Meeting Called By:

Christopher Whelan, Sanjay Sisodiya

Apologies:

Angelo Labate

Boris Bernhardt

Donald Gross

Graeme Jackson

Neda Jahanshad

Paul Thompson

Patrick Kwan

Renzo Guerrini

Roland Wiest

Sean Hatton

Simon Keller

Terence O'Brien

Call time:

- **08.00** | Los Angeles
- **09.00** | Edmonton
- **10.00** | Mexico City
- **11.00** | New York, Montreal
- **12.00** | Campinas
- **16.00** | London, Dublin, Liverpool, Cardiff
- **17.00** | Genoa, Bonn, Bern
- **18.00** | Kuopio
- **01.00** | Melbourne, Austin

Attendees:

Andrea Bernasconi

Anna Elisabetta Vaudano

Bernd Weber

Chantal Depondt

Christopher Whelan

Derrek Hibar

Emanuele Bartolini

Fernando Cendes

Gianpiero Cavalleri

Helen Cross

Jack Ren

Khalid Hamandi

Luis Concha

Maria Savina Severino

Mario Mascalichi

Niels Föcke

Reetta Kalviainen

Mark Richardson

Matthias Koepp

Neda Bernasconi

Orrin Devinksy

Pasquale Striano

Saud Alhusaini

Sanjay Sisodiya

Stefano Meletti

Thomas Thesen

Minutes

1. Introduction

Presenter: Sanjay Sisodiya   **Notes Taken?** Some

Discussion:

- **Sanjay Sisodiya** welcomed everyone to the new ENIGMA-Epilepsy working group.
- He remarked on the impressive caliber of researchers who have already agreed to participate.
- Many people who have joined ENIGMA-Epilepsy also participated in the ILAE GWAS meta-analysis project (doi: **http://dx.doi.org/10.1016/S1474-4422(14)70171-1**).
    - o   This project established a trusting and collaborative environment for the epilepsy genetics community and we hope to achieve something similar with ENIGMA-Epilepsy.
- **Sanjay** noted that 18 groups have already signed the Memorandum of Understanding and encouraged those remaining groups to sign as soon as possible.

2. Hypotheses

Presenter Name: Christopher Whelan   **Notes Taken?** Yes

Discussion:

- **Chris Whelan** stated that one major tenet of consortia efforts like ENIGMA is that they commence with very broad hypotheses (aiming to identify broad neuroanatomical changes) before progressing onto more specific research questions. Therefore, it is important that we establish a concrete hypothesis from the onset.
- **Chris** suggested the following hypothesis (which can be expanded or re-worded at a later date):
    - o   *'Epilepsy is a network disorder, involving distinct structural abnormalities across cortical and subcortical regions'.*
- **Matthias Koepp** asked why we would need ENIGMA to answer such a question, when many neuroimaging studies, dating back as early as the 1990s, have already provided some answers.
- **Sanjay** reflected that the epilepsy genetics community had worked through these same considerations. The ILAE GWAS consortium, for example, started off by asking whether there are any shared variables between all epilepsy phenotypes. They felt it was important to nurture the collaboration, focus on straightforward hypotheses that might capture 'low-hanging fruit', and then investigate more specific epilepsy phenotypes once the consortium were established. The initial hypotheses were the same as many groups had worked on individually or in smaller groups. So the large sample sizes and enhanced power afforded to us by the ENIGMA framework may help identify common variables in a way that was not achievable with individual, low-powered MRI studies.
    - o   **Thomas Thesen** stated that he could see the appeal of this approach.
    - o   **Andrea Bernasconi** found the ENIGMA framework appealing, arguing that it could be very informative to look for a common denominator across many heterogeneous epilepsy subtypes
- **Derrek Hibar** highlighted some examples from other ENIGMA working groups – the bipolar disorder project, for instance, investigated subcortical morphometry across a broad range of phenotypes despite the prior literature being somewhat heterogeneous. This 'low-hanging fruit' approach worked very well, allowing the group to disentangle structural differences in BPD.

Conclusions:

- The group was happy with the hypothesis originally proposed by Sanjay and Chris.

Action Items:	Person Responsible:	Deadline:
None	N/A	N/A

3. Protocols

Presenter Name: Christopher Whelan   **Notes Taken?** Yes

Discussion:

- **Chris** asked the group if they had looked at the ENIGMA protocols and, if so, whether they had any questions or concerns.
- **Khalid Hamandi** asked whether we should assume the DTI protocols and FreeSurfer protocols represent independent studies.
- **Chris** confirmed that these projects are only loosely connected. It's fine if some groups can only contribute to one or the other.

Conclusions:

- The group did not report any issues with the ENIGMA protocols.

Action Items:	Person Responsible:	Deadline:
None	N/A	N/A

4. Covariates

Presenter Name: Christopher Whelan   **Notes Taken?** Yes

Discussion:

- **Chris** suggested that we include the following covariates in all analyses:
  - Age
  - Gender
  - Handedness.
  - Intracranial volume (ICV).
- **Thomas** asked about including other covariates, like duration of epilepsy or seizure frequency.
- **Gianpiero Cavalleri** suggested that it might be useful to create and circulate a phenotype template for each group to populate; similar to what was conducted for the ILAE GWAS collaboration. Information like the date of scan, diagnosis, duration of epilepsy (etc.) could be collected, if available.
  - **Chris** and **Sanjay** agreed that this would be very useful.
  - **Pasquale Striano** offered to help with this phenotyping sheet.

Conclusions:

- Age and gender will be included as covariates. A phenotype sheet will be circulated to all groups to see about the possibility of including other covariates.

Action Items:	Person Responsible:	Deadline:
Circulate a phenotype sheet to each group.	**Chris, Sanjay, Pasquale**	**June 2015**

6. Inclusion / exclusion criteria   **Presenter Name:**   Christopher Whelan   **Notes Taken?**   Yes

Discussion:

- **Chris** asked whether we should have specific exclusion criteria for each analysis.
- **Derrek** stated that the quality control (QC) procedures, included as part of the ENIGMA protocols, should flag any obvious outliers (e.g. patients with tumours). He recommended that each site should survey their images, one by one, to identify scans that may introduce noise.
- **Sanjay** asked whether we should still exclude people with lesions from the offset.
  - o For example, we could run a full analysis, including all patients, and then a second analysis, whereby we exclude patients with lesions/tumors/sclerosis.
  - o But what about patients with mental retardation, evidence of epileptic encephalopathy or psychiatric comorbidities? Should we include if their MRI is okay?
  - o **Reetta Kalviainen** argued that it might confound our results if we include people with these comorbidities.
- **Derrek** acknowledged that while the situation may be slightly more complicated for epilepsy, the typical approach taken by other ENIGMA groups is as follows:
  - o Start off by including everyone – all patients and controls at our disposal.
  - o Then pare down to a more focused analysis of specific phenotypes and start excluding people with lesions, tumours, etc.
  - o Prior ENIGMA studies have tried both approaches. When we have such large numbers at our disposal, it doesn't appear to make much of a difference whether we employ strict exclusion criteria or not.
  - o **Derrek** suggested that we exclude people with known tumours or lesions.
- **Matthias** disagreed with Derrek's suggestion. He argued that heterogeneity might be our friend here.
- **Derrek** responded that ultimately, we should not include someone if his or her brain volumes cannot be measured properly. However, this will ultimately come down to the QC procedure.
- **Andrea** argued that, as long as the image quality is good, we should include the scan.
- **Emmanuele Bartolini** again highlighted issues with including patients with encephalopathies or cortical dysplasias.
  - o **Sanjay** emphasized how this parallels the genetics studies. In these studies, people raised issue with the inclusion of patients with encephalopathies, etc. However, in the end, when we put together a large cohort which must have included some people with monogenic epilepsies, dysplasia, etc., we still found effects that informed the biological underpinnings shared across epilepsies .
- **Khalid** reiterated that FreeSurfer will not segment pathological brain regions properly, anyway.
- **Derrek** added how there is typically a 5% segmentation failure rate using FreeSurfer, even when analyzing healthy controls.
- **Reetta** asked whether we will segregate childhood, adolescent and adult cases.
  - o **Chris** said that this will be performed as part of a follow-up analysis.
- **Chris** stated that it may be best to continue this conversation on a future call. He emphasized how the ENIGMA protocol does not require groups to specify exclusion or inclusion criteria a priori. Rather, groups can commence analysis and exclude participants from their CSV files at a later stage.

Conclusions:

- Groups will commence analysis and decide upon exclusion criteria at a later date.
- To continue this discussion, especially with regard to age

Action Items:	Person Responsible:	Deadline:	
Commence analysis using the protocols available on the website: http://enigma.ini.usc.edu/ongoing/enigma-epilepsy/enigma-epilepsy-protocols/	**All ENIGMA-Epilepsy groups**	**October 2015**	

7. Timeline

Presenter Name: Christopher Whelan   **Notes Taken?** Yes

Discussion:

- **Chris** asked the group whether they were happy with the proposed analysis timeline of **May to September 2015**.

- While some parties **(e.g. Fernando Cendes)** were happy with this timeline, others requested an extension to October 2015.

Conclusions:

- Chris will extend the analysis deadline to October 2015.

Action Items:	Person Responsible:	Deadline:
Extend analysis deadline on website to October 2015	**Chris**	**May 2015**

8. Other business

Presenter Name: Sanjay Sisodiya   **Notes Taken?** Yes

Discussion:

- **Chris** will follow up with a phenotyping sheet and a Doodle poll for the next meeting.
- The next meeting will most likely take place in one month's time – either before or after the OHBM 2015 conference in Hawaii.

Action Items:	Person Responsible:	Deadline:
Circulate minutes + phenotype sheet. Arrange Doodle poll	**Chris + Sanjay**	**May 2015**