Teleconference minutes | November 12th 2015

8am PST / 9am Edmonton / 10am Mexico City / 11am EST / 2pm Campinas / 4pm UK / 5pm Germany / 6pm Kuopio / 3am Melbourne

Access Numbers

Toll Free Access Number:* *(888) 921-8686***

International Toll Number: ***(678) 259-1049***

Conference ID ***3102675114***

Chair: Christopher Whelan

Attendees Present:

- Angelo Labate
- Carrie McDonald
- Christian Rummel
- Christopher Whelan
- Derrek Hibar
- Emanuele Bartolini
- Karen Blackmon
- Luis Concha
- Mark Richardson
- Niels Focke
- Nuria Bargallo
- Reetta Kalviainen
- Sarah Carr
- Sonya Foley
- Stefano Meletti

Apologies:

- Chantal Depondt
- Clarissa Yasuda
- Gianpiero Cavalleri
- Paul Thompson
- Sanjay Sisodiya
- Simon Keller

Action Items:

- Chris to write and circulate an R script / statistical analysis protocol in the **next 10 days**.
- Subgroup members who disagree with the covariates we plan to include in this script should let Chris or Sanjay know ASAP.
- The 16 subgroups who have finished processing their MRI data should complete statistical analysis by **December 4th**.
    - The 5 remaining subgroups should complete analysis by **January 15th**.
- Chris to run a meta-analysis of cross-sectional volumetrics results before **December 31st**.
- Chris and all ENIGMA-Epilepsy members to collaborate on an abstract submission for OHBM 2015, due **January 7th**.
- Groups contributing to ENIGMA-Epilepsy DTI should complete analysis by **January 15th**.

Business:

1. Finalize covariates for statistical analysis

- **Chris** thanked the group for completing the clinical characteristics spreadsheets. He surveyed the most widely available clinical characteristics with Sanjay. After some discussion, Chris and Sanjay suggested that **we could run three continuous regressions** using the R statistics package:
    - The first analysis would include **age, sex and intracranial volume (ICV)** as covariates.
    - The second analysis would include **age, sex, ICV, handedness** and **prior clinical MRI findings** (e.g. sclerosis) as covariates.
    - The third analysis would investigate the association between **duration of epilepsy** and subcortical/cortical brain volumes.
- As we previously agreed, this statistical analysis will focus on four main epilepsy phenotypes (compared with healthy controls):
    - All epilepsies (i.e. anyone with a syndromic diagnosis of epilepsy, aged 18-55)
    - Generalized epilepsies (aged 18-55)
    - Focal epilepsies (including TLE, OLE, FLE, PLE; aged 18-55)
    - Temporal lobe epilepsies (including MTS+ and MTS-; aged 18-55).
- **Nuria** asked whether an imbalanced sample size between cases and controls could cause issues for the meta-analysis. For example, her group (IDIBAPS) has N=240 adult epilepsy patients and N=30 healthy controls.
    - **Derrek** said that this will not cause any issues. His meta-analysis script does not require cases and controls to be age- or gender-matched.
    - **Chris** said that other ENIGMA disease working groups (e.g. ENIGMA-Major Depression & ENIGMA-Schizophrenia) also featured imbalanced case:control groups, but their findings were still robust and they were published in high-impact journals (see Schmaal et al., *Molecular Psychiatry*, 2015 and van Erp et al., *Molecular Psychiatry*, 2015).

- **Karen** suggested that we should aim to control for the quadratic relationship between age and gray matter volume. For example, we could segregate patients into those aged 12 years old and below, 13 to 15, 16 to 18, etc.
    - **Chris** clarified that for this first-phase analysis, **we will only study participants aged 18-55.** Therefore, it is not strictly necessary to control for the relationship between age and gray matter. Nonetheless, we should re-visit this issue when we run the DTI analysis, as Karen highlighted that there is evidence to suggest a quadratic relationship between age and white matter microstructure in adults.
- **Chris** also highlighted the possibility of segregating patients based on their **side of seizure onset**. Typically, ENIGMA disease working group report bilaterally averaged measures (e.g. "gray matter atrophy in the hippocampus", instead of "gray matter atrophy in the left/right hippocampus") to avoid flipping issues and stringent multiple comparison corrections, however, we may need to make an exception for focal forms of epilepsy.
    - **Mark** commented that it would be very difficult to get a bilaterally-averaged study of temporal lobe epilepsies past reviewers. Reviewers typically expect focal epilepsies to be split into those with left/right-sided seizures so that findings can be interpreted ipsilateral/contralateral to side of seizure onset.
    - **Chris** agreed with **Mark** and suggested the following compromise: we should examine bilaterally-averaged brain volumes for the 'all epilepsies' analysis and the 'generalized epilepsies' analysis. However, **for the 'focal epilepsies' analysis and the 'temporal lobe epilepsies' analysis, we should split patients up based on their side of seizure onset**.
- The group agreed that running a bilateral analysis for 'all epilepsies' and 'generalized epilepsies', and running a left/right-sided analysis for 'focal epilepsies' and 'temporal lobe epilepsies', seemed like a sensible compromise.

2. Finalize deadline for statistical analysis (Project 1: ENIGMA-Epilepsy Volumetrics)

- **Chris** said that now we have finalized the covariates to include in our statistical analysis, he can code an R script for statistical analysis with support from Derrek Hibar, Neda Jahanshad and others at the ENIGMA Center. This R script will be circulated to all groups in the next 1-2 weeks. Preparation of Excel spreadsheets containing volume measures and covariates should take no longer than 1 hour at each site, whereas the script itself should only take seconds to run.
- **Chris** reminded the group that 15 sites have completed the image processing and QC sections of Project 1 (ENIGMA-Epilepsy Volumetrics).
    - **Christian** corrected Chris, clarifying that his site (Bern) have also finished the data processing, so the total number of sites ready to proceed is **16**.
- Based on the fact that 16 sites have finished image processing and a further 5 sites need additional time to process their data, Chris suggested that we set **two deadlines for groups to run the R script:**
    - **DECEMBER 4th** for groups who have finished image processing.
    - **JANUARY 15th** for groups who are still processing their images.

- **Carrie** mentioned that the American Epilepsy Congress (AES) meeting commences on December 4th. Groups attending this meeting may find it difficult to meet the December 4th deadline.
    - **Chris** said that if we set a later deadline (e.g. December 18th), it may interfere with the Christmas holidays. We would like to meet the abstracts deadline for the Organization for Human Brain Mapping (OHBM - January 7th). Therefore, he suggested that we keep the December 4th deadline, but groups attending AES should not feel pressure to meet this deadline. We should still have enough data for a 'preliminary findings' abstract.
    - The group was happy with a deadline of **December 4th** for **completion of analyses at 16 sites** and a hard deadline of **January 15th** for **completion of analyses at all sites.**

3. Possible submission of preliminary results as a conference abstract

- **Chris** asked the group if they would be happy to submit any preliminary findings to for the 2016 meeting of the Organization for Human Brain Mapping in Geneva (OHBM - see http://www.humanbrainmapping.org/i4a/pages/index.cfm?pageID=3662). The abstracts deadline is January 7th 2016.
- The group was happy to submit to OHBM 2016.
- **Chris** also asked the group if there were any other upcoming neurology or neuroscience conferences that they would like to present potential results at. No additional conferences were suggested; however, groups are welcome to contact Chris with suggestions at a later date.

4. Extend deadline for ENIGMA-Epilepsy DTI

- **Chris** told the group that 4 of a possible 15 sites have completed the image processing protocols for our second project, ENIGMA-Epilepsy DTI.
- Although these numbers are small, he commented that ENIGMA disease working groups do not typically conduct the gray matter and white matter projects simultaneously; the DTI project usually comes after the FreeSurfer project. It is therefore quite encouraging that we already processed images at 4 sites.
- **Chris** suggested that we aim for a more realistic deadline of **January 15th** for all groups to complete image processing.
- The group was happy with this extended deadline.

5. Other business

- **Nuria** asked Chris what the total sample size is, after the numbers of patients and controls are added up across all sites.
- **Chris** said that the numbers might be as high as **6,800 people with epilepsy** and **2,500 healthy controls.** However, these are only estimates: the numbers will likely be smaller when groups apply exclusion criteria or if certain groups cannot complete the analysis in time. A more

realistic estimate may be N~4,000 epilepsy patients and N~2,000 HCs. Even with these numbers, our study should still serve as the largest ever brain imaging collaboration in epilepsy.