Sixth meeting on the EADC-ADNI Harmonization of Protocols for Hippocampal Segmentation
AAIC, Vancouver, Wednesday, July 18, 2012

Hosts:
Giovanni B. Frisoni and Marina Boccardi – IRCCS S. Giovanni di Dio - Fatebenefratelli, BS, Italy
Simon Duchesne - Laval University, Québec City, Canada

Participants:
Clifford R. Jack - Mayo Clinic, Rochester, MN, USA
Charles DeCarli - UC Davis, CA, USA
Stefan Teipel, Michel Grothe - University of Rostock, Rostock, Germany
Meredith McNeil, Heather Snyder, Maria Carrillo - Alzheimer's Association, Chicago, IL
Derek Hill - IXICO Ltd, USA
Andy Simmons - (NEUROMED), London, UK
Louis Collins – McGill University of Montreal, Canada
Andreas Fellgiebel – University Hospital of Mainz, Mainz, Germany
Adam Schwarz, Peng Yu – Lilly
Lei Wang – Northwestern University Feinberg School of Medicine, Chicago, USA
Michela Pievani - IRCCS S. Giovanni di Dio - Fatebenefratelli, BS, Italy
Gerald Novak - JNJ
Laurie Ryan, Creighton Phelps - National Institute on Aging, Bethesda, Maryland
Lisa Silbert - Oregon Health & Science University School of Medicine
Lennart Thurfjell - GE Healthcare
Hui Jing Yu - Bioclinica
Rod Corriveau - National Institutes of Health
Patricia Cole - Imagepace
Manuel Menendez - Hospital Álvarez-Buylla, Mieres, Spain
Amber Dance - Alzforum
Florent Roche
Joel Schaerer

List of in person participants may not be exhaustive

Remote participants:
Martina Bocchetta - IRCCS S. Giovanni di Dio – Fatebenefratelli, BS, Italy
Adam Christensen - Northwestern University – Chicago, IL
Diane Stephenson - C-PATH
Thorsten Bartsch - University Hospital Schleswig-Holstein, Kiel
Simone Lista - Goethe-University of Frankfurt, Frankfurt am Main
Josefina Maranzano - NeuroRx Research, Montreal, QC
Richard Camicioli - University of Alberta, Edmonton, AB
Lei Wang - Northwestern University Feinberg School of Medicine, Chicago, IL
Patricia Patterson – AstraZeneca, Wilmington, DE

Background
Dr. GB Frisoni introduced the second AA funded-year project work, underling the important aim to harmonized the heterogeneities among over 40 different protocols of hippocampal segmentation, in order to reliably compare hippocampal volumetry across different centres worldwide.

The issue of standardizing the scans acquisition has been largely addressed by ADNI, while the harmonization of orientation and segmentation of MRIs was the aim of the project "A harmonized protocol for hippocampal tracing: An EADC-ADNI joint effort".
We surveyed the 12 most frequently used segmentation protocols in the AD literature, we operationalized the differences among these protocols into Segmentation Units, that allowed to assess measurement properties of each Segmentation Unit (stability of segmentation, contribution to total hippocampal volume and contribution to AD-related atrophy). All this quantitative information was given to a panel of 16 experts through the Delphi method. In 5 rounds, the Delphi Panel converged on an evidence-based final definition of the Harmonized Protocol. This Harmonized Hippocampus covered the 100% of hippocampal tissue, captured the 100% AD-related atrophy and showed very reliable features (>.96).

Benchmark Images
Dr. M. Boccardi described the first version of the Harmonized Protocol draft, turning the Delphi panel criteria into operational instructions. This version was given to 5 acknowledged experts in hippocampal segmentation (L. Apostolova, M. Bocchetta, R Ganzola, G. Preboske and D. Wolf), called Master Tracers, to segment a set of benchmark images (40 hippocampi for each tracer, for a total sample of 100 segmented hippocampi on 1.5T and 100 on 3T images).
We computed the ICC values and the results were very high ("absolute" intra-rater >.9 and inter-rater >.95). We also computed the Dice's coefficient, which showed the spatial overlapping agreement on segmentation and we modified it for computing the overlap among 5 tracers. The mean values for this last computation were 0.71 for 1.5T and 0.75 for 3T images. The values were not so high, but it should be considered that they show the overlapping agreement among 5 tracers, not only between 2.
We checked the benchmark segmentations twice: once considering the single segmentations of each Master Tracer and then the 5 segmentations together, mapped on each correspondent MRI slice.
Once identified the main heterogeneities, we defined whether (i) they corresponded to reasonable, and thus acceptable, variability; whether (iii) they represented some error in the segmentation, which was not adhered to the Harmonized Criteria, and thus we asked to correct them if the Tracers agreed; or whether (iii) they were caused by possibly ambiguous definitions or insufficiently defined anatomy in the Harmonized Protocol and thus we improved the description in the Protocol. If the tracers did not agree with correction, it was required to discuss the required editing with the coordinator.
The final aim was to obtain not just homogeneous, but the segmentation most appropriately representing the Harmonized Protocol.

Update of Harmonized Protocol
The first version of the Harmonized Protocol was edited based on the criteria defined by the Delphi Panel, sent to panelists on December 2011, and minor revisions were received within January 2012. Progressive adjustments were made based on the observation of Master Tracers' difficulties in applying the Delphi criteria and based on the identification of the main heterogeneities among benchmark segmentations. A second version with major changes, was again sent to panelists in July to obtain their comments and feedback. The protocol currently consists of 23 pages, including 22 figures, one summary table and one summary figure providing an example of tracing slice by slice.

Qualification Platform
Dr. S Duchesne described the online platform developed to certificate tracers for the Harmonized Protocol. It contains some downloading sections, where a tracer can download the segmentation tool MultiTracer (for whose distribution we obtained the approbation of LONI), the learning screenshot of images, the training and the proper Qualification set of images. During the Training Phase, one can upload his/her own segmentation and check performance through both Quantitative

and Qualitative verification. The first will allow an automatically computation of a selected image segmentation versus the expert reference (slice by slice or considering the whole hippocampus) and showed statistical comparisons and results. The Qualitative feedback will consist in a contemporary visualization of both one's segmentation and the reference on the same MRI slice.
The feedback for the Qualification Phase will not include the visualization of performances, but only the final result "CERTIFIED" or "NOT CERTIFIED" in accordance to the thresholds, which will take into account the average of the 5 expert tracers' segmentations and the variability among them.
The training set will be not available until the completion of the whole Validation Phase of the project.

Update on the Validation Phase 2
20 Naïve Tracers will be asked to train on a set of images that will be provided and then we will give them a feedback for correctness of their segmentations. Naïve Tracers will formally qualify in the certification platform and then they will segment again the same images of Phase 1, this time following the Harmonized Protocol criteria. Another branch of the Validation Phase scheduled that the best 5 qualified Naïve Tracers will segment 240 hippocampi each, to assess the variance due to side, trace-retrace, atrophy, time, scanner and tracer.

Scientific papers schedule
3 papers have been already published/accepted for publication, 3 are in progress and others are planned. GBF says that participation of centres whishing to work on these data for publication of additional papers is welcome and can be discussed.

Publication policy of project products
Dr. GB Frisoni briefly described the Publication Policy and its contents. The project deliverables (i.e. the Harmonized Protocol, the digital Master Tracers hippocampal masks and the training set of images and masks) will be available to the public only at the end of the whole Validation Phase. If one wishes to be a beta-tester, he/she can submit his/her proposal to the Steering Committee and the deliverables can be available after having signed a written cooperation agreement.

The presented slides are available at www.hippocampal-protocol.net.
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Questions/comments from the audience:
Q=question
A=answer
C=comment

Q: Charles DeCarli asked about the management of most rostral and caudal slices, that typically give rise to the largest disagreement.
A: M Boccardi answered that for the first rostral slice we should admit some variability due to the actual difficulties in detecting the first appearance of the alveus and the variability of its appearance, with hippocampal digitations variably and intermittently intercepting the most rostral coronal plane. Instead, for the most caudal slice the Protocol has been improved, in order to reduce variability in the segmentation of the most caudal slice.

C: C DeCarli underlined that some issues may be taken into account regarding the segmentation tool (MultiTracer) chosen for the project.

Q: S Teipel asked whether and how the new approach of segmenting hippocampal subfields may impact the protocol, for instance considering T2-images.
A: GB Frisoni answered that it may impact, but difficult to predict how at the moment.

Q: It was asked whether the Master Tracers must re-segment all images or whether they are just required to edit them, and correct based on the improvements of the protocol and the required corrections.
A: M Boccardi said that they must only edit and correct, not re-segment it all.

Q: D Hill said that the design of the Validation allows to control for many variables, but misses the variability of individual brains and hippo morphologies, since few subjects are examined, who underwent many scans (at different time points, with different scanners, different teslas, etc). He wished that images from many more subjects could be segmented in order to account for individual variability. Enlarge the number of scans will be useful also to train the automated algorithms.
A: GB Frisoni answered that this would require funding for being carried out; if funded it can be done.

C: CR Jack said that he would like that the Master Tracers could provide an independent segmentation of all of the images of the validation branch, in addition to the segmentations of the "Naïve" Tracers, as reference. All participants agreed that this may be useful.

C: A. Simmons underlined that this protocol is ADNI-compatible, but it should also be considered for different kinds of acquisition parameters in different samples. CR Jack said that ADNI parameters are ok and appropriate, so there is no reason to work for different parameters. A. Simmons underlined that anyway there are many trials not using the ADNI parameters. C. DeCarli said to agree with CR Jack and that the possibility to adapt to different acquisition is a different problem.
C: Louis Collins said that in this case the whole protocol should be recreated from zero –i.e. from SUs – starting from images acquired using different parameters.