- For neuroimaging, it was felt that new analysis methods are needed, that better take into account brain activity/structure networks. These methods should then be made applicable to genetics studies.
- A number of phenotypes of energy metabolism and cardiovascular system function were discussed and decided to be useful, a decision was formed to apply for European funding on this project as soon as possible.
- For the longer term we decided to set up comprehensive multilevel biobanking, including RNA (for transcriptome data), plasma (for proteome and metabolome data) and diurnal variation data (on metabolic parameters).

- A twin-study on adult ADHD is currently missing from the literature to formally establish the extent of the heritability of adult ADHD. It was decided to look at possibilities to set up a twin study in adult ADHD.
- Epigenetics (DNA-methylation) was also identified as a potential new research possibility in adult ADHD, but since this is highly tissue-specific and there is no real data on the comparability of brain- and peripheral methylation, yet, this would have to be a first step before this can be applied to (adult) patients. First results in literature and IMpACT member sites are encouraging.

The meeting ended with a joint dinner at which all participants agreed that this workshop had been very useful for the group and should become a regular (yearly) event.

Surrounding the two days of the workshop, we also organized two symposia at which one of the workshop participants gave a lecture to members of the Donders Institute for Brain, Cognition and Behavior. One was organized on May 4th for Eric Mick, an IMpACT participant from the US, the other was organized on May 7th for Phil Asherson, the UK participant in IMpACT.

On Juni 3, a pre-proposal has been submitted with the Brain and Cognition Excellence Program by Dr. Barbara Franke. This project proposal, entitled 'From genetic pathways to cognition in ADHD: a matter of the right connections?', describes interdisciplinary research in adults with ADHD, including members of IMpACT.