IMpACT meeting Florianopolis, Brazil, 19-20 of November 2015

Present: Claiton, Peter, Eugenio, Bru, Toni, Marta, Alejandro, Nina, Andreas, Astri, Jan H, Marieke Klein, Angelien (summary)

Agenda:

- Welcome by Claiton and Barbara
- Business meeting
    - Website news (Angelien)
    - Internet-based testing
        - First proposal of a task battery (Barbara)
    - Grants
        - (EU) projects: how to coordinate and integrate existing ones? What works well, what does not? Opportunities for new grants? (Barbara, Andreas)
    - Sharing of exome chip data
    - How to move on with individual GWAS hits?
    - Result highlights from individual site studies (10 minutes for each site, with slides)
- Brainstorm session
    - Progress on personality project (Claiton, Toni, 15minutes)
    - Progress of exome sequencing in ADHD (Barbara, 15 minutes)
    - The microbiome in ADHD – progress and plans (Alejandro, 15 minutes)
    - Progress on induced pluripotent stem cells for ADHD research (Andreas, 15 minutes)
    - Plans for GWAS-MA on adult ADHD (Marta, Bru, 20 minutes)
    - Epigenetics in ADHD – is the time ripe? (Peter, 20 minutes)
    - Adult-only ADHD – what is it – and can we bring this field forward with IMpACT? (Eugenio, 30 minutes)
    - Plans for projects involving the IMpACT database for 2016: per country (skipped because of lack of time)

<u>Business meeting (morning session)</u>

Website (Angelien)

Angelien presented the new lay-out of the IMpACT website. All people were very positive about the updated version.

Member login should become accessible for all members of IMpACT, not only PIs. We can then use this protected area to share recent articles, posters, and presentations (and also some nice foto's) and have a more active usage by all members.

Everybody should add links to IMpACT website to their websites.

Internet- based testing- first proposal of a task battery (Barbara)

We got funding from the ECNP to develop a task-/questionnaire battery for shared acquisition of phenotyping data via the internet. With part of this money, a manager was paid to make a first selection of potential instruments to be used. All selected instruments can be translated into the site-specific language by a language institute. Subsequently, we will have Delosis build the internet-based platform to take the tests.

Barbara explained all instruments of the first proposal. The first selection would result in a battery of in total 125 minutes length. This is too long. We decide to split the battery up in different chunks that can be provided to the patients and healthy participants at different time points. We make a first raking of the instruments:

Measurement	# Items	Duration	Chunk
Demographics (occupation, income, education, father's/mother's age at birth) and add if ADHD is present in the first relatives	14 items	3 min	1
Weight & height, waist circumference	3 items	2 min	1
Adjusted version of the Family Interview for Genetic Studies (FIGS)	19 items	2 - 20 min	Take out, question added to demographics
Adapted version of the List of Threatening Life Events (LTE)	22 items	4 min	1
EuroQol-6D questionnaire (EQ6D) (quality of life)	19 items	4 min	2
ASESA questionnaire (inattention, sleep, circadian rhythm, eating pattern, mood, and general health questionnaire)	67 items (selection of total)	10 min	1, but needs further shortening, if possible
Adult ADHD Self-Report Scale (ASRS, including emotional lability)	18 items	6 min	1
Behavior Rating Inventory of Executive Function (BRIEF-A)	75 items	??	Take out, as licences are needed, replace with other cognitive tasks
Delay discounting task	n/a	20 min	2
Shortened version Temperament and Character Inventory (VTCI)	105 items	20 min	Take out, replace by Zuckerman
Empathy Quotient (EQ)	60 items	6 min	3
Autism-spectrum Quotient (AQ)	50 items	6 min	1
The Inventory of Callous-Unemotional traits (ICU)	24 items	4 min	1
Reactive-Proactive Aggression Questionnaire (RPQ)	23 items	4 min	1
Barratt Impulsiveness Scale (BIS-11) or suckerman	30 items	5 min	1
Sensitivity to Reward and Sensitivity to Punishment Questionnaire (SRSPQ)	??	??	3
Drug Abuse Screening Test (DAST)	10 items	2 min	1,2,3 (for consistency)
Fagerstrøm Test for Nicotine Dependence	9 items	2 min	1,2,3
Alcohol Use Disorders Identification Test (AUDIT)	10 items	2 min	1,2,3

Claiton suggested to integrate such a battery somehow into the treatment, but this might be hard at several of the IMpACT sites. Including psycho-education could help: how are those measurements related to ADHD, but we might not want to make it person-specific. Giving feedback to the participant upon completion of battery might be nice, but hard to implement.
Andreas asks whether those tasks cannot be implemented into the systems at their own site. As we want to collect the data uniformly in a single database, this is not desirable. There will be a link on the website, which will provide a portal for access to a safe environment. Every patient will get their own code. Barbara will ask Delosis to send information on the security measures for their platform, which might be needed for ethics application at several sites.
Would it be possible for the patient to get a report and to take this to a docter? About this idea there are mixed feeling from the different sites. It is decided that every site PI can make their own decision about giving a report to a patient. It has to be clear, however, that this is not a clinical assessment, it is a research assessment. The battery comes on top of each site's clinical assessment.
After a certain number of months, we should evaluate the battery and remove/add questions, if necessary.
Missing measurements: WURS, medication adherence questionnaire from Brazil, and possibly Sheehan disability score.

Grants: EU projects: how to coordinate and integrate existing ones? What works well, and what does not? Opportunities for new grants? (Barbara, Andreas)

- Barbara presented a slide with different grants and projects we have achieved within IMpACT by working together in an active and cooperative way.
- In the future, we should try to organize all general meetings back to back.
- Do we want more grants? We answered yes, but not soon. Peter Lesch and Alejandro are willing to coordinate a new grant proposal for the EU, should there be an opportunity.
- Grants opportunities in the coming years:
    - Promoting mental health and well-being in the young (RTD) Deadline 2017
    - Jacobs foundation
    - Food safety call, 12 million, Impulsivity and compulsivity and the link with nutrition lifestyle and socio-economic status. Apparently, Jaanus Harro is planning a project proposal. Barbara will contact him to see if people from IMpACT can be included.
    - Another ITN?

Sharing of exome chip data

Barbara asks Jan H, if the full summaries from the exome chip data analysed Tetyana can be shared with the other IMpACT members (e.g. allele frequencies of all variants in cases and controls, potentially broken down by site). Sharing data within the consortium is no problem, but sharing data outside the consortium is dependent on the ethics approvals from different sites.

How to move on with individual GWAS hits?

Now that we finally have significant findings for ADHD from GWAS, we can think about designing interdisciplinary projects on individual hits. Important is that we need to be sure that those hits are also relevant for adult ADHD. We should prioritize the different variants, make a list of the genes

implicated by the hit, and investigate how to perform the functional analysis. This is actually already put in motion as part of Aggressotype.
Marta has funding for RNA studies on 300 patients, Andreas, Jan H, and Barbara have collected RNA from patients. Marta will send an email about the protocols used for the isolation, how much RNA, how many samples, ect, and perhaps we can centralize the processing to reduce heterogeneity.
We can also look at follow-up: make a distinction between children who had ADHD and remit and children who had ADHD and persist with the longitudinal follow-ups of the IMAGE cohort at the UK and Dutch IMpACT sites.

Results highlights from individual site studies
Germany, Wuerzburg, Peter Lesch: CHD13: Towards characterization of the CDH13 risk gene of ADHD. Results of histology studies and behavioural assessments were presented.

Netherlands, Marieke: Title presentation: Genetic overlap between Intellectual Disability (ID) and ADHD. There is genetic overlap between ADHD and ID, and we have selected 3 genes of interest for ADHD. Discussion points: 389 ID genes analyzed with KGG and 392 with MAGMA, suggested to do both analysis with 389 genes. Is there a correlation between IQ and inattentive and can we correct for that? It was also suggested to perform gene-set analysis of nominally significant genes (of PGC ADHD risk analysis) with inattentive and hyperactive/impulsive symptom counts in the IMAGE cohort.

Norway, Jan H and Astri Lundervold: (1) Publication Tetyana on exome chip results. Back-to-back submission with ADHD-BPD paper did not work, for the latter we are fighting problems with contact to BPD-PGC group. **(2)** C-section: Hypothesis: Link autism and ADHD, large sample sizes available and connect this with the Swedish register. **(3)** Neuropsychological data of all IMpACT sites could be combined, and therefore we could use the help from Astri.

Spain, Marta/Toni: (1) miRNA analysis, funding for miRNA analysis of 300 patients. **(2)** Taskforce ADHD and Bipolar: Join all data from different sites about ADHD and Bipolar and investigate more in the bipolar/ ADHD connection. Brazil mentioned that it has also data from bipolar patients.

Brazil, Claiton: Adult ADHD Persistence-Remission in adults; remission does exist in people diagnosed with adult ADHD, too. Therapy has no influence on this group.

Several groups have published nice papers on IMpACT-related subjects individually, that others were not aware of. It could be beneficial to share the results or plans with the IMpACT members. We could then find out whether others also have data that could be used, which could improve power and impact of a publication. Sometimes there are good reasons not to include data from other sites, and this fine also, of course, but it might be good to inform the other sites after all. We decide that we will create an item on our monthly TCs to share results/paper plans.

Brainstorming session

Progress on personality project (Nina): Nina presented the progress on the harmonization of the IMpACT data. This is not complete yet. In the meantime, there is more data collected. Nina will write all members an email with the outline of the project and the related research questions and what

she need from all members to answer the question. The aim is to characterize the patients in a better way. The mathematics for the analysis is there (Alejandro). Barbara, Claiton, Toni and Alejandro will have a meeting to frame the work.

Progress of exome sequencing (WES) in ADHD (Barbara): Currently, there are three main approaches for WES within IMpACT: (1) Use of large pedigrees (collaboration with Peter, Würzburg, Jordi is drafting a manuscript); (2) case-control analyses of IMpACT-NL samples (collaboration with Ditte Demontis, Denmark; submitted to JAACAP); (3) future plans on sequencing isolated cases (probably genome sequencing), using NeuroIMAGE cohort; including the age of the father, about 30 families are available. Norway also has WES data available.

The microbiome in ADHD (Alejandro): Taxonomically identification of the bacteria present in the faeces is done by sequencing of the 16 s RNA region. After analysis of cases and controls there is a difference between cases and controls in the numbers of bifidobacterium. Bifidobacterium is involved by the phenylalanine pathway (precursor of dopamine). Number of phenylalanine-producing bacteria is correlated with reward response in the brain. Now collecting faeces samples from IMpACT-NL. Question: Who would like to join this research? Spain has already joined; Brazil is interested. Question after the presentation: Which portion of phenylalanine is coming from the gut? This is 100%. Phenylalanine might be blocking the tyrosine receptor?? How can this be explained?

Progress on induced pluripotent stem cells for ADHD research (Andreas): The aim is to model ADHD and ASD risk variants. This work is part of the MiND project. For ADHD, patient cells are available for PARK2 CNVs and for ASD patients with CNTNAP2 SNPs were selected for this study. Andreas mentioned that they are willing to test additional genes of interest, if patient material is available. At the moment, it is not clear if the PARK2 CNV is stable across the passages, but this will be checked. The group is working on a blood cell protocol, which would be very helpful for the consortia effort. For now, patients with CNVs might be more promising, because of the large effect sizes of such variants, but future sequencing studies might also provide SNVs of interest.

Plans for GWAS-MA on adult ADHD (Marta): Sent a proposal to PGC, waiting for their approval. Genetic correlation between childhood and adult ADHD, cross-sectional study will be done, and not a longitudinal study, as to not overlap with Jonna's plans for MiND. 23&me may also be included. Ben Neale needs to register you as a user and then you can use the data.
Additional project being prepared: Genetic relation between cannabis use and ADHD using the international Cannabis Consortium samples and PGC-ADHD samples. Heritability rate of cannabis is 23%. Approval of both consortia only for the summary statistics is obtained. This may not enough, given the overlap between ADHD and cannabis use. Results may only be meaningful if the overlap is removed. Patients with abuse of or dependence on cannabis also available in Brazil. Exclude patients with psychiatric disorders from the cannabis cohort but also cannabis users from the ADHD samples. Marta thinks this will be possible. Children don't use cannabis until now but for the future you never know. Other IMpACT samples can also be added to this study because you have the information from the patients if it is using cannabis or not. Analysis could concentrate more on the biology than on polygenic scores.

Epigenetics in ADHD (Peter): Prenatal stress in 5-HTT-deficient mice (heterozygotes) showed differential programming of genome-wide promoter methylation. Due to GxE, expression of myelin-associated genes in the hippocampus was altered. This was correlated with anxiety-like behavior. In the future, CDH13, LPHN3, and TPH2 will also be tested. Also the link between methylation and mitochondrial dysfunction will be investigated. Marta mentioned that they have funding for MiND to test methylation in PMCs in ADHD patients and controls (genome-wide). Medication might affect methylation patterns. Also the immune system might be involved in variable methylation patterns. As in patients only blood samples are considered, one must keep in mind that methylation patterns in the brain might be different.

Adult-only ADHD (Eugenio): Second and third finding of significant proportion of adults with ADHD who did not have childhood symptoms. Those findings show similar impairment in those adult-only cases as in persistent cases. We have very animated and constructive discussion about those findings and the underlying theory.

- Adult persistent ADHD and adult-only ADHD, are those two different ADHD adult phenotypes or is it one phenotype with the same underlying biology?
- Are symptoms in childhood just overlooked?
- Andreas: this should be further investigated, but we shouldn't call it ADHD. This would cloud the process of finding out what the etiology of ADHD is.
- Barbara: yes, but DSM-IV ADHD is not a single concept with a single etiology – so why not call this new phenotype ADHD, too?
- Toni: Perhaps the biology is the same, and this type is due to the environment.
- Alejandro: maybe they can better deal with their impairment over a long period of time.
- Claiton: We accept patients who had no problems until the age of 12 years and treat them as ADHD patients.
- Barbara: different levels of stressful life events and genetic vulnerability might make people reach the threshold to get ADHD at different stages.
- Andreas: Everybody agrees on the fact that this is a neurodevelopmental disorder, we should not mix this up.
- Toni: ADHD is the most specifically diagnosable disease using the DSM-IV criteria.
- Barbara: <u>This topic should be discussed in a paragraph of our review from the ECNP network ADHD across the Lifespan</u>.

Plans for 2016 IMpACT projects per site

<u>Angelien will send e-mail to collect the slides people prepared.</u>