HARMONIZATION OF PROTOCOLS FOR THE MANUAL TRACING OF THE HIPPOCAMPUS DEVELOPMENT AND VALIDATION OF A UNIFIED STANDARD PROTOCOL: AN EADC-ADNI JOINT EFFORT

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ABSTRACT

Background: acknowledged markers of Alzheimer's disease include atrophy of the medial temporal lobe structures that can be measured on MRI. At the present, the most reliable and largely used procedure in research and clinical trials of Alzheimer's drugs is volumetry of the hippocampus through manual outlining by an expert tracer. However, different data acquisition, tracing software, anatomical boundaries, and brain size correction result in markedly different estimates across laboratories worldwide, thus preventing the comparison of the different studies and trials.

Aim: to harmonize the available protocols for the manual tracing of the hippocampus and validate the resulting unified standard protocol.

Methods: In phase I, the measurement protocol will be defined. After a review of the pertinent literature, a Delphi technique will be used to reach consensus on the hippocampal boundaries to be used for tracing. The working group will discuss the most appropriate MRI acquisition, tracing software and intracranial volume measurements in order to minimize variability.
In phase II, protocol validation will be carried out in non atrophic and atrophic brains. Non atrophic brains will be those of the 3 young volunteers of the pilot European ADNI study scanned in 7 different scanners; variance due to scanner and tracer will be addressed. Atrophic brains will be taken from NA-ADNI scans of 40 converted MCI, 40 Alzheimer's with MMSE $\geq$24, and 40 Alzheimer's with MMSE <24 and will address variance due to tracer and disease. Validation will be forerun by the development of a web-based tool that will allow tracers to familiarize with all the protocol features.

Expected results: The project will lead to a protocol whose variability across scanner and tracer will be lower than variability across volunteers, side, and disease severity. This might become the golden standard for the many automated algorithms that are presently being developed aiming to extract hippocampal volume with no human input, and as surrogate measure in clinical trials of drugs for Alzheimer's disease.

Background

The recent proposal for the new criteria for the diagnosis of Alzheimer's disease includes atrophy of the hippocampus, amygdala, and entorhinal cortex as a disease marker (Dubois et al., Lancet Neurol 2007;6:734-46). Wanting an automated method, the most accurate and reliable procedure for the measurement of the volume of these structures to date is through manual outlining by an expert tracer. However, despite being largely used in research settings, manual tracings are carried out with widely heterogeneous protocols leading to volume estimates that differ up to almost 3-fold (see excerpt below from Geuze et al., Mol Psychiatry 2005;10:147-59).

Reference	*Image acquisition sequence/ Scanner*	*Hippocampal measurement*	*Most anterior slice*	*Most posterior slice*	*Medial border*	*Lateral border*	*Inferior border*	*Additional notes*	*Normative hippocampal volume (cm^3)*	
									Left	*Right*
Watson et al[20]	3D GRE TR/TE/FA 75/16/60 Philips 1.5 T	Whole hippocampus	The CSF in the uncal recess of the temporal horn, when visible, is the most reliable boundary between the hippocampal head and the amygdala, if not visible, the alveus may be used, if neither is visible, then a straight line is drawn connecting the plane of the inferior horn of	Slice where the crura of the fornices are seen in full profile	Mesial edge of the temporal lobe	Temporal horn of the lateral ventricle	Include the subicular complex and the uncal cleft with the border separating the subicular complex from the parahippo-campal gyrus	Subicular complex, dentate gyrus, alveus, and fimbria included in measurement. These are the most popular anatomical criteria which are used by 15% of the studies	4.903	5.264
Zipursky et al[84]	MEFCCG TR/TE 2800/ 40,80 GE 1.5 T	Whole hippocampus	Slice where hippocampus was clearly distinguished from the amygdala	One slice (3 mm) anterior to the image where the vertical fissures of the Sylvian fissure are no longer present	The regional outline at the choroidal fissure	Not mentioned	The interface of the hippo-campal tissue and parahippo-campal gyrus white matter	This method excludes the most posterior region of the hippocampal body and tail	1.990	2.070

This proposal aims to harmonize the available protocols for the manual tracing of the hippocampus, the structure for which the most reliable measures can be obtained, and validate the resulting unified standard protocol. In order to obtain an optimally accurate protocol, the factors contributing to inflate the variability of measurement will be assessed in detail: (i) Anatomical landmarks, (ii) Acquisition sequences/scanner, (iii) Tracing software, (iv) Slice thickness and voxel size, (v) Contrast adjustment, and (vi) Intracranial volume measurement procedure used for normalization to head size. The harmonized protocol will allow to define age norms, necessary for the use of volumetry in single case diagnostic decision making.

Methods

PHASE I. PROTOCOL HARMONIZATION (weeks 1-21)

A Delphi technique (anonymous iterative expert judgement) will be used to reach consensus on the unified standard protocol: setup of questionnaire, first round of experts' comments, development of second questionnaire, second round of experts' comments, development of draft protocol version, experts' revision, and development of final protocol version. The Delphi panel will be defined through literature review. Each centre will be counted as one in the Delphi panel, although more than one physical person per centre may contribute. Based on a preliminary literature review, we anticipate that about 20 centres will be part of the Delphi panel.

In order to collect information about manual tracing protocols, a review of the protocols for hippocampal volumetry and intracranial volume measurement used in the Alzheimer's literature will be done, and experts with first hand experience on hippocampal tracing will be asked to comment.

Scanner and image acquisition effects: the working group will discuss the downsides of decreasing measurement variability by applying the tracing protocol only to 3D T1-weighted MP-RAGE ADNI images. The use of native DICOM or grad-warp corrected images will also be discussed.

Tracing software effects: the working group will discuss the benefits of decreasing measurement variability by choosing a software that allows to trace on the coronal plane, with simultaneous check of the axial and sagittal planes, and editing of the tracings in all planes. The impact on inclusion/exclusion of the traced rim of voxels will also be addressed. An overview of the entire tracing workflow will be also evaluated and discussed among the partners.

Intracranial volume measurements: the working group will discuss which intracranial volume measure is sufficiently stable and reliable to be used taken on 3D T1-weighted MP-RAGE images for normalization purposes.

Effort involved in phase I will approximate 14 hours' time each from experts (2 full working days) + 6 person/months from the coordinating centre.

A teleconference will be arranged on the 18th week to discuss the final version of the protocol.

PHASE II. PROTOCOL VALIDATION (weeks 22-32)

Method. Validation will be carried out on non-atrophic and atrophic brains. Validation on non-atrophic brains will make use of the pilot European ADNI volunteer scans and will address variance due to scanner and tracer (intra-and inter-rater); validation on atrophic brains will make use of North American ADNI scans of Alzheimer's patients and will address variance due to tracer (mainly inter-rater) and disease severity. Validation will be forerun by the development of a web-based tool that will allow tracers to familiarize with all the protocol features (anatomical landmarks, tracing software, and intracranial volume measurement).

The list of tracers will be defined by the PIs of the working group centres.

1. *Validation on non-atrophic brains*. The pilot European ADNI volunteer scans are 3D T1-weighted 1.5T MP-RAGE ADNI images of 3 young volunteers scanned in 7 different scanners from all 3 major manufacturers. The hippocampus will be traced by at least 5 different tracers under 2 different conditions: (i) following the routine procedures for hippocampal volumetry of each research lab, each tracer tracing 21 right and 21 left hippocampi, and (ii) following the consensus tracing protocol, each tracer tracing the same 42 hippocampi twice at least 2 weeks apart (total of 84 hippocampi). Tracers involved will come from at least 5 different centres. Effort involved in phase II will approximate 11 person days per tracer (25 minutes/hippo for pure tracing x 126 hippos + 50% image and file management time @ 7 working hours/day) all inclusive + 6 person/months from appropriate personnel from the coordinating centre.

The 126x5=630 hippocampal volumes will be analyzed to estimate the variance due to tracing protocol, volunteer, scanner, tracer, and side.

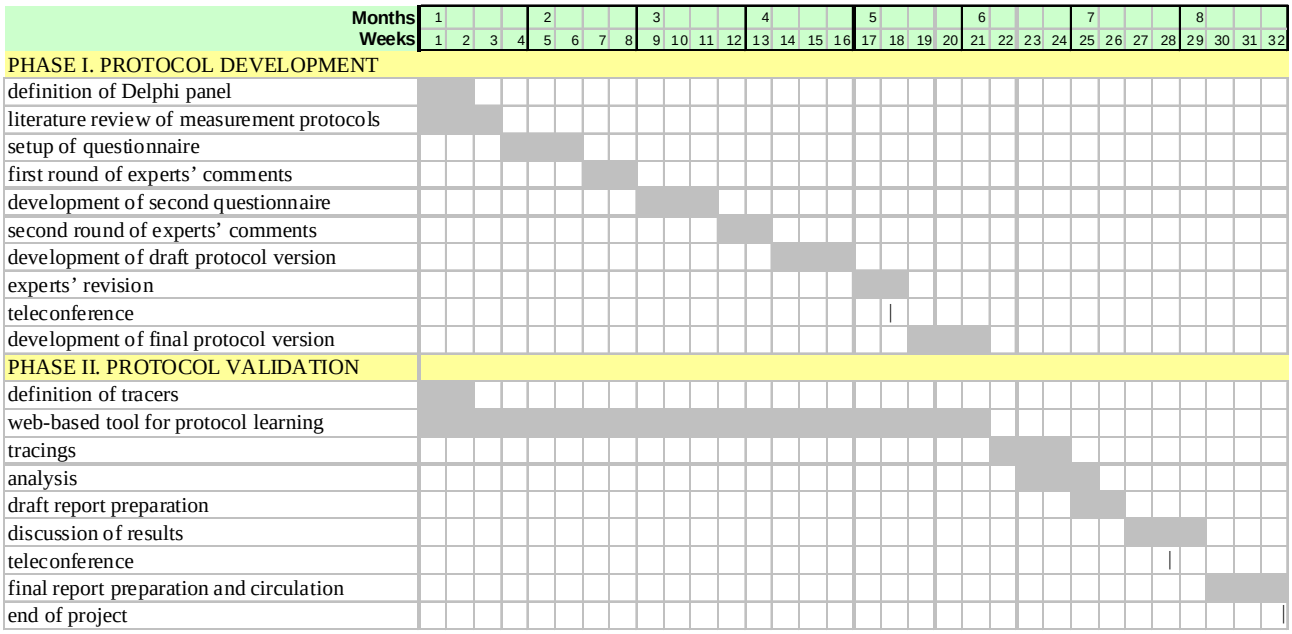
2. *Validation on atrophic brains*. 3D T1-weighted 1.5T MP-RAGE images will be selected of 40 converted MCI, 40 Alzheimer's with MMSE $\geq$24, and 40 Alzheimer's with MMSE <24. The ensuing procedure will mirror that of (ii) validation on non-atrophic brains: the same at least 5 tracers from at least 5 different centres will trace 120 right and 120 left hippocampi and only 2 tracers will assess intra-rater variability by re-tracing the 240 hippocampi 2 weeks apart. Effort involved will approximate 21.5 or 43.0 person days per tracer (25 minutes/hippo for pure tracing x 240 or 480 hippos + 50% image and file management time / 7 working hours/day) + 12 person/months from appropriate personnel from the coordinating centre.

Deliverables and project outcome. It is anticipated that variability across scanner and tracer will be lower than variability across tracing protocol, volunteer, side, and disease severity.

Outcomes of the project will be a technical report, a scientific paper, and a knowledge transfer event. A draft technical report will be prepared to and circulated among working group members in the last few weeks of the project (see gant-t chart) and a teleconference will be hold to discuss results on the 28th week. A final technical report will then be prepared, circulated, published in the EADC website, and disseminated to EADC and ADNI centres. A symposium will be arranged by the working group at a major international meeting open to Alzheimer's specialists worldwide aimed to disseminate and illustrate the harmonized protocol.

TIMING

The project start is tentatively fixed on Sept 1 2008, but flexibility will be required based on the availability of funds coming from the other funding agencies (see budget).



Expected results

The project will lead to a protocol whose variability across scanner and tracer will be lower than variability across volunteers, side, and disease severity.

From the point of view of scientists, this might become the golden standard for the many automated algorithms that are presently being developed aiming to extract hippocampal volume with no human input.

From the point of drug companies, that might wish to use it in clinical trials of disease modifying drugs, the harmonized protocol will:
- have a robust description of its accuracy features carried out by a group comprising the most distinguished scientists in the world;
- make approval of hippo volumetry as surrogate outcome by FDA easier;
- allow to compare the effect of different drugs tested in different trials in the same way as today the effect on ADAS-Cog for cognitive performance is compared.

Working group

EADC centres

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IP

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Authorships of scientific papers. The technical report will acknowledge the contribution of all participants and the pertinent contribution. The scientific paper will include all persons listed in the working group that will actively contribute to the project proceedings as well the tracers. The number of authors might approach 30.