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Foreword

HarP: The EADC-ADNI Harmonized Protocol for manual hippocampal segmentation. A standard of reference from a global working group

This special issue of *Alzheimer's & Dementia* marks the completion of an initiative kick-started as long as 6 years ago. At the time, hippocampal atrophy was regarded by International Working Group criteria as one of the biomarkers for the early diagnosis of Alzheimer's disease (AD) [1], academic memory clinics were pioneering its use in real life diagnostic studies [2–4], and clinical trials of disease modifiers were starting to use hippocampal atrophy rates as a secondary outcome measure [5]. Widely different measurement protocols prevented the comparison of diagnostic accuracy and biologic drug efficacy. Standard operating procedures were clearly needed—an effort greatly facilitated by the availability of ADNI (Alzheimer's Disease Neuroimaging Initiative) harmonized image acquisition parameters and procedures [6].

The initiative was kicked off at a feasibility workshop organized by the Alzheimer's Association in Chicago in 2008 where ADNI and European Alzheimer's Disease Consortium key members took part, and experts in imaging biomarkers. A survey was set out to identify the 12 most frequently used protocols for hippocampal segmentation in the Alzheimer's literature and differences in image treatment procedures and anatomical landmarks (Fig. 1), a mandatory step to develop a harmonized protocol [7]. In an exercise reminiscent of a LEGO block game, the preliminary phase did a virtual break down of the hippocampi resulting from the aforementioned protocols in a finite number of three-dimensional (3D)-units summarizing their entire anatomical variability. Biometric features of the 3D-units were then empirically quantitated (e.g. measurement stability, contribution to Alzheimer's-associated atrophy) and fed to a panel of world experts, including the developers of the 12 originally selected protocols, who were charged of coming out with a unique and harmonized segmentation protocol. Thanks to a Delphi procedure adapted to accommodate quantitative information, it took experts five rounds to converge onto a definitive version (the harmonized protocol—HarP).

Five expert researchers on hippocampal segmentation ("master tracers") were then asked to segment 40 representative hippocampi taken from the ADNI database following the HarP, that would be used as the standard of truth of any ensuing procedure (so-called "benchmark labels"). Fourteen tracers coming from 12 imaging laboratories from eight countries in three continents which had not been exposed to the development of the HarP were asked to segment another set of 40 hippocampi representative of the ADNI dataset, trained and qualified to segment following the HarP on an ad hoc web-based environment, and asked to re-trace the same ADNI hippocampi following the HarP. An appropriately balanced design allowed to test the concurrent validity of the HarP versus local protocols, and compare the error variance of hippocampal volume estimates due to the HarP with other sources of error. Finally, HarP hippocampal volumes were validated versus pathological findings in a sample of brains where both high-resolution structural magnetic resonance imaging and a post-mortem examination were available, and publicly available HarP labels were expanded to a large set of 270 ADNI hippocampi to allow the training of automated segmentation algorithms based on machine learning technology.

Clearly, participation to the project was effortful and time consuming at all levels. Protocol developers were engaged in multiple hour-long teleconferences to tease out the finest details of their protocols, master tracers were pressed to carry out the assigned segmentations in due time, Delphi panelists were forced to go through similar sets of questions and issues over and over again until the convergence of most panelists, and naive tracers had to segment dozens (some of them hundreds) of hippocampi in a restricted time frame. Everyone's engagement was astoundingly intense.

Importantly, the HarP is the result of the concerted effort of many minds (Fig. 2). The working group met twice a year for the past 5 years and at each meeting the project was fine-tuned and its experimental design continuously improved thanks to input from participants. An off-workplan expansion of the number of segmented hippocampi was required by automated segmentation algorithm developers, and duly carried out. A large and representative set of certified hippocampal labels obtained with the HarP is now publicly available in the web that can be used to train and qualify human tracers and automated algorithms.

Thanks to the HarP, it is now possible to directly compare the segmentation accuracy of the many automated

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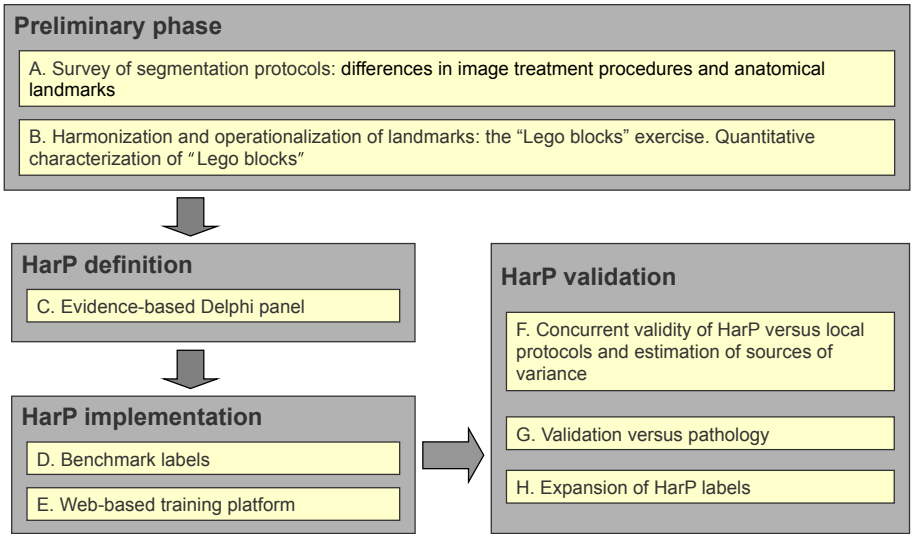

Fig. 1. Steps followed to develop the European Alzheimer's Disease Consortium (EADC)-Alzheimer's Disease Neuroimaging Initiative (ADNI) harmonized protocol for manual hippocampal segmentation (HarP). References to each step are listed below. (A) Appendix I to this Special Issue: "Preparatory Work: Survey of Protocols for the Manual Segmentation of the Hippocampus". (B) Boccardi M, Bocchetta M, Ganzola R, Robitaille N, Redolfi A, Duchesne S, et al. Operationalizing protocol differences for EADC-ADNI manual hippocampal segmentation. *Alzheimers Dement*. 2015;11:184-94. Boccardi M, Bocchetta M, Apostolova LG, Preboske G, Robitaille N, Pasqualetti P, et al. Establishing magnetic resonance images orientation for the EADC-ADNI manual hippocampal segmentation protocol. *J Neuroimaging*. 2014;24:509-14. (C) Boccardi M, Bocchetta M, Apostolova LG, Barnes J, Bartzokis G, Corbetta G, et al. Delphi definition of the EADC-ADNI Harmonized Protocol for hippocampal segmentation on magnetic resonance. *Alzheimers Dement*. 2015;11:126-38. (D) Bocchetta M, Boccardi M, Ganzola R, Apostolova LG, Preboske G, Wolf D, et al. Harmonized benchmark labels of the hippocampus on magnetic resonance: the EADC-ADNI project. *Alzheimers Dement*. 2015;11:151-60. (E) Duchesne S, Valdivia F, Robitaille N, Mouiha A, Valdivia FA, Bocchetta M, et al. 2015;11:161-74. (F) Frisoni GB, Jack CR, Bocchetta M, Bauer C, Frederiksen KS, Liu Y, et al. The EADC-ADNI Harmonized Protocol for manual hippocampal segmentation on magnetic resonance: evidence of validity. *Alzheimers Dement*. 2015;11:111-25. (G) Apostolova LG, Zarow C, Biado K, Hurtz S, Boccardi M, Somme J, et al. 2015;11:139-50. (H) Boccardi M, Bocchetta M, Morency FC, Collins DL, Nishikawa M, Ganzola R, et al. Training labels for hippocampal segmentation based on the EADC-ADNI harmonized hippocampal protocol. *Alzheimers Dement*. 2015;11:175-83.

algorithms that have been and are currently being developed worldwide. Hippocampal atrophy might enter the diagnostic routine of persons with cognitive disturbances in the same way as today we use serum glycaemia for diabetes or erythrocyte sedimentation rate for inflammatory diseases. The effect of different disease modifying drugs on hippocampal atrophy will be directly comparable with a unified metric—of course if one will ever prove effective in the first place.

What next? Clearly, the future of hippocampal volume measurement stays with valid and appropriately certified automated procedures. The web-based environment that human tracers used for training and certification has been released for general use, and will allow algorithm developers test the performance of their products as a preliminary step before submission to scientific journals or regulatory agencies. The Alzheimer's Association is planning the development of a certification procedure for automated hippocampal segmentation algorithms based on the HarP as the standard of truth.

Low hippocampal volume has been qualified by the European Medicine Agency for the purpose of enrichment in AD clinical trials at the predementia stage [8], and a similar application is currently being reviewed in the United States by the Federal Drugs Administration. The qualification of hippocampal atrophy rates or other structural marker of disease progression as a surrogate outcome in clinical trials of disease modifiers will represent a major advancement for the development of effective drugs—the ultimate aim that scientists are working for, that physicians need for their interventions to be more meaningful, and that patients and families have been longing for decades.

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All materials pertinent to the HarP including benchmark and certified hippocampal labels, slide kits, and videos can be found at www.hippocampal-protocol.net.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jalz.2014.05.1761.

Fig. 2. The extended European Alzheimer's Disease Consortium (EADC)-Alzheimer's Disease Neuroimaging Initiative (ADNI) working group for the harmonized protocol for manual hippocampal segmentation (HarP): site principal investigators and co-workers. **Project manager**: Martina Boccardi. **Assistant project manager**: Martina Bocchetta. **Delphi panelists**: Liana G Apostolova, Josephine Barnes, George Bartzokis, Charles DeCarli, Leyla DeToledo-Morrell, Michael Firbank, Lotte Gerritsen, Clifford R Jack, Wouter Henneman, Ronald J Killiany, Nikolai Malykhin, Jens C Pruessner, Hilkka Soininen, Lei Wang, Craig Watson, Henrike Wolf. **Authors of Protocols**: George Bartzokis, John C. Csernansky, Leyla DeToledo-Morrell, Mony deLeon, Clifford R Jack, Stephane Lehericy, Ronald J Killiany, Nikolai Malykhin, Johannes Pantel, Jens C Pruessner, Hilkka Soininen, Craig Watson. **Master tracers**: Liana G Apostolova, Martina Bocchetta, Rossana Ganzola, Gregory Preboske, Dominik Wolf. **Naive tracers**: Corinna Bauer, Melanie Blair, Claire Boutet, Emma Burton, Enrica Cavedo, Adam Christensen, Kristian S Frederiksen, Michel J Grothe, Sarah Hollander, Mariangela Lanfredi, Yawu Liu, Oliver Martinez, Masami Nishikawa, Marileen Portegies, Gregory Preboske, Margo Pronk, Travis Stoub, Tim Swihart, Mat Tinley, Felix van Dommelen, Chadwich Ward. **Industry advisory board**: Bioclinica (Chahin Pachai), Brain Image Analysis LLC (Ronald Piersen), IXICO Ltd. (Derek Hill), Roche (Emilio Merlo-Pich), Synarc (Joyce Suhy), and True Positive Medical Devices Inc. (D. Louis Collins), Lilly (Adam Schwarz). **Logistics**: Alzheimer's Association (Meredith McNeil, Heather Snyder). **Statistics and ICT Solutions**: Simon Duchesne, Nicolas Robitaille, Fernando A. Valdivia, D. Louis Collins, Patrizio Pasqualetti, Clarissa Ferrari, Alberto Redolfi, Luigi Antelmi, Gabriele Corbetta, Daniele Tolomeo. **EADC Centres PIs**: Giovanni B Frisoni, Hilkka Soininen, Bruno Dubois, Stephane Lehericy, Harald Hampel, Stefan Teipel, Lars-Olof Wahlund, Christoph Hock, Frederik Barkhof, Philip Scheltens, Nick C Fox, Andy Simmons. **ADNI Centres PIs**: Clifford R Jack; Charles DeCarli, Craig Watson, George Bartzokis/Liana G Apostolova/Paul M. Thompson, Michael W Weiner, Leyla deToledo-Morrell, David Bennet, John C. Csernansky, Ronald J Killiany, Marilyn S. Albert, Mony De Leon, Jeffrey Kaye. **Other centres PIs**: Andreas Fellgiebel, Hiroshi Matsuda, John O'Brien. **Population-based Studies and Advisors**: PATH through life Study (Permindev Sachdev, Jerome J Maller), SMART-Medea Study (Mirjam I. Geerlings), Rotterdam Scan Study (Tom denHeijer), Leonore Launer, William Jagust. **Clinical Advisors**: Peter-Jelle Visser, Bengt Winblad, Lutz Froelich. **Dissemination & Education Advisors**: Gunhild Waldemar.

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