Minutes 3rd TC ENIGMA-ADHD-We 5 Feb 2014

Attendees:
Janneke Dammers, Maarten Mennes, Theo van Erp, Paul Thompson, Phillip Shaw, Thomas Frodl, Pamela Douglas, Patrick de Zeeuw, Steve Faraone, Lizanne Schweren, Jan Haavik, Annette Conzelman, Ben Neale, Yannis Paloyelis, Danny Brandeis, Sarah Medland, Alysa Doyle, Marcel Zwiers, Katya Rubia, Barbara Franke, Janita Bralten, Kathrin Zierhut (we missed a few additional people).

Agenda:

- **Abstract HBM**
- **Progress so far**
- **Descriptive and analysis plan**
- **Other points of discussion**

Abstract HBM

Attached in the e-mail the abstract that has been sent to OHBM can be found. If you have not done so please fill in your name and affiliations on the authorlist to be named for the abstract and so we can put the correct affiliations on the ENIGMA website so everybody who is contributing in our working group is visible.

Progress so far

The excel sheet that is attached to the e-mail summarizes how far we are in compiling the data. Most data is complete. The data inclusion will end this week on Friday. The numbers we have so far are exceptionally large for an ADHD study on brain volume as we have around 1400 cases and controls. Katya Rubia mentioned their sample was sent in yesterday, Patrick de Zeeuw remarked their sample will be sent in on Friday, and Phillip Shaw commented that their analysis was run with MAGet, but they reran the segmentations with Freesurfer as well. They used the data of timepoint one from their longitudinal dataset. However the quality control steps for Freesurfer are not finished yet and will not finish before Friday, although they will be finished by the end of the month. The volumes that you get with MAGet are comparable, however not all the structures are the same, for example you do not get the hippocampus and the amygdala, and the striatum you get as a whole. Philip is just now busy to disentangle the striatum volumes. Details on this will be discussed in a smaller group.

Descriptives and analysis plan

An overview of the distribution of age and gender was attached to the e-mail. This overview was done for around 2000 individuals, so not the complete group yet. The age distribution looks ok, even though there is a peak at the younger ages, there are still also a number of adult samples. For gender, there are more male ADHD cases, which is in line with the literature being dominated by boys with ADHD. We discuss that we need to match on age and gender. As the number of samples is high it can be possible to match on age and gender between the groups. Simply correcting for gender will not solve the problem. As there might be complex age x diagnosis effects it is felt by all that it is important to match.

Criteria that were used for the diagnosis of ADHD in adults should be checked throughout the samples to evaluate if different sites used different cut-off criteria (5 versus 6 symptoms).

Considering the analysis steps the first point that was discussed is the QC check for outliers. It is always a discussion if outliers should be excluded, and the proposal was to exclude individuals if their volumes were more than 3 standard deviations away from the mean. Quality control steps on outliers can be quite arbitrary, and there are outliers detection methods out there. Three options were mentioned, the first is a statistical option, the second is to analyse with and without outliers, and the third is visual inspection of the brain data. We will investigate how other working groups are dealing with this issue to keep the studies as comparable as possible. It also needs to be checked if the data distributions are comparable across sites.
Additionally Pamela will circulate a paper that uses the selection of an ROI of the background noise to check for outliers that investigates if the noise is non-homogeneous. This might be interesting to take into account in future analyses.

For the primary analysis the idea is to perform a mega-analysis for different structures, which would be the individual subcortical structures and total brain volume. Another option would be to perform an analysis across all volumes together. The suggestion is to perform an PCA/ICA decomposition across all volume, defining components in there. This way you would need to correct for less tests (compared to the single structure analysis). Next to that it can give additional information as a component might represent a network. As the sample size is large, possibilities of finding the components in one half of the data and testing them in the other half of the data are also possible. As these multivariate analysis methods are more complicated, it is suggested that this should better be postponed for a second paper.

A point raised by Theo was that mega-analyses possibly have smaller effect sizes than meta-analyses. Therefore it might be worthwhile to test both. This might be because of sample differences, but it is hard to tell. Statisticians might be interested in this. This will also be interesting for the comparisons of the results to other disorders and might need to be addressed in the supplementary materials.

Next to the main analyses age should also be addressed. This could be done in age bins or as a continuous variable, which will depend on the distribution and comparability between sites. Lizanne mentioned that medication use should also be addressed when investigating age. Medication use might need to have its own additional analysis. Opted was that age should be corrected for when medication use is investigated and vise versa. Difficulty with medication use is the availability of data, as medication use is measured differently at different sites. This will be looked at. The idea is to take medication into account but most likely it will not be possible to differentiate much for medication use. It is felt as an interesting point to differentiate between different medications. We shortly discuss whether or not it makes sense to look at whether patients were off medication for the imaging, as for other medications (notably antipsychotics) short term effects on brain volume have been described, and MPH is known to affect blood pressure. The suggestion was made to keep the age effect corrections simple in the first paper en potentially make another paper that will look into the age effects.

Another point will be comorbidity. An important point on comorbidities will be to check what was measured between different sites to make sure that the all comorbidity is checked for. In that regard it will be possible to make a group of ADHD individuals that have a certain comorbidity and compare to controls, but it might be more difficult to make the group of ADHD individuals that do not have the comorbidity as it is possible that the comorbidity has not been checked for.

Other points of discussion

Sarah raised the point that it can be useful in the paper to comment on variances between cases and controls, this considering that ADHD individuals might have more head movement in the scanner.

If the first paper is ready it will be interesting to compare the results to other disorders. We need to take into account that the other disorders will have samples that are adults, so therefore a split analysis for 2-3 age groups would be useful to have in the first paper.

To do next:

- Put your name on the author list if not done so yet
- Send in your data, if possible, before the weekend when we will close the inclusion
- Check cut off criteria for diagnosis between sites
- Check medication data and information on comorbidity data between sites