Minutes of the International Multicenter Persisting ADHD Collaboration (IMPACT)
Amsterdam meeting, 11-12 February 2008

1. ***Selection of a name for the group***
   There are no additional suggestions for names, from the available suggestions IMPACT (International Multicenter Persisting ADHD CollaboraTion) is chosen

2. ***Selection of coordinator of the group and definition of tasks***

   > Tasks to be coordinated:
   - Updating of mailing list
   - Call for meetings
   - Take minor decisions for the group to prevent frantic e-mailing
   - Centralize information
   - Lead application to some grant proposals (depending on the type of grant)

   > Barbara will be the coordinator for the first year, after this year we will again consider this point.

3. ***Inclusion of additional groups into IMPACT***
   We decide that we will not include additional groups within the coming year, as we want to gain some experience in collaborating in the current, small group, first. However, we keep an open mind to further expansion of the group as we might want replication samples in the future. The samples we would consider should be of European Caucasian ethnic background and each sample should be at least 200 cases and (screened) controls in size.

4. ***Relationship with non-active members of IMPACT***
   We are very happy that Steve and Phil want to be part of the group. Their contribution in theoretical background on adult ADHD and the ADHD genetics field is greatly valued. We would prefer them to become active members, though, who also contribute samples. We will ask an estimate for the time they will need to include at least 200 cases and (screened) controls.
   The steering committee of IMPACT will consist of the groups contributing samples to the collaboration.

5. ***Status of general agreement***
   The agreement has been signed by most groups now. When signatures are complete, a signed original will be sent to every site.
   For every new project we propose we will need all signatures, but this is not necessary if we make it clear that this new project is to be viewed as part of the larger agreement and that the same conditions apply. This has to be part of every project proposal (please use the form distributed earlier).

6. ***Presentation of phenotyping details at the 4 groups by Toni***
   → see presentation and tables attached
   - all groups have contributed DSM IV diagnosed adult ADHD
   - all groups have info on ADHD severity, though assessed in different ways
   - all groups have comorbidity data
   - many groups have neuropsychology data

   > For future studies it would be very important to use a minimum clinical protocol common to all sites with the following aspects:
   - structured interview
   - scale of severity
   - comorbidity assessment
   - (life events scale (childhood and adulthood))
   - (minimum set of neuropsychological tests)

> Toni will make a proposal for a common protocol, we will ask Phil and Steve for input regarding this. We will propose to circulate this protocol within the ADHD Molecular Genetics Network and also put it on the website for other groups to use in new studies.

> Andreas will circulate the life events scale (short form of the Life History Calendar of Caspi et al) and the Fagerstrom self report scale for the assessment of smoking, which might be an important aspect in severity assessment and functional (neuropsychological and –physiological) studies.

7. Short presentations by the 4 contributing groups on their work/institute/vision, sample, plans and hot topics in the pipeline, including the plans for projects within this collaboration.

Nijmegen: 245 cases, 530 controls, still recruiting. Candidate gene approaches, risk alleles. Findings for dopamine-related genes, currently submitted or in preparation. Interested in endophenotyping in neuropsychology and neuroimaging, functional analysis of polymorphisms.

Bergen: 540 cases, 596 controls. Candidate gene approaches. Findings for dopamine and serotonin-related genes, published and submitted. Interested in ADHD spectrum and enzymes involved in monoamine metabolism.

Barcelona: 304 adult cases, 2000 controls, still recruiting. Multiple-candidate gene approaches in serotonergic, neurotrophins, dopaminergic and cerebral asymmetry pathways. Findings for different pathways, published, in preparation. Interested in methylphenidate effects/genetics, GWAS, parent of origin effects, personality traits, Imaging and epidemiology of ADHD symptoms.

Würzburg: 730 cases, XXX controls, still recruiting. Pooled GWAS, linkage in extended pedigrees, cytogenetic analysis. Findings for different pathways, converging evidence from different approaches, in press, in preparation, under analysis. Interested in pathways from candidate genes to disease (also animal models).

Barcelona is presenting plans for pooled GWAS in (adult) ADHD. Pooling of only blood samples, in different stages, possibly only combined type ADHD, gender-specific pools? Pools stratified by comorbidity or severity of ADHD? Bru sends round requirements for participation in the study, also to get info about numbers of (blood) samples available.

8. Results of meta-analysis of combined data on DAT1 and DRD4

Genes with at least one polymorphism genotyped in >500 cases and by at least 2 groups:

	cases	controls
DAT1	1226	1797
DRD4	1182	1616
COMT	1212	1985
DBH	1004	1245
TPH2	800	1085
MAOA	697	1473
DRD5	646	1008
5HTT	990	1665
BDNF	757	1377
LPHN3	1156	1345

Meta-analysis of DAT1 3' UTR VNTR and DRD4 exon 3 VNTR data by Stefan:
DAT1 3' UTR VNTR: 1338 cases, 2106 controls. For 10R allele versus all others the OR is 0.92 (0.83-1.02), p=0.13. Genotype analysis needs to be performed. Hypothesis (of Barbara) from other studies in adults might be that 9R allele is risk allele for ADHD in adults.
DRD4 exon 3 VNTR: control of HWE in the genotypes analyzed by gel electrophoresis has shown problems in HWE. Bergen uses Genescan analysis, which seems to work better. Groups will look into the problem and re-genotype at least some of the samples. Also, Stefan agrees to genotype 20-

25 samples from each group to confirm genotyping results (groups will select samples with problematic genotypes as well as presumably unproblematic ones). Stefan will inform us about the required amount of DNA (for DRD4 and DAT1, see below) and the exact address for mailing the samples.

Meta-analysis of DRD4 120 bp promoter insdel data by Bru:
DRD4 promoter insdel: 275 cases + 430 controls from Spain and 199 cases + 519 controls from the Netherlands. Genotype frequencies differ between countries, first analysis with a subsample of patients does not show significant results. These analysis will be repeated as a meta-analysis in one of the papers to be published from our group. No additional genotyping by the other two groups seems indicated.

9. Prioritizing of projects for the combined data/samples

Nijmegen:

1) Paper on existing data for DAT1 3' UTR VNTR meta-analysis, stratification by gender and ADHD-subtype, respectively. Look at effect of age? This paper will also describe the phenotyping by the individual groups and introduce the IMPACT study group. With the numbers of samples analysed, we will try to get the paper as a short report into Mol. Psychiatry. Barbara is taking the lead in this paper, this will be the first paper of our group. Stefan will send the genotyping and gender data, and each group will send the ADHD subtype information to Barbara.
2) Paper on DAT1 3'UTR VNTR and intron 8 haplotype, DRD4 exon 3 (and promoter insdel) and COMT Val158Met polymorphism, looking at effects of gender and ADHD subtype. For this, the intron 8 VNTR needs to be genotyped by most of the groups and the DRD4 problems have to be cleared. Barbara will distribute the protocol for genotyping of the intron 8 VNTR, but you are also welcome to send your samples to Nijmegen for genotyping. Also the necessary info for this will be sent. Stefan will provide the group with the protocol for DRD4 genotyping via fragment analysis.

Barcelona:

1) Dopamine system genes: replication of earlier findings (consecutive inclusion of groups from IMPACT, depending on available funding).
2) Laterality genes: replication of earlier findings (consecutive inclusion of groups from IMPACT, depending on available funding).

Bergen:

1) TPH1 and TPH2, replication of earlier findings. Will include the TPH2 data already available in the group.
2) SLC6A4, replication of earlier findings. Will include HTTLPR data already available in the group.

Würzburg:

1) GLUT3 and 6, replication of converging evidence from earlier studies.
2) NOS1, replication of earlier findings.

We also have the data from BDNF for a large group, only the Dutch sample would have to be genotyped. Given the results in depression, it might be interesting to look at gender effects and/or comorbidity. This would be a nice student project. (Norwegian group is possibly interested)

10. Practical organization of the work, database, genotyping (including aspects of costs) and quality control (across sites)

> Practical considerations with regard to each planned projects (e.g. amount of DNA needed, where to carry out genotyping) will be explicated in the individual project proposal.

> Bru has summarized the genotyping costs for different numbers of SNPs in different numbers of samples in Barcelona, Bergen and at Prevention Genetics (see attachment). Genotyping at the German site is comparable with regard to price. Except for Prevention Genetics, access to the genotyping facilities is through our collaboration. Depending on the number of samples and SNPs to be analyzed, we might want to choose different sites for genotyping.

> Quality control issues: With regard to re-analysis of DRD4 we will send samples to Stefan. Stefan has also agreed to take along the DAT1 3' UTR VNTR to confirm genotyping results of this assay. For quality control across sites in future assays we will take along 8 CEPH cell line samples. Bru sends us the numbers of the cell lines to choose, so that we all use the same samples and can compare the results for polymorphisms that are genotyped by more than group. Each site already has quality control measures, taking along blancs and duplicates on each plate.

11. Authorship issues

Every group lists the number of people involved in the work at heir site. Not all of them might need to co-author each publication, but for some of the publications we might want to list everybody.

Würzburg:	3 junior clinicians, 1 senior clinician, 1 junior labperson, 2 seniors/groupleaders	= 7
Barcelona:	3 geneticists, 2 senior clinicians, 2 PhD students, 2 junior labpersons	= 9
Bergen:	2 geneticists, 2-3 PhD students, 2 junior clinicians, 2 senior clinicians	= 9
Nijmegen:	1 PhD student, 3 senior clinicians, 2 geneticists	= 6
Non-active members:	Steve, Phil	= 2

In total, these are 33 persons.

Depending on the manuscript, we will need to decide who gets on, at which position. Replication papers will probably be treated different from papers with a whole new idea. As we are planning a considerable number of papers, we expect no problems in the authorship issues.

12. Future meetings/contacts, acquisition of external funding

> We decide to have 1-2 meetings per year, one preferably combined with a scientific congress that most of us are visiting anyway. Additional meetings will be by phone or video conference.

> The next meeting might be planned at the ECNP which is to be held from 31-8 to 5-9 2008 in Barcelona.

> It will be important that our group is represented and presented at the major scientific meetings, to gain publicity (of course we first need some interesting results). We have to think about oral presentations at the ECNP, the WCPG etc. For 2009 we will propose a symposium at the ECNP about (cause and course of) adult ADHD, with 5 people from our group presenting on e.g. genetics, phenotype, endophenotypes, diagnosis and treatment of adult ADHD. Andreas will prepare a first draft of this proposal.

> After publication of a few papers by our group, we want to apply for external funding. For large projects we might look at the European Framework program (perhaps we have to suggest a project to Brussels, first?) and perhaps the NIH. Other suggestions are welcome.