

Hippocampal Harmonization Meeting  
Minutes of meeting – July 17, 2013  
Boston, Massachusetts

- I. Welcome from **Giovanni Frisoni** to this 8<sup>th</sup>, and last meeting of the Alzheimer's Association-supported EADC-ADNI Hippocampal Harmonization Protocol project. Collaborators from around the world are joining this meeting remotely from Europe, Australia, and United States.
- II. Background (Giovanni Frisoni).
  - a. Standardized protocol for determining hippocampal volume needed as biomarker and surrogate marker to track progression. Also to validate automated algorithms.
  - b. Harmonization needed in acquisition (addressed by ADNI); orientation, and segmentation (addressed by Hippocampal Harmonization Project).
- III. Reviewed steps in project (Giovanni Frisoni).
  - a. Survey of 12 most frequently used protocols for manual segmentation.
  - b. Identify individual tracing units that represent core blocks; putting them back together allow reconstruction of hippocampus and accounts for all variants of manual segmentation protocols in literature.
  - c. Identified 7 individual units whose properties we have measured.
  - d. 16 experts on Delphi panel over 5 rounds assisted in defining benchmarks and other technical issues; converged into one single way of segmenting hippocampus.
  - e. Then asked 5 “master tracers” with extensive experience to segment a number of hippocampi. This represents the “gold standard”.
  - f. Then Simone Duchesne and colleagues developed online platform for anyone wishing to trace hippocampi according to the protocol.
  - g. Finally, trained 14 naïve people and asked them to segment a large number of hippocampi, with the aim to validate the use of the Harmonized Protocol.
- IV. Validation (Marina Boccardi)
  - a. Experimental design: We planned to recruit 20 tracers to segment 40 hippocampi based on their local protocols; then they had to learn how to segment based on the harmonized protocol and then resegment the exact same images using harmonized protocol. Actually had 21 tracers that completed segmentation by localized protocols. 13 of them completed 3 rounds of training and qualification (one additional tracer qualified through a different procedure). 14 tracers completed resegmentation with harmonized protocol.
  - b. During the training, tracers received feedback to see how close their segmentation is to the gold standard. We collected numerous statistics, and compared two different methods of computing overlapping indices (Dice and Jaccard). Jaccard was a much more dynamic measure.
  - c. First phase of validation–Data presented in poster P2-136 at AAIC.

- i. 14 tracers completed both rounds of segmentation. 10 ADNI subjects balanced by 5 degrees of MTA scores; other variables not as well balanced.
  - ii. Inter-rater ICC – compared absolute method vs. consistency method. Giovanni said if you use absolute method ICC you appreciate the concordance/reliability of the harmonized protocol much better than if you use the consistency method. Consistency not sensitive to systematic over or under measurement. Charlie DeCarli added that variance around local tracers is really high. Giovanni added that some of local protocols were in fair agreement with harmonized protocol but others were in poor agreement.
- d. Second phase – Selected 5 best tracers and have them segment a much larger number of hippocampi (240). Some images were re-segmented so we could assess intra-rater reliability. went into greater depth into major sources of variance – side, trace-retrace, atrophy, time, scanner, rater. 15 subjects – repeated for magnet field, scanners, time points, etc. 1.5T and 3T scanners. All manufacturers represented.
  - i. High consistency and absolute volume scores for ICC
  - ii. Inter-rater reliability – all over .90; Consistency and absolute methods almost perfectly related for three tracers. Tracers did a great job!
  - iii. Preliminary analysis of variance – variability of tracer much lower than the variability due to atrophy severity and even lower than variance due manufacturer. Analyses will be re-done with cleaned-up dataset.
- e. Next we will be looking at validation vs. pathology – to see whether volumes correlate with published work on pathological specimens. Will use samples from Mayo (50) and UCLA (17) with postmortem scan taken at 7T in UCLA. Also collaboration with people segmenting subfields trying to harmonize subfield segmentation.
- f. Follow up study – to expand the number of subjects and labels – accomplished with funds from the Alzheimer's Association, Savitz family, anonymous donation in memory of Chris Clark, and 50% from industry. This project aimed at extend set of physiological variability to allow greater representation.
  - i. Selected 135 subjects, 270 hippocampi, 5 tracers with best performance
  - ii. Well balanced for many variables – age, scanners, etc.
  - iii. Inter-rater reliability – very high for both consistency and absolute methods.
  - iv. We are gradually releasing material – 100 labels, oriented images, files, etc.; image codes are already on the HP website. By September 15 full suite of products will be online and available to community.
  - v. We are releasing deliverables of the HP project – the harmonized protocol (the manual) can be downloaded freely as well as the training platform can be freely accessed.
- g. Publications: handed out published, submitted, and in preparation manuscripts. Other papers in development.

- V. Next steps (Giovanni Frisoni) – In discussions about developing independent expert committee to advise algorithm developers about using the automated algorithm for hippocampal segmentation in clinical practice and clinical trials.
  
- VI. Discussion
  - a. Feedback from manual tracers – there were challenges in transitioning the software, but it was easy to adapt and understand the protocol. Important to have a really detailed manual on harmonized protocol and this is in development.
  - b. Charlie DeCarli recommended that if you are going to do manual segmentation, better tools are needed. Derek Hill noted that if different tools are used, there is no guarantee you will get the same volume. Will affect qualification. Cliff Jack said this was one of the main points of this project – establishing a standard and was successful in identifying an algorithm despite the tool being using.
  - c. Comment that this type of effort is helpful for using hippocampal volume as a tool for regulatory agencies. Diane Stephenson from CAMD/ C-PATH also urged detailed protocols from the manual segmentation and how they apply to automated methods be shared so that it's clear when sponsors choose to use this as a biomarker they understand how to do segmentation and what protocols increase confidence. Group agreed.
  
- VII. Giovanni Frisoni closed the meeting with thanks to the tracers, funders, all participants and those supporting and facilitating the project in different ways. A special thank you was given to the Alzheimer's Association and the generosity of Mike and Barbara Urbut; Stuart and Amy Savitz; and Harriet K. Burnstein who made the project possible.