Alzheimer's Association

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If renewal, current grant:

Resubmission? Yes | Prior App: 01/08/2009

RFA? | RFA Title:

TITLE OF PROJECT *(Titles exceeding 81 characters, including spaces and punctuation, will be truncated.)*

A harmonized protocol for hippocampal volumetry: an EADC-ADNI effort

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PROGRAM ELIGIBILITY INFORMATION: *(Responses to selected fields displayed below. For some grant programs this section may be blank.)*

U.S. Citizenship: Non-U.S. Citizen		
Highest Degree Conferred: specialist neurologist		
Date Conferred: 06/04/1990		

DATES OF PROPOSED PROJECT *(MM/DD/YYYY)*

From 9/1/2010 Through 8/31/2012

PROPOSED BUDGET

239639

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HUMAN SUBJECTS ☐ No ☐ Yes

Human Subjects Assurance No. IRB Status: Not Applicable
IRB Date:

VERTEBRATE ANIMALS ☐ No ☐ Yes

Animal welfare assurance no. IACUC Status:
IACUC Date:

RECOMBINANT DNA No

Status:
Date:

BIOHAZARDS No

APPLICANT ASSURANCE: I certify that the statements herein are true, complete and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application.

SIGNATURE OF APPLICANT
(In ink. "Per" signature not acceptable.)

DATE

SIGNING OFFICIAL ASSURANCE: I certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with the grantor's terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

SIGNATURE OF SIGNING OFFICIAL
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DATE

ADDITIONAL SIGNATURE (follow guidelines for required signatures): I certify that the statements herein are true, complete and accurate to the best of my knowledge.

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PROBLEM STATEMENT (1 Page)

In the field of Alzheimer's disease (AD) research and drug development, there exists an urgent need for an harmonized protocol aimed at estimating hippocampal atrophy accurately. In the revised criteria for the diagnosis of AD the estimate of hippocampal atrophy obtained via structural magnetic resonance imaging (MRI) is one of the key supportive markers (Dubois et al., Lancet Neurol 2007;6:734-46). The potential availability of drugs that can effectively alter the progressive cognitive deterioration associated with AD makes diagnosis at the earliest possible stages imperative. A trial with tramiprosate (Gauthier S et al., JNHA 2009;13:550-7) has shown benefit on hippocampal atrophy rates in AD patients. The use of hippocampal atrophy as an outcome in trials of disease modifying drugs is clearly an area of active study and one where it will be important to compare and replicate measurements.

While results of studies in different laboratories consistently show 15 to 40% tissue loss in AD patients vs. controls, agreement is lacking on the anatomical landmarks and measurement procedure. As a consequence, estimates of normal hippocampal volumes differ up to 2.5-fold (see excerpt below from Geuze et al., Mol Psychiatry 2005;10:147-59). A meta-analysis of atrophy rates also showed a wide range of rates (Barnes et al., Neurobiol Aging 2008;30:1711-23). In the absence of consistency of methods it is difficult to determine if these differences are true or if the different measurement protocol accounts for all the variance.

Ref.	Most ant slice	Most post slice	Med border	Lat border	Inf border	Norm. hippo vol (cm^3)	
						Left	Right
Watson et al	CSF in uncal recess of temp horn or alveus.	Slice where crura of fornices seen in full profile	Mesial edge of temporal lobe	Temp horn of lat ventr	Incl subicular complex & uncal cleft w/ border separating subicular complex from parahippo gyrus	**4.903**	**5.264**
Zipursky et al	Slice where hippocampus clearly distinguished from amygdala	One slice ant to where vert Sylvian fissures are no longer present	Regional outline at choroidal fissure	Not ment'd	The interface of hippocampal tissue and parahippocampal gyrus white matter	**1.990**	**2.070**

The most validated procedure to estimate hippocampal atrophy is to calculate hippocampal volumes with manual outlining using anatomical landmarks by an expert rater on high resolution T1-weighted MRI (Bosscher & Scheltens, In: Evidence-based Dementia Practice, Blackwell 2002). Manual volumetry is also taken as the gold standard for the validation of automated segmentation algorithms (Colliot et al., Radiology 2008;248:194-201; Brewer et al., AJNR 2008:A1402; Morra et al., NeuroImage 2008 in press; Barnes et al., NeuroImage 2008; 40:1655-71; Duchesne et al., NeuroImage 2002;17:515-31), but in the absence of a single reference protocol for manual volumetry, the comparison of the accuracy of different methods is virtually impossible.

The aim of this project is to develop an optimally harmonised measurement protocol for the estimation of hippocampal volume with manual tracing. Sources of variability such as acquisition parameters, anatomical landmarks, tracing software, and normalization to cranial size will be accurately estimated. The protocol will be developed at 1.5T; it will be tested at both 1.5 and 3T in that the latter will become the standard for clinical imaging in the coming years. The key measure of performance will be decreased variability among raters of the harmonised versus traditional protocols. The main deliverables of this project will be a set of publicly-available hippocampal tracings, probabilistic maps, and tracing manual.

The availability of a standard protocol for hippocampal volumetry and hippocampal probabilistic maps will foster the validation of the new diagnostic criteria and their use in clinical settings, allow to compare the effect of disease modifying drugs, and represent the gold standard for automated segmentation algorithms. In the long run, the availability of a standard protocol will allow pooling data from compatible datasets such as North American, Japanese, Australian, and European ADNIs thus leading to increased knowledge on the disease itself.

WORK PLAN (5 Pages)

This project involves an International working group made of neuroscientists from North American and Europe and is expected to last 24 months. A number of preparatory activities (Preparatory Phase) have been carried out between Sept. 2008 and the date of the writing of this application (Dec. 2009) thanks to unrestricted grants from two drug companies, which underlines the interest of the pharmacological sector in the success of this endeavor. The AA-funded part of this project will consist of 4 phases: (i) harmonization of existing protocols at 1.5T; (ii) validation of the harmonized protocol in representative image sets at 1.5T and 3T; (iii) development of hippocampal probabilistic maps; and (iv) deliverable preparation.

PREPARATORY PHASE. We reviewed the literature papers reporting protocols for manual hippocampal segmentation. We selected the 10 most frequently used protocols for hippocampal tracing in AD: (1) Killiany et al., Arch Neurol 1993; 50:949-54; (2) Jack et al., Epilepsia 1994; 35 Suppl 6:S21-9; (3) Lehéricy et al., AJNR 1994; 15:929-37; (4) Soininen et al., Neurology 1994; 44:1660-8; (5) Convit et al., Neurobiol Aging 1997; 18:131-8; (6) Haller et al., Radiology. 1997;202:504-10; 18:131-8; (7) Bartzokis et al., Psychiatry Res 1998;82:11-24; (8) Pantel et al., Hippocampus 2000;10:752-8; (9) Pruessner et al., Cereb Cortex 2000;10:433-42; (10) Malykhin et al., Psychiatry Res 2007;155:155-65.

We surveyed protocols to extract anatomical landmarks such as areas explicitly included/excluded in the tracing, anterior and posterior boundaries, and medial, lateral, inferior, and superior borders of head, body, and tail separately for each protocol (www.centroalzheimer.it/public/SOPs/online). We traced the hippocampi of one representative healthy control and one AD patients taken from the ADNI dataset following the landmarks of each protocol. We arranged individual interactive teleconferences with the Author of each protocol, to verify the appropriate execution of the correspondent tracing, and correct it when necessary. We corrected the tracings based on the Authors' indications, and re-sent for last correction/confirmation (see same www link). Lastly, we extracted salient differences among protocols (see same www link): (a) definition of the boundary with the amygdala at the level of the most anterior slices, (b) inclusion/exclusion of hippocampal white matter (alveus/fimbria), (c) separation between subiculum and enthorinal cortex, and (d) most posterior slices and boundaries.

PHASE I. HARMONISATION OF EXISTING PROTOCOLS (months 1-8).

We hypothesize that a Delphi technique can be used to reach consensus on harmonised protocols for the hippocampal tracing on 1.5T MR images. To test this hypothesis, we will use the differences among protocols extracted in the preparatory phase (http://www.centroalzheimer.it/public/SOPs/online/v3/file/landmark_differences.pdf) to develop a questionnaire that will be sent to an expert working group made of the Authors of the 10 protocols and neuroscientists worldwide who have published manuscripts on hippocampal volumetry, where these protocols were adopted to study cognition in clinical or population settings. The composition of the panel is reported in Table 1. All listed experts have agreed to take part to the present application.

The Delphi method is a systematic, interactive forecasting method in which a panel of independent experts answers questionnaires in successive rounds. After each round, a facilitator provides an anonymous summary of the experts' forecasts from the previous round and the reasons they provided for their judgments. Participants revise their earlier answers in light of the replies of other members of the group. It is believed that during this process the range of the answers will decrease and the group will converge towards the "correct" answer. We plan to complete at least two commenting rounds of the Delphi review and one interactive teleconference review of the final protocol, but more rounds will be completed if necessary until convergence.

WORK PLAN (5 Pages)

Table 1. The expert working group.		
EADC centres	F Barkhof/ Ph Scheltens, Amsterdam	B Dubois/S Leherici, Paris
N Fox, London	GB Frisoni, Brescia	H Hampel, Dublin
H Soininen, Kuopio	S Teipel, Rostock	L-O Wahlund, Stockholm
US ADNI centres	G Bartzokis, UCLA, CA	D Bennett, Rush ADC, Chicago, ILL
J Csernansky, Northwestern U, WA	C DeCarli, UC Davis, CA	M De Leon, New York, NY
CR Jack, Rochester, MN	J Kaye, Portland, OR	R Killiany, Boston USM, MA
PM Thompson, LoNI, UCLA, CA	M Weiner/S Mueller, UCSF, CA	
Other clinical centres	J O'Brien Newcastle, UK	
R Camicioli, Univ Alberta, AB, Canada	J Pantel, Univ Frankfurt/Mein, GER	J Pruessner, McGill Univ, QC, Canada
Population-based studies		
Rotterdam Scan Study, M Breteler/T den Heijer	PATH through life, P Sachdev/JJ Maller	

PHASE II. VALIDATION OF THE HARMONISED PROTOCOL (months 1-15). We hypothesize that the inter-rater variability of the harmonized hippocampal volumes will be smaller than non-harmonized hippocampal volumes and non-protocol effects. To test this hypothesis we will (a) develop a common environment for hippocampal tracing to be used by all expert raters, and define criteria for rater qualification; (b) test that the harmonized protocol will reduce the effect on the variability of the rater by center interaction; (c) test that the variance of harmonized hippocampal volumes due to atrophy and atrophy rates is greater than that due to rater, scanner, and side; and (d) test that *in vivo* harmonized volumes will correlate with volumes measured in pathological specimens at least as highly as *in vivo* non-harmonized volumes.

a) Environment for hippocampal tracing and qualification. In order to guarantee optimal tracing quality, we will develop a qualification and tracing environment to be used by all raters. We will make available a WWW tracing application in order for raters to use it remotely on appropriate local hardware. We will develop a qualification procedure specific to the tracing environment. Five expert raters with intimate knowledge of the procedures used to develop the harmonized protocol will outline a number of "benchmark" hippocampi (Table 3). These will be chosen in order to be representative of the atrophy range that can be encountered in clinical trials and clinical practice through stratification with Scheltens's atrophy score (Scheltens et al., JNNP 1992). We will automatically compute global volume and local voxel-by-voxel confidence intervals based on the expert rater segmented hippocampi labels, using the MINC image processing toolbox and in-house statistical analysis software from Laval University, Canada. We will use this information as statistical criteria for comparison and qualification.

Table 3. Study design of the development of the environment for hippocampal tracing and qualification.

N of raters	Images	Design	Total n of hippos
5	• 1.5T ADNI scans • Benchmark hippos: 2 x each of the 5 Scheltens's atrophy score	• expert raters will trace benchmark images • global and local 95% confidence intervals will be computed	100
5	Same on 3T ADNI scans	Same	100
20	• 1.5T ADNI scans • Benchmark hippos: 2 x each of the 5 Scheltens's atrophy score	• 20 naive raters will trace all images • 95% confidence intervals derived from expert raters	100
20	Same on 3T ADNI scans	Same	100

Naive raters, i.e. consortium members who have not taken part to the development of the harmonized protocol and will be involved in phases IIb, IIc, and IId, will trace the same benchmark hippocampi. Naive raters will qualify if their tracings fall within 95% confidence interval of expert tracing.

(b) Test that the harmonized protocol will reduce the effect on the variability of the rater by center interaction by keeping the rater effect constant. Naive raters from the centers listed in Table 1 will be asked to trace a set of images following the traditional protocol in use in each center, then qualify for the harmonized protocol on the benchmark images (see IIa), and finally re-trace the experimental set of images following the harmonized protocol. Naive raters will need to have familiarity with hippocampal tracings following local protocols but will not have been involved in the development of the harmonized protocol. This will prevent raters to use knowledge coming from the harmonized protocol procedure to be transferred into the local protocols. The experimental set of images will come from the ADNI dataset but will *not* include any of the benchmark images. The procedure will be carried out with the same design on 1.5T and 3T images (Table 4).

The obtained tracings will also allow to (i) map the local reliability of the harmonized protocol, i.e. locating hippocampal areas where the protocol is more and less reproducible; (ii) flag areas with relatively low reproducibility for future raters to pay special care; and (iii) highlight "problem" areas for automated algorithms to segment.

Table 4. Study design to test the hypothesis that the harmonized protocol will reduce the effect on the variability of the rater by center interaction.

N of raters	Images	Design	Total n of hippos
20	• Experimental set (1.5T ADNI): 2 sides x 2 scans x 5 Scheltens's atrophy scores x 20 raters (tot 200 right and 200 left hippos) • Benchmark set	• Tracing the experimental set following local protocols • Qualification for the harmonised protocol on benchmark set • Re-tracing the experimental set following the harmonised protocol • RM-ANOVA: test of rater and rater by center terms	400 100 400
20	Same on 3T ADNI scans	Same	900

(c) Test that the variance of harmonized hippocampal volumes due to atrophy and atrophy rates is greater than that due to rater, scanner, and side. The five raters of the 20 of phases IIa and IIb with the highest value of intrarater, interrater and test-retest reliability will trace images taken at 3 different time points 6 months apart, and acquired with scanners representative of the main manufacturers (Siemens, GE, and Philips). The same procedure will be carried out with the same design on 1.5T and 3T images (Table 5).

The above design will allow to measure: (i) intra-rater variability using scan-rescan; (ii) inter-rater variability using tracing from the 5 raters; (iii) hemisphere variability using left/right; (iv) manufacturer variability using Siemens, GE, and Philips; (v) variability due to true medial temporal atrophy using Scheltens atrophy scores; (vi) variability due to disease progression using serial scans.

Table 5. Study design to test the hypothesis that the variance of harmonized hippocampal volumes due to atrophy and atrophy rates is greater than that due to rater, scanner, and side.

N of raters	Images	Design	Total n of hippos
5	• 1.5T ADNI scans	• Tracings with the harmonised	750

	• 2 sides x 2 scan-rescan x 5 Scheltens atrophy score x 2 time points x 3 scanners x 5 raters + rescan for timepoint 1 • Total new tracings 375 R and 375 L hippos (including tracings from Table 4, 450 L and 450 R hippos)	protocol • RM-ANOVA: test of main effects side, scan-rescan, atrophy, time, scanner, rater	
5	Same on 3T ADNI scans	Same	750

(d) Test that in vivo harmonized volumes will correlate with volumes measured in pathological specimens at least as highly as *in vivo* non-harmonized volumes. The pathologically verified dataset from the New York University will be used (Bobinski, De Leon, et al., Neuroscience. 2000;95:721-5) where published hippocampal volumes post-mortem are available as well as *in vivo* on MR images taken weeks to months before death (Bobinski, De Leon, et al., Neuroscience. 2000;95:721-5). The hippocampi will be segmented by a single rater following the harmonized protocol. The hypothesis here is that the harmonised volumes will yield at least as high a correlation with pathologically verified volumes as the measurements obtained with the traditional protocol. This approach implicitly takes into account the issue of fixation and lower volume in ex vivo.

In analogy with IIb, one rater from De Leon's centre will trace the pathologically verified set following the traditional protocol in use at that centre, qualify for the harmonized protocol on the benchmark images, and finally re-trace the pathologically verified set of images following the harmonized protocol (Table 6).

Table 6. Study design to validate the harmonised protocol using histopathologically confirmed specimens.

N raters	**Images**	**Design**	**Total n of hippos**
1	• 20 1.5T 3D T1-weighted scans of brains from Bobinski et al., 2000 • Benchmark set	• Tracing the pathologically verified set following local protocols • Qualification for the harmonised protocol on benchmark set • Re-tracing the pathologically verified set following the harmonised protocol • RM-ANOVA: test of protocol main effect	40 10 40

PHASE III. HIPPOCAMPAL PROBABILISTIC MAPS (months 16-18). One probabilistic mask for each hippocampus at 1.5T and 3T will be developed based on the tracings from the 5 tracers described in Phase IIc (450 R and 450 L hippocampi at 1.5T and as many at 3T). These masks will be constructed by (i) co-registering all subjects within an identical reference space; (ii) transforming the labels using the same co-registration matrix; and (iii) computing a voxel-by-voxel fused label within the reference space. Based on the rater dispersion matrix, we will select an optimal fusion technique from three established techniques (voting; expectation-maximization; shape-based averaging), using the MINC image processing toolbox and in-house statistical analysis software from Laval University, Canada. The same procedure will be carried out on 1.5T and 3T images.

The accuracy of the probabilistic map is obviously related to the number of hippocampi used to build the map. A power analysis follows of the scenario of the present study:

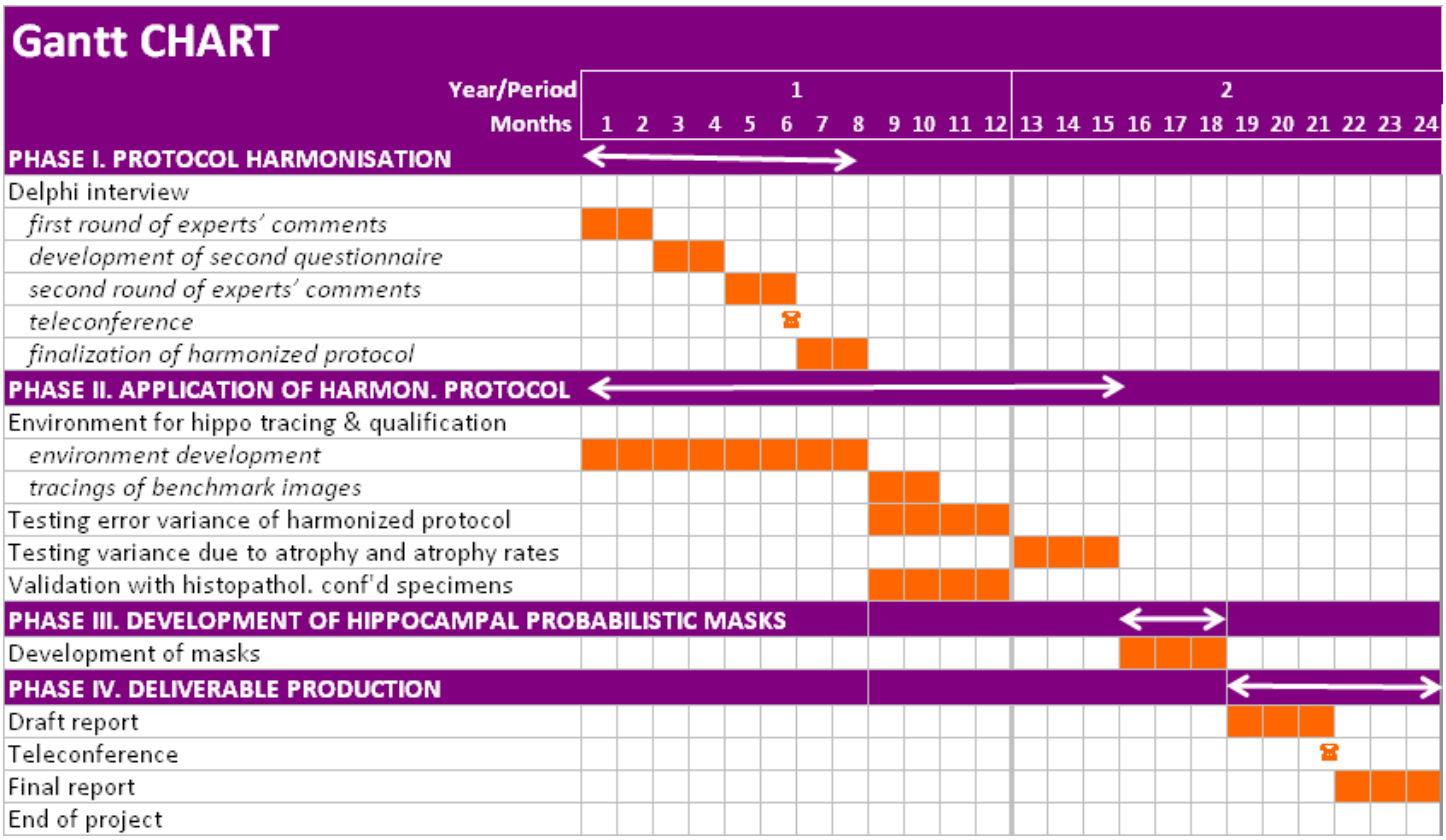
	Confidence interval			
Result	1%	5%	25%	50%
5 raters x 90 labels (450 samples)	**0.9**	**2.0**	**4.0**	**4.6**

Reading example: given 450 samples of a given variable, whether or not a voxel belongs to the hippocampus of a subject, we are 95% confident that when given a result of 1% across samples (i.e. "outside the hippocampus")(or, conversely 99%, i.e. "inside the hippocampus") when averaging over all raters, the true result in the population at large (n=1.000.000), from which the sample is drawn, will be around 99% +/- 0.9. Practically, it means we are pretty sure that it is in or out, because in the population at large it would fall between 98.1 and 99.9%.

WORK PLAN (5 Pages)

PHASE IV. DELIVERABLE PRODUCTION (months 19-24). Outcomes of the project will be (i) a technical report, (ii) at least one scientific paper to be submitted to a major journal, (iii) a knowledge transfer event, (iv) an online, user-friendly, illustrated educational "tracing guideline manual" and tracing software which could enable future investigators to unambiguously reproduce the protocol, and (v) probabilistic masks and a gold standard training set of hippocampal tracings available to the public for future use in research and clinical trials. A draft technical report will be prepared to and circulated among working group members and a teleconference will be hold to discuss results between months 27 and 28. A final technical report will then be prepared, circulated, published online, and disseminated to EADC and ADNI centers. The knowledge transfer event will be a symposium at a major international convention for Alzheimer's specialists (e.g. ICAD) with the aim of illustrating the features and merits of the harmonized protocol.

GANTT CHART



BOARDS. The coordinator will be supported by: (i) *co-Principal Investigator* Clifford Jack, MR core leader of ADNI, (ii) a *statistical working group* headed by Simon Duchesne, Laval University, Canada, and including Louis Collins, MNI, McGill, Montreal and Patrizio Pasqualetti, AFaR, Roma; (iii) an *advisory board* including EADC PIs Bruno Vellas, Toulouse, France and Bengt Winblad, Stockholm, Sweden; ADNI PI Mike Weiner, UCSF, US; (iv) a *clinical advisor*, Pieter Jelle Visser, Maastricht, The Netherlands; (v) a *population studies* advisor, Lenore Launer, NIA, Bethesda, (vi) a *dissemination and education advisor*, Gunhild Waldemar, Copenhagen, Denmark; and (vii) *industrial advisors*, i.e. representatives from the sponsoring pharma companies.

AVAILABLE RESOURCES & BUDGET JUSTIFICATION (2 Pages)

AVAILABLE RESOURCES

This project will make use of 1.5T and 3T ADNI MR scans, available in the public domain. Activities will take place in four basic settings: (a) coordination at the LENITEM – Laboratory of Neuroimaging of the IRCCS Fatebenefratelli in Brescia, Italy, and (b) Diagnostic Radiology, Mayo Clinic, Rochester, MN; (c) statistical analysis at the Centre de Recherche de l'Université Laval Robert Giffard, Québec, Canada; and (d) Delphi interview and hippocampal tracings in the EADC, ADNI, and other Alzheimer's imaging centres with expertise in hippocampal volumetry.

(a) The **LENITEM – Laboratory of Neuroimaging of the IRCCS Fatebenefratelli** is one of the scientific sites of the AFaR – Associazione Fatebenefratelli per la Ricerca (www.AFaR.it). The laboratory is located in the main building of the IRCCS Fatebenefratelli – The National Centre for Research and Care of Alzheimer's Disease (www.irccs-fatebenefratelli.it). The 8 rooms of the lab are equipped with 22 working stations (PCs, WebServers and SGIs) running under Windows and Linux. The LENITEM boasts state-of-the-art hardware and software computational facilities and broadband internet access that will be provided to the present project. In particular, the LENITEM has access to and expertise in the use of software for the post-processing of digital images and the development of interactive websites (SPM5, Freesurfer, CIVET, 3D Slicer, FSL, Mipav, Loni Pipeline, Brain Suite) and computational neuroimaging (hippocampal radial mapping among the others).

In addition to the Director of the Lab (GB Frisoni), the human resources of the LENITEM who will take part to the present project are: (i) trained personnel with expertise in manual hippocampal segmentation that has taken part to a number of scientific publications (see for example Brain 2008;131:3266-76); (ii) a bioinformaticist who is presently involved in the development of a grid-based infrastructure that will allow high performance computing on MR images (www.neuGRID.eu), and (iii) a webmaster with long standing expertise in the development of interactive websites.

(b) The **Diagnostic Radiology, Mayo Clinic, Rochester, MN** is the MRI Core Leader of the ADNI.

The Alzheimer's and Dementia Imaging Research (ADIR) Lab is located in the newly constructed Opus building at Mayo Clinic Rochester. The ADIR laboratory staff includes 6 image analyst technicians, 3 engineers for data base management and system administration, one study coordinator, two junior faculty, two post docs, and five imaging scientist/programmers. The laboratory contains 21 workstations which are linked to form a grid computing network. The workstations in Dr. Jack's ADIR laboratory are electronically interfaced to the Mayo Institutional Digital Image Archive System (MIDIA) as well as within-laboratory storage. Data is stored on a NetApp SAN (storage area network) with a storage capacity of 4TB mirrored between two campus data centers and backed up to a data center tape silo. In addition, the lab has 1.2TB of NAS (network attached storage) replicated to two locations and 6TB of direct attached storage.

As co-P.I. of this project, the Director of the facility (CR Jack) will assist the project P.I. (GB Frisoni) in the strategical issues of the implementation of the workplan, Delphi study, data analysis, and interpretation of the results. Thanks to his pre-eminent role in the ADNI effort and his worldwide authoritativeness in the field of hippocampal volumetry and brain imaging at large, he will be instrumental in the dissemination of the harmonized protocol to clinical and research facilities worldwide.

(c) The **Centre de Recherche de l'Université Laval Robert Giffard,** dedicated to the study of neurosciences and mental health, is experiencing rapid growth, with more than 54 faculty and 150 registered students. Within the Center Dr Simon Duchesne is head of the Medical Data, Information and Knowledge (MEDICS) Laboratory, which focuses on neuroimaging and dementias. Specific scientific responsibilities within the project for Dr Duchesne will include statistical and image processing advice, and the supervision of two key personnel: Mr Burt Crépeault, research assistant at the MEDICS Laboratory, and responsible for the large-scale image processing software architecture, and Mr Florent Prel, Ph.D. candidate, who will be in charge of creating the

AVAILABLE RESOURCES & BUDGET JUSTIFICATION (2 Pages)

probabilistic masks. The MEDICS Laboratory has 4 high-throughput workstations assembled in a grid configuration, and can access the large facilities of the Université Laval – CLUMEQ supercomputers.

(d) The **Alzheimer's imaging centres** are listed in the Work Plan, Table 1. In the present project these will use the basic hardware (PCs) and software facilities (Windows' Office) and internet broadband connection required to carry out the Delphi interview and hippocampal tracing in the standardized environment.

BUDGET JUSTIFICATION

Coordination. This will involve:

- Phase I activities related to coordination of the delphi interview through email or via the world-wide web, organization and guidance of the teleconference, and finalization of the harmonized protocol;
- Phase II activities related to the development of the environment for hippocampal tracing and qualification, tracings of benchmark images, contribution to hippocampal tracings to test the variance of the harmonised protocol, and coordination of protocol validation with histopathologically confirmed specimens;
- Phase III activities related to the coordination of the development of hippocampal probabilistic masks; and
- Phase IV activities related to drafting the final report, circulating it to experts and collecting feedback, organizing and guiding the teleconferences, obtaining feedback from advisors, making the probabilistic masks available to the public, leading the writing of scientific papers, and organizing the knowledge transfer event.

Expert working group. In Phase I, PIs of the expert centres will be asked to take part to the Delphi interview. It is estimated that each PI will need to allocate 1 working day. Costs are estimated at a rate of € 8,000 (US$ 11,250) per month.

Raters. In Phase II, one rater per each of the expert centres will qualify and manually segment a number of hippocampi within the tracing environment. It is estimated these will take about 30 minutes per hippocampus for pure tracing + 50% for image and file management time = 45 minutes per hippocampus. Costs are estimated at a rate of € 1,900 (US$ 2,660) per month. The only exception is represented by the New York centre (PI DeLeon) where also validation of the harmonised protocol using histopathologically confirmed specimens will take place.

Statistics. The development of the probabilistic maps will take 4 months of a PhD student; costs are estimated at a rate of € 2,500 (US$ 3,500) per month. The advice of two statistical experts will be sought that is estimated to take 1 working day each.

Advisors. The advice of EADC and ADNI PIs, a clinical advisor, principal investigators of population-based studies, and a dissemination and education advisor will be sought in the last 6 months of the project, at the time of the discussion of the results and deliverable preparation. It is estimated that each advisor will need to allocate 1 working day; costs are estimated at a rate of € 8,000 (US$ 11,250) per month.

Cost share. Applicant co-share will be referred to part of personnel cost, hardware and software computer facilities, and internet broadband connection. Other cost share will be referred to € 65,350 (US$ 91,900) that the Coordinator has received from pharma companies (Lilly and Wyeth) for this project. These funds will be used for travels, dissemination activities, and teleconferences.

BIOGRAPHICAL SKETCH

Provide the following information for all key personnel.
Follow the sample format for each person found in **Biosketch Sample**. **DO NOT EXCEED FOUR PAGES.**

NAME	**POSITION TITLE**
Frisoni Giovanni B. (P.I)	Deputy scientific director

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	**DEGREE** *(if applicable)*	**YEAR(s)**	**FIELD OF STUDY**
University of Brescia	M.D.	1986	Medicine
University of Parma	Board certification	1990	Neurology

Positions and Honors

Clinical appointments

1991: founding staff neurologist at the Alzheimer's Unit, Scientific Institute of Research and Care Fatebenefratelli, Brescia, Italy (IRCCS-FBF). The IRCCS-FBF was the first Italian Alzheimer's Clinic and is funded by the National Health System to carry out research and provide advanced care to patients with Alzheimer's disease.

1991-1999: Head of the Day Hospital at IRCCS-FBF.

2005-to date: Head of the Psychogeriatric Ward at the IRCCS-FBF.

Scientific appointments

1999-to date: head of the LENITEM – Laboratory of Epidemiology Neuroimaging & Telemedicine at the IRCCS-FBF.

2003-to date: founding member of the editorial board of *The Lancet Neurology*.

2003-to date: Scientific Coordinator of the Northern Italy branch of the *AFaR – Associazione Fatebenefratelli per la Ricerca*, the scientific arm of the Fatebenefratelli hospital network.

2007-to date: Vice Scientific Director of the IRCCS-FBF

2009: Imaging Section Editor, *NeuroBiology of Aging*.

Selected peer-reviewed publications (in chronological order)

(15 selected from about 250 peer-reviewed publications)

1. **Frisoni GB**, Beltramello A, Weiss C, Geroldi C, Bianchetti A, Trabucchi M. Linear measures of atrophy in mild Alzheimer disease. *AJNR Am J Neuroradiol*. 1996;17:913-23

2. **Frisoni GB**, Laakso MP, Beltramello A, et al. Hippocampal and entorhinal cortex atrophy in frontotemporal dementia and Alzheimer's disease. *Neurology*. 1999;52:91-100.

3. **Frisoni GB**, Geroldi C, Beltramello A, et al. Radial width of the temporal horn: a sensitive measure in Alzheimer disease. *AJNR Am J Neuroradiol*. 2002;23:35-47.

4. Ashburner J, Csernansky JG, Davatzikos C, Fox NC, **Frisoni GB**, Thompson PM. Computer-assisted imaging to assess brain structure in healthy and diseased brains. *Lancet Neurol*. 2003;2:79-88.

5. **Frisoni GB**, Scheltens P, Galluzzi S, et al., Neuroimaging tools to rate regional atrophy, subcortical cerebrovascular disease, and regional cerebral blood flow and metabolism: consensus paper of EADC. *J Neurol Neurosurg Psychiatry* 2003;74:1371-81.

6. Boccardi M, Sabattoli F, Laakso MP, Testa C, Rossi R, Beltramello A Soininen H, **Frisoni GB**. Frontotemporal dementia as a neural system disease. *Neurobiology of Aging* 2005;26:37–44

7**. Frisoni GB**, Sabattoli F, Lee AD, Dutton RA, Toga AW, Thompson PM. In vivo neuropathology of the hippocampal formation in AD: a radial mapping MR-based study. *Neuroimage*. 2006;32:104-10

8. **Frisoni GB**. Dementia: important advances in research in 2006. *Lancet Neurol*. 2007;6:4-5.

9. DeCarli C, **Frisoni GB**, Clark CM, et al. Qualitative estimates of medial temporal atrophy as a predictor of progression from mild cognitive impairment to dementia. *Arch Neurol*. 2007;64:108-15
10. **Frisoni GB**, Pievani M, Testa C, et al. The topography of grey matter involvement in early and late onset Alzheimer's disease. *Brain*. 2007;130:720-30.
11. **Frisoni GB**, Galluzzi S, Pantoni L, Filippi M. The effect of white matter lesions on cognition in the elderly--small but detectable. *Nature Clin Pract Neurol*. 2007;3:620-7.
12. **Frisoni GB**. Imaging of amyloid comes of age. *Lancet Neurol* 2008;7:114-5.
13. Caroli A, Geroldi C, Nobili F, Barnden LR, Guerra UP, Bonetti M, **Frisoni GB**. Functional compensation in incipient Alzheimer's disease. *Neurobiol Aging*. 2008 Jun 13.[Epub ahead of print]
14. **Frisoni GB**, Ganzola R, Canu E, Rüb U, Pizzini FB, Alessandrini F, Zoccatelli G, Beltramello A, Caltagirone C, Thompson PM. Mapping local hippocampal changes in Alzheimer's disease and normal ageing with MRI at 3 Tesla. *Brain*. 2008;131:3266-76.
15. Babiloni C, **Frisoni GB**, Pievani M, Vecchio F, Lizio R, Buttiglione M, Geroldi C, Fracassi C, Eusebi F, Ferri R, Rossini PM. Hippocampal volume and cortical sources of EEG alpha rhythms in mild cognitive impairment and Alzheimer disease. *Neuroimage*. 2009;44:123-35.

Research Support

1997: Scientific coordinator of *SCUD – The Special Care Units for Demented: a Controlled Study of Effectiveness*, funded by the European Commission

2005: Principal Investigator of the *ENIR – European NeuroImaging Repository*, funded by the European Commission under Framework Programme 6 (www.enir.eu).

2005-2006: Principal Investigator of the *Pilot E-ADNI - The European Alzheimer's Disease Neuroimaging Initiative: a pilot study of the European Alzheimer's Disease Consortium*, funded by the Alzheimer's Association (http://www.centroalzheimer.it/E-ADNI_project.htm).

2008-to date: Principal Investigator of *neuGRID - A Grid-Based e-Infrastructure for Data Archiving/ Communication and Computationally Intensive Applications in the Medical Sciences*, a € 2.8 M project funded by the European Commission under Framework Programme 7 (www.neuGRID.eu).

2009-to date: Principal Investigator of *outGRID – a worldwide e-infrastructure for computational neuroscientists,* Coordination and Support Action Funded by the European Commission (DG-INFSO) within the Framework Programme 7 (www.outgrid.eu).

BIOGRAPHICAL SKETCH

Provide the following information for all key personnel.
Follow the sample format for each person found in Biosketch Sample**.** DO NOT EXCEED FOUR PAGES.

NAME	**POSITION TITLE**
Jack, Jr., Clifford R.	Professor of Diagnostic Radiology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Michigan, Ann Arbor, MI	B.Sc.	1971-1975	Zoology
Wayne State University, Detroit, MI	M.D.	1975-1979	Medicine
Henry Ford Hospital, Detroit, MI	Residency	1979-1983	Radiology
Mayo Clinic, Rochester, MN	Fellowship	1983-1984	Neuroradiology

Positions and Honors

Positions and Employment

1984-1985: Department of Radiology, Division of Neuroradiology, Henry Ford Hospital, Detroit, MI
1985-1991: Assistant Professor of Radiology, Department of Radiology, Mayo Clinic, Rochester, MN
1991-1995: Associate Professor of Radiology, Department of Radiology, Mayo Clinic, Rochester, MN
1995- to date: Professor of Radiology, Department of Radiology, Mayo Clinic, Rochester, MN
2002-2005: Chair, Division of Research, Dept of Radiology, Mayo Clinic and Foundation, Rochester, MN
2002- to date: Clinician Investigator, Mayo Clinic and Foundation, Rochester, MN

NIH Review and Advisory Panels

1993 – 2009: Study Sections or Review Panels for NICHD, BDCN1, BDCN2, BDCN MCSS, NIMH, NHLBI, and NIA
2000 to date: External Advisory Committee, Washington University, PO1-AG03991
2001 to date: External Advisory Committee, USC Davis, P01-AG12435
2004 to date: External Advisory Committee, University of California-Davis, P30: Alzheimer's Disease Center
2009 to date: Data Safety and Monitoring Board Nerve Growth Factor trial, by NIA and ADCS
2009 to date: Scientific Advisory Committee: P41 Research Resource, San Francisco VA,

Other Experience

1991-1998: Editorial Board, Radiology
1998-2001: Editorial Board, American Journal of Neuroradiology
1995, 2005: Certificate of Added Qualifications in Neuroradiology
2002-2005: Scientific Program Committee, International Society of Magnetic Resonance in Medicine

Honors

1972: William J Branstrom Freshman Prize, University of Michigan, Ann Arbor
1974: Phi Beta Kappa, University of Michigan, Ann Arbor
2000: Carmen Award for Research Excellence, Mayo Clinic
2005: Fellow, International Society of Magnetic Resonance in Medicine
2006: Alzheimer's Disease Neuroimaging Award, best Alzheimer's imaging research paper published between 2004-2006, Alzheimer's Association
2007: American Society of Neuroradiology Career Research Award; Neuroradiology Education and Research Foundation Award for Outstanding Contributions in Research
2007: Mayo Clinic named Professorship: The Alexander Family Professorship in Alzheimer's Disease Research
2008: Co-recipient of the Potamkin Prize for Research in Pick's, Alzheimer's and Related Diseases, American Academy of Neurology

Patents

Jack CR Jr, Ward HA, Riederer SJ. "Real-Time Shimming of Polarizing Field in Magnetic Resonance System" US Patent No. 6,472,872 Issued 10/29/2002

Jack CR Jr, Manduca A, Welsh EB, Grimm R. "Reduction of Motion Artifact in NMR Images using Spherical Navigator Signals" US Patent No. 7,127,092 Issued 10/24/2006

Selected peer-reviewed publications

(in chronological order from over 250 peer-reviewed publications)

1. **Jack CR Jr,** Petersen RC, O'Brien PC, Tangalos EG. MR-based hippocampal volumetry in the diagnosis of Alzheimer's disease. *Neurology* 1992; 42:183-188.
2. **Jack CR Jr,** Petersen RC, Xu YC, Waring SC, O'Brien PC, Tangalos EG, Smith GE, Ivnik RJ, Kokmen E. Medial temporal atrophy on MRI in normal aging and very mild Alzheimer's disease. *Neurology* 1997; 49:786-794.
3. **Jack CR Jr,** Petersen RC, Xu YC, O'Brien PC, Waring SC, Tangalos EG, Smith GE, Ivnik RJ, Thibodeau, SN, Kokmen E. Hippocampal atrophy and apolipoprotein E genotype are independently associated with Alzheimer's disease. *Annals of Neurology*, 1998; 43:303-310.
4. **Jack CR Jr**, Petersen RC, Xu Y, O'Brien PC, Smith GE, Ivnik RJ, Tangalos EG, Kokmen E. Rate of medial temporal lobe atrophy in typical aging and Alzheimer's disease. *Neurology* 1998; 51:993-999.
5. **Jack CR Jr,** Petersen RC, Xu Y, O'Brien PC, Smith GE, Ivnik RJ, Boeve BF, Waring SC, Tangalos EG, Kokmen E. Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. *Neurology* 1999; 52:1397-1403.
6. **Jack CR Jr,** Petersen RC, Xu Y, O'Brien PC, Smith GE, Ivnik RJ, Boeve BF, Tangalos EG, Kokmen E. Rates of hippocampal atrophy in normal aging, mild cognitive impairment, and Alzheimer's disease. *Neurology* 2000; 55:484-489.
7. Xu Y, **Jack CR Jr,** O'Brien PC, Kokmen E., Smith GE, Ivnik RJ, Boeve BF, Tangalos EG, Petersen RC. Usefulness of MRI measures of entorhinal cortex vs hippocampus in AD. *Neurology*, 2000; 54:1760-1767.
8. **Jack CR Jr,** Dickson DW, Parisi JE, Xu Y, Cha RH, O'Brien PC, Edland SD, Smith GE, Boeve BF, Tangalos EG, Kokmen E, Petersen RC. Antemortem MRI findings correlate with hippocampal neuropathology in typical aging and dementia. *Neurology* 2002; 58:750-757.
9. **Jack CR Jr**, Shiung MM, Gunter JL, O'Brien PC, Weigand SG, Knopman DS, Boeve BJ, Ivnik RJ, Smith GE, Cha RH, Tangalos EG, Petersen RC. Comparison of different MRI brain atrophy rate measures with clinical disease progression in AD. *Neurology* 2004; 62:591-600.
10. **Jack CR Jr,** Shiung MM, Weigand SD, O'Brien PC, Gunter JL, Boeve BF, Knopman DS, Smith GE, Ivnik RJ, Tangalos EG, Petersen RC. Brain atrophy rates predict subsequent clinical conversion in normal elderly and amnestic MCI. *Neurology* 2005; 65:1227-1231.
11. Whitwell JL, Przybelski SA, Weigand SD, Knopman DS, Boeve BF, Petersen RC, **Jack CR Jr.** 3D maps from multiple MRI illustrate changing atrophy patterns as subjects progress from mild cognitive impairment to Alzheimer's disease. *Brain* 2007; 130 (7):1777-86.
12. Whitwell JL, Shiung MM, Przybelski S, Weigand SD, Knopman DS, Boeve BF, Petersen RC, **Jack CR Jr.** MRI patterns of atrophy associated with progression to AD in amnestic mild cognitive impairment. *Neurology*, 2008; 70: 512-520..
13. Vemuri P, Gunter JL, Senjem ML, Whitwell JL, Kantarci K, Knopman D, Boeve BF, Petersen RC, **Jack CR Jr**. Alzheimer's disease diagnosis in individual subjects using structural MR images: validation studies. *NeuroImage* 2008; 39: 1186-1197
14. **Jack CR Jr,** Lowe VJ, Weigand SD, Wiste HJ, Senjem ML, Knopman DS, Shiung MM, Gunter JL, Boever BF, Kemp BJ, Weiner M, Petersen RC, Alzheimers Disese Neuroimaging Inititative. Serial PIB and MRI in normal, MCI, and AD: implications for sequence of pathological events in AD. *Brain* 2009 Mar 31, epub doi:10.1093/brain/awp062.
15. Vemuri P, Wiste HJ, Weigand SD, Shaw LM, Trojanowski JQ, Weiner MW, Knopman DS, Peterson RC, **Jack CR Jr.,** and the Alzheimer's Disease Neuroimaging Initiative. MRI and CSF biomarkers in normal, MCI, AD: predicting future clinical change. Accepted for Publication in *Neurology.*

Research Support

Ongoing Research Support

RO1 AG11378-16 Jack (PI) 6/01/2008-5/31/2013
NIH/NIA
Identifying Mechanisms of Dementia: Role for MRI in the Era of Molecular Imaging
Scientific goal; to test the hypothesis that multi modality MRI and 11C PIB PET amyloid imaging can identify specific mechanisms underlying the progression to dementia.
Role: PI

U01 AG032438 Morris (PI) 2008-2014
NIH/NIA
Dominantly Inherited Alzheimer Network (DIAN)
Scientific goal: to establish a worldwide network to collect longitudinal imaging, clinical and biomarker data in subjects and family members at risk for dominantly inherited Alzheimer's disease
Role: Co-I

U01 AG024904-01 Weiner (PI) 9/30/04-09/2920/2010
NIH/NIA
Alzheimer's Disease Neuroimaging Initiative
Scientific goals: create a generally accessible data repository, which describes longitudinal changes in brain structure and metabolism in patients with AD, MCI, and elderly controls
Role: PI of MRI Core; Co-Investigator on overall grant

Completed Research Support

R01 AG023195-04 Knopman (PI) 9/01/03-2/28/2009
NIH/NIA
Frontotemporal Degeneration: A Basis for Clinical Trials
Scientific goal: to perform a natural history trial of patients with frontotemporal degeneration in order to develop clinical, psychometric, and imaging criteria for conducting future therapeutic trials in this disorder.
Role: Co-Investigator

P50 AG16574-09 Petersen (PI) 6/15/04-4/30/2009
NIH/NIA
Mayo Alzheimer's Disease Research Center - Project 1 - Roch - Tensor Based Regional Atrophy Rate Measures from Serial Structural MRI in Normal Aging, AD, and FTD
Scientific goal: to measure rates of regional brain atrophy in FTLD an AD with TBM
Role: PI of Project 1, Co-Investigator on overall grant

BIOGRAPHICAL SKETCH

Provide the following information for all key personnel.
Follow the sample format for each person found in **Biosketch Sample**. **DO NOT EXCEED FOUR PAGES.**

NAME	**POSITION TITLE**
Marina Boccardi	MA, PhD, Researcher

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	**DEGREE** *(if applicable)*	**YEAR(s)**	**FIELD OF STUDY**
University of Kuopio, Kuopio, Finland	PhD	2002-2006	Neuroscience
University of Padua, Padua, Italy	MA	1999-2005	Psychobiology
Grammar School "Arnaldo", Brescia, Italy	Secondary school	1994	

A. Positions and Honors.

2000 - to date: Senior researcher at LENITEM (Laboratory of Epidemiology, Neuroimaging and Telemedicine), IRCCS S. Giovanni di Dio – Fatebenefratelli – Brescia, Italy

B. Selected peer-reviewed publications (in chronological order).

1. **Boccardi M**, Almici M, Bresciani L, et al. Clinical and medial temporal features in a family with mood disorders. Neurosci Lett. 2010;468(2):93-7.
2. **Boccardi M**, Ganzola R, Rossi R, et al. Abnormal hippocampal shape in offenders with psychopathy. Hum Brain Mapp. 2009 Aug 28. [Epub ahead of print]
3. Sabattoli F, **Boccardi M**, Galluzzi S, et al. Hippocampal shape differences in dementia with Lewy bodies. Neuroimage. 2008 Jul 1;41(3):699-705. Epub 2008 Mar 14.
4. **Boccardi M**, Sabattoli F, Laakso MP, et al. Frontotemporal dementia as a neural system disease. Neurobiol Aging. 2005;26(1):37-44.
5. **Boccardi M**, Laakso MP, Bresciani L, et al. The MRI pattern of frontal and temporal brain atrophy in fronto-temporal dementia. Neurobiol Aging. 2003 24(1):95-103.
6. **Boccardi M**, Pennanen C, Laakso MP, et al. Amygdaloid atrophy in frontotemporal dementia and Alzheimer's disease. Neurosci Lett. 2002;335(2):139-43.
7. **Boccardi M**, Laakso MP, Bresciani L, et al. Clinical characteristics of frontotemporal patients with symmetric brain atrophy. Eur Arch Psychiatry Clin Neurosci. 2002 Oct;252(5):235-9.

C. Research Support.

2009: "Study of features and risk factors of neurodegenerative and psychiatric conditions using advanced neuroimaging postprocessing methods"
AFAR (Associazione Fatebenefratelli per la Ricerca) Rome, Italy
Principal investigator
2008: "Validation and implementation of the new diagnostic criteria for Alzheimer's disease"
AFAR (Associazione Fatebenefratelli per la Ricerca) Rome, Italy
Principal investigator
2006: "Cognitive and movement disorders: clinical, genetics and biological aspects in sporadic and familial tauopathies and sinucleopathies"
Italian Ministry of Health
Operative Unit Coordinator

2006 "Feasibility o fan integrated telemedicine system for the rehabilitation of patients with chronic central nervous system disorders, and physical and cognitive deficits"
Italian Ministry of Health
Operative Unit Coordinator

NAME	POSITION TITLE
Duchesne Simon	Associate professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Royal Military College of Canada, Kingston, Canada	B.Eng.	1993	Engineering Physics
Universite du Quebec a Hull, Hull, Canada	Diploma	1997	Project Management
McGill University, Montreal, Canada	M.Sc.	2001	Medical Physics
McGill University, Montreal, Canada	Ph.D.	2005	Biomedical Engineering
Unit/Team VISAGES, INRIA/INSERM, France	Post-doc	2007	Medical Imaging Science

Positions and Honors

Academic appointment

1993: Research assistant at the High Energy Astrophysics Laboratory, Australian Defense Force Academy, Canberra, Australia

2006: Invited lecturer at the Masters level program, Signals and Images in Biology and Medicine, Universite de Rennes I, Rennes, France

2005-2007: Post-doc at the Unit/Team VISAGES, INRIA/INSERM, France

2007-to date: Associate professor of the Radiology Department, Faculty of Medicine, Laval University

2007-to date: Researcher at the Robert Giffard Laval University Research Center

Other appointment

1988-1998: Officer-communications and electronics at the Department of National Defense (DND), Canada

1994-1997: Satellite communication systems engineer at the Directorate Electronics, Communications and Spectrum Services, DND Headquarters, Ottawa, Ontario, Canada

1997-1998: Troop commander at the 1ST Canadian Division Headquarters and Signals Regiment, Kingston, Ontario, Canada

1998-2000: Field/systems engineer at the NSI Communications, Ville St-Laurent, Quebec, Canada

2003-to date: Vice-president at the DT&R Inc., St-Bruno, Quebec, Canada. Course organizers - Breast Diseases: Detection, Intervention and Therapy (The Breast Course^{TM}, http://www.thebreastcourse.com)

Honors

2000: Best Student Paper Award, Canadian Radio-Protection Association

2001-2002: Alma Mater Travel Awards, Alma Mater Society, McGill University, Canada

2002: Doctoral award, Canadian Council of Professional Engineers

2004: Travel scholarship, Institute for Pure and Applied Mathematics, UCLA, CA

2001-2004: Doctoral scholarship, Quebec Health Research Funding Agency, Quebec, Canada

2005-2007: Postdoctoral Scholarship, National Institute for Health and Research in Medicine, France

2007: John F. Davis Award, McGill University

2008: F. Langelier Award, Laval University

Selected peer-reviewed publications (in chronological order)

1. **Duchesne S**, Bocti C, de Sousa K, Frisoni GB, Chertkow H, Collins DL. Amnestic MCI future clinical status prediction using baseline MRI features. *Neurobiol Aging*, accepted for publication, 2008.

2. **Duchesne S**, Rolland Y, Vérin M. Automated computer differential classification in parkinsonian syndromes via pattern analysis on MRI. *Acad Radiol*, accepted for publication, 2008.

3. Canu E, Boccardi M, Testa C, Pievani M, **Duchesne S**, Ghidoni R, Benussi L, et al. HOXA1 A218G polymorphism is associated with smaller cerebellar volume in healthy human. *J Neuroimaging*, accepted for

publication, 2008.
4. **Duchesne S**, Caroli A, Barillot C, Frisoni GB, Collins DL. MRI-based automated computer classification of probable AD versus normal controls. *IEEE Trans Med Imaging*. 2008;27:509-520.
5. **Duchesne S**, Jannin P. Proposing a manuscript peer-review checklist. *NeuroImage*; 2008;39:1783-1787.
6. Aleong R, **Duchesne S**, Collins DL, Paus T. Assessment of adolescent body perception: development and characterization of a novel tool for morphing images of adolescent bodies. *Behav Res Methods.* 2007;39:651-666.
7. **Duchesne S**, Bernasconi N, Bernasconi A, Collins DL. MR-based neurological disease classification methodology: application to lateralization of seizure focus in temporal lobe epilepsy. *NeuroImage*. 2006;29:557-566.
8. Duchesne N**,** Jaffey J, Florack P, **Duchesne S**. Redefining criteria for ultrasound appearance of positive axillary lymph nodes. *CAR J*. 2005;56:289-296.
9. Bernasconi N, **Duchesne S**, Janke A, Lerch J, Collins DL, Bernasconi A. Whole-brain voxel-based statistical analysis of gray matter and white matter in temporal lobe epilepsy. *NeuroImage*. 2004;23:717-723.
10**. Duchesne S**, Pruessner JC, Collins DL. Appearance-based segmentation of medial temporal lobe structure. *NeuroImage*. 2002;17:515-531.
11. Camborde M, **Duchesne S.** Summary of current positions on breast cancer incidence using mammography. *Bulletin of the Canadian Association of Radio-Protection*. 2000;21:16-25.

Research Support

2004-2005: Key personnel of the project at the Canadian Institute of Health Research aimed at translating imaging research from epilepsy to Alzheimer's dementia (CDN$ 100,000/1 year)
2006-2008 *:* Key personnel of *NEUROMIME* project at the Institut National de Recherche en Informatic et en Automatic (France). This project was aimed at fostering relationships between French and Canadian laboratories. This grant supported travel during post-doctoral research at EQUIPE VISAGES, Rennes, France (€ 20,000/2 years).
2008-2010: Principal Investigator of the start-up funds for research dedicated to neuroimaging in dementias of the Centre de Recherche Universitè Laval-Robert Giffard (CDN$ 90,000/3 years)
2008-2010: Principal Investigator of grant by MDEIE- Programme de Soutien à la Recherche: Soutien aux initiative internationales de recherche et innovation. This international collaborative grant, in consort with the LENITEM laboratory in Brescia, Italy, is aimed at characterizing genetico-structural relationships in aging and Alzheimer's dementia via voxel-based morphometry (CDN$ 150,000/3 years) .
2009-2011: Principal Investigator of the industrial- academic partnership with AGF Healthcare INC. This industrial –academic partnership is aimed at creating a knowledge-based reasoning system for aid to diagnostic in dementias (CDN$ 1000,000/2 years)

NAME	POSITION TITLE
Cavedo Enrica	Researcher

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Padova	PsyD	2008	Psychology

Positions and Honors

2008-to date: Research fellowship at the IRCCS Fatebenefratelli, Brescia

Selected peer-reviewed publications (in chronological order)

1. Boccardi M, Frisoni GB, Hare RD, **Cavedo E**, Najt P, Pievani M, Rasser PE, Laakso MP, Aronen HJ, Tiihonen E, Vaurio O, Thompson PM, Tiihonen J. The Cortical and Amygdalar Morphology of Psychopathy: A Predatory Brain? *Nature Neuroscience,* submitted.

2. Boccardi M, **Cavedo E**, Beltramello A, Caltagirone C, Thompson P.M, Frisoni G.B. Mapping Amygdalar structural differences in Alzheimer's patients with 3T MRI. Abstract submitted at the 2010 American Academy of Neurology.

3. Frisoni G, **Cavedo E**, Galluzzi S, Boccardi M, Pievani M, Lorenzi M. Norms for imaging markers of cognitive reserve. Abstract submitted at the 2009 Italian Society of Neurology.

NAME	POSITION TITLE
Redolfi Alberto	Researcher

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Milan	Master degree in Functional Genomics and Bioinformatics	2005	Biomedical Information Technology
University of Milan	Graduate degree in Industrial and Environmental biotechnology	2003	Biotechnology

Positions and Honors

2008-to date: Research fellowship at the IRCCS Fatebenefratelli, Brescia
Main activities and responsibilities:
- Supervisor of the neuGRID project.
- Technical manager of neuGRID technology in the Fatebenefratelli core lab.
- Research on algorithm parallel computing.
- Construction and Population of the neuGRID Medical Imaging Database.
- Definition and characterization of the neuGRID brain imaging services.
- Definition of the grid services available in the neuGRID platform.
- Developer of the Fatebenefratelli computing core lab.
- User and system requirement analysis.
- Algorithms gridification,

2006-2008: Fellow at the Molecular Pharmacology Lab & TOP (Transgenic Operative Products) SrL
Main activities and responsibilities:
- Research on the activity of estrogens receptors and their modulated intracellular signal within the EWA (Estrogens in Women Aging) project, through reporter mice models and cells lines engineered and visualized using CCD camera technology.
- Identification, through micro array studies, of tissue-dependent genes modelled by estrogens, to be used as endogen markers of the receptors activity.
- Development and management of TOP (Transgenic Operative Products) S.r.l. spin-off of the University of Milan.

2007: Winner of the overall grant *INGENIO 2007*, funded by "Regione Lombardia" and Finlombarda SpA for the development of a multi-modal reporter organism in the field of molecular imaging.

2005-2006: Product Specialist at the ADIENNE Pharma & Biotech
Main activities and responsibilities:
- Research and Development of new molecules in the oncohematology field.

Selected peer-reviewed publications (in chronological order)

1. **Redolfi A**, McClatchey R, Zijdenbos A, et al. Grid infrastructures for computational neuroscience: the neuGRID example. *Future Medicine / Future Neurology* 1st November 2009.

2. Giovanni B Frisoni, Marina Boccardi, Rossana Ganzola, Simon Duchesne, Nicolas Robitaille, **Alberto Redolfi**, George Bartzokis, John G. Csernansky, Mony J. de Leon, Ronald J. Killiany, Stéphane Lehéricy, Nikolai V. Malykhin, Johannes Pantel, Jens C. Pruessner, Hilkka Soininen, Clifford Jack. Survey of Protocols for Manual Hippocampal Volumetry: Preparatory Steps for an EADC-ADNI Harmonized Protocol. Abstract submitted at the 2010 American Academy of Neurology.

NAME	POSITION TITLE
Podavini Marco	Researcher

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Brescia	Graduate degree in engineering	1991-2000	Electronic Engineering – Information Technologies
National Technical and Industrial Institute	High school	1986-1991	Computer science, electronic, automated systems, industrial electronics

Positions and Honors

2008-2010: Fellow at the IRCCS Fatebenefratelli, Brescia (neuGRID project: Application and web developer, mainly based on information managing through the use of database)
2006-2007: Fellow at the IRCCS Fatebenefratelli, Brescia (E-ADNI project)
2003-to date: Teacher, coordinator of computer science area in a Technical High School, Brescia
2002-2003: Quality manager (ISO 2000 – EVision), IT and network manager, Production manager in an Electronic Company, Brescia
2000-2002: Project manager, developer and team manager for web site projects in a Multiutility Enterprise, Brescia

Selected peer-reviewed publications (in chronological order)

The professional profile is such that M.P. is not involved in scientific publication but in the development and maintenance of websites. A selection of these follows:

- FATEBENEFRATELLI INSITUTIONAL SITE: institutional site describing the activities of the National Centre for Research and Care of Alzheimer's and Mental Diseases. Includes facilitated publication system
http://www.irccs-fatebenefratelli.it/mini-siti/pagine/laboratorio_scelta.php?lab=a
Technology: Html, PHP, Adobe Photoshop, MySQL
- NEUROIMMAGINI.IT: institutional site for the Imaging Study of the Italian Neurological Society (SIN)
http://www.neuroimmagini.it/sito/home.php
Technology: Html, PHP, Adobe Photoshop
- FITNESS & SOLIDARIETA': site for the Italian Alzheimer's day
http://www.irccs-fatebenefratelli.it/fitness/sito/home_page.htm
Technology: Html, PHP, Adobe Photoshop
- NEUGRID.EU: official site of FP7 neuGRID project featuring public and reserved areas. The system is a proprietary CMS to publish and update information and document sharing/upload/download.
http://www.neugrid.eu
Technology: Html, PHP, Adobe Photoshop, MySQL, configuration of Virtual Server
- CENTROALZHEIMER.IT: site to collect donations for research in the field of Alzheimer's Disease, including an e-commerce section for on-line donations.
http://www.centroalzheimer.it/dol/sito/home.php
Technology: Html, PHP, MySQL, Adobe Photoshop
- CENTROALZHEIMER.ORG (work in progress): institutional site for physicians, patients, and relatives showing the latest techniques for the early diagnosis of Alzheimer's disease.

http://www.centroalzheimer.org/bozza/sito/home.php

Technology: Html, PHP, Adobe Photoshop

MOD 5 U.G.
UNSTAMPED PAPER

Minister of the Health

OFFICE FOR THE ORGANIZATION OF BUDGET AND PERSONNEL
OFFICE III

1998/SOBP/3/3 /

THE MINISTER OF THE HEALTH

SEEN the documented appeal with which the legal representative of the association *"Fatebenefratelli per la Ricerca Biomedica e Sanitaria" (A.F.a.R.)* - constituted in Rome on the day 22nd March 1994, by notorial deed executed under seal of dr. Nicolò Bruno, notary in Rome, repertoire n.100663/33285, among the "Casa Generalizia dell'Ordine di San Giovanni di Dio, Fatebenefratelli" – asked, under article 12 of the civil code, the juridical recognition of the same association;

SEEN the Statute attached to the record of the Special Meeting of the aforesaid association compiled on 16th March 1998 by notorial deed executed under seal of the dr.ssa Maria Chiara Bruno, notary in Rome, repertoire n.369/70;

CONSIDERED that the association aims to promote and to realize activities of basic and oriented research in the biomedical field and in the field of public health in general and especially to use and to apply researches on resources optimization and on humanization of the performances in relationship to pathologies of the sensory system, to the psychiatric rehabilitation and of the cerebral aging, also building, in this field, connections and liaisons among Institutes of the Fatebenefratelli, as well as among other health and care structures of the same Order of San Giovanni di Dio;

SEEN the positive opinion of the Prefect of Rome;

SEEN the quoted article 12 of the civil code and article 2 of the dispositions for the implementation of the same code;

SEEN the law n.296 of 13th March 1958;

SEEN the article 2 of the law n.13 of 12th January 1001;

SEEN the article 2, paragraph 2, of the legislative decree n.266 of 30th June 1993;

SEEN the article 5, paragraph 2, of the decree of the President of the Republic n.196 of the 2nd February 1994, and following modifications;

SEEN its own decree n.704 of 27th December 1996;

SEEN articles 1 and 2 of its own decree on 26th June 1996;

SEEN the article 17 of the law n. 127 of 15th May 1997, and following changes and integrations;

DECREES

That the legal personality of the *Association Fatebenefratelli per la Ricerca Biomedica e Sanitaria (A.F.a.R.*) headquartered in Rome, via della Nocetta n.263 is recognised.
Its Articles of Associations are approved, whose text is enclosed - that forms integral part of the this decree - composed of 22 articles, duly approved.
The present decree will be published, in summary, in the Official Gazette of the Italian Republic.

Rome, 2nd October 1998

P. THE MINISTER
THE STATE SECRETARY
(Sen. Monica Bettoni Brandani)

AFAR/b
VG/rl

MINISTER OF HEALTH

Recognition of the legal personality of the association Fatebenefratelli per la Ricerca Biomedica e Sanitaria (A.F.a.R., in Rome).

With ministerial decree 20th October 1998 it has been recognized the legal personality of the association Fatebenefratelli per la Ricerca Biomedica e Sanitaria (A.F.a.R.), headquartered in Rome, and contextually the its Articles of Association composed of 22 articles have been approved.
98A10137

Prefecture in Rome
Territorial office of the Government

RECORD OF LEGAL ENTITITES

EXAMINED THE REGISTER OF THE LEGAL ENTITITES AND THE RELATED ACTIONS DEPOSITED IN THIS OFFICE

C E R T I F I E S

THAT THE LEGAL ENTITY Association FATEBENEFRATELLI per la Ricerca Biomedica e Sanitaria (A.F.a.R.)

HEADQUARTERED IN ROME – VIA DELLA NOCETTA N.263

IS RECORDED IN THE REGISTER OF THE LEGAL ENTITIES HELD BY THIS UTG
N° 31 1.999

THAT THE LEGAL REPRESENTATIVE IS KNOPP GEBHARD ALOIS

BORN IN KAHL AM MAIN (Germany) ON 18/01/1958

RELEASED ON DEMAND OF THE PARTY FOR THE USES ALLOWED BY THE LAW

Rome, 13/12/2007

THE OFFICER
(Dr.ssa Pari him)

Directory n. 18278 Collection n. 6163

ATTACHMENT "A." TO THE N. 6163 OF FILE

ARTICLES OF ASSOCIATION OF THE ASSOCIAZIONE FATEBENEFRATELLI PER LA RICERCA BIOMEDICA E SANITARIA (A.Fa.R.)

ARTICLE 1 - CONSTITUTION AND HEADQUARTER

It is hereby constituted the association Fatebenefratelli per la Ricerca Biomedica e Sanitaria (A.Fa.R.), headquartered in Rome, via della Nocetta n. 263.

The association is an independent, non-profit making organ.

ARTICLE 2 - PURPOSES OF THE ASSOCIATION

The association, inspiring itself to the finalities and charisma of the hospitality of the Hospital order of San Giovanni di Dio Fatebenefratelli in harmony with the fundamental principles of the Italian legal system, aims to promote and to realize activities of basic and oriented research in the biomedical field and in the field of public health in general and especially to use and apply researches on resources optimization and on humanization of the health and care performances. It also builds, in the same field, connection and liaisons among the structures of the same Order San Giovanni di Dio in Italy, in the European Union and in the rest of the world.

The researches promoted by the association will be realized in strict connection with the activities of hospitalization and care, with the purpose of:

a) valorising the care approach of the order of S. Giovanni di Dio, based on the respect and on the active solidarity with the afflicted;

b) applying human sciences to health, by identifying and implementing criteria of global assistance, aimed to the improvement of the therapeutic acts' quality, given the respect of the most efficient management of resources;

c) promoting the transfer of acquired knowledge toward other institutions of hospitalization and care, toward the personnel in view of a permanent and up-to-date preparation;

d) promoting, in collaboration with other corporate bodies, experimental plans within the field of the associative purposes.

For the fulfilment of the exposed finalities laboratories, working groups, research contracts, scholarships, publications, conventions and collaborations are activated with institutions and centres of research in Italy and foreign countries, conferences, courses and seminars and other initiatives for transfer of knowledge. Moreover, the Associated Organizations are deemed to adjust their own structures in harmony with the technical-organizational and scientific indications under current dispositions for the implementation of the activities of scientific-wise hospitalization and care.

ARTICLE 3 – DURATION

The duration of the association is set up as running up to 31st December 2024.

Being the decision approved with favourable vote of the 2/3 of the representatives of the In-partnership Corporate body, the Assembly will be able, before such date, to prepare an extension for further twenty years and subsequently every twenty years.

ARTICLE 4 – ASSOCIATED ORGANIZATIONS

All Italian and foreigner ecclesiastical Organizations of the order of San Giovanni di Dio that intend to collaborate with A.Fa.R can assume the quality of Associated Organizations in the research activity as reported at the art. 2 of these Articles of Association.

The accession is subordinate to the presentation of a request which shall undergo the approval of the Board of Directors which shall indicate the appointment to the aforesaid collaboration and the payment of the initial and annual contributions as deliberated by the Assembly.
The acceding Organization will be able in any moment to recede from the association. The recess will be effective after thirty days from the receipt of the declaration of recession, to be delivered via registered mail to the President of the Board of Directors of the association.
The missed payment of the annual associative quota will be interpreted by the association as notification of the wish of the associate to recede from the group of participants.
Moreover, the quality of Associate is lost by decision of the Board of Directors, after the ascertaining of ascription and heard the interested Organization, for acts made in contrast to what specified in these Articles of Association or if serious reasons that forbid the prosecution of the associative relationship have occurred.
Against the provision of exclusion, the excluded associate has 30 (thirty) days of time to appeal to the Assembly, without prejudice to the faculty for the same to resort to the judicial authority under article 24 C.C. second paragraph.

The associates that withdrew from the association cannot claim the return the contributions paid and are not entitled to any rights on the company assets.

Within the framework of the associative purposes and in support of its own research programs, the association can collaborate with the existing Provinces of the order in other Countries, on which Institutes of hospitalization and care or health and care structures depend, where clinical and research experimentations are conducted.

With decision of the Assembly, research programs are established every three years and must be followed in the predisposition of programs and projects of the association, keeping in mind also the indications and national, European and international general plannings.

The association is in charge of the predisposition and implementation of single projects coordinating their management and also involving structures and operators to them assigned by the single Associated Organization.

ARTICLE 5 - MEANS

The means for the implementation of the activity of the association are constituted by:

a) the social fund;

b) public and private contributions and financings, assigned to studies and researches carried out by the association;

c) legacies and donations transferred to the association;

d) structures and services made available by the Associated Organization for the fulfilment of the associative purposes, given the autonomy of properties of the each Organization;

e) associative quotas and any additional contributions deposited annually by the Associated Organization as established by the Assembly;

f) the contributions' quota arranged and all the proceeds derived from researches carried out for outside bodies by the Associated Centres;

g) possible leftovers.

The association can found operational centres or suppress pre-existing centres with decision of the Board of Directors, heard the Scientific Director.

The financial year of the association closes on 31st December of every year.

ARTICLE 6 - ORGANS OF THE ASSOCIATION

The organs of the association are: the Assembly, the President, the Deputy President, the Board of Directors, the Scientific Technical Committee, the General Secretary, the Scientific Director, the Board of Auditors.

ARTICLE 7 - THE ASSEMBLY

The Assembly is composed by a religious representative for each of the Associated Organizations; moreover, can participate to the Assembly without right of vote:

- the General Secretary;
- the Scientific Director;
- the President of the Board of Auditors of the association.

The Assembly meets ordinarily at least twice a year, within December 30th for the approval of the general program and the estimates of the future exercise and within April 30th for the approval of the appropriation account.

The Assembly is called and chaired by the President of the association, entitled following article 10.

It is up to the President to assess the right to intervene in the Assembly, the possible delegations and the legality of the constitution.

The Secretary taking minutes will be designate by the President, from time to time, among the components of the Assembly, except the cases in which the person taking minutes is a notary.

Meetings shall called by registered mail letter to be sent to each participant at least ten days prior the date scheduled for the call or via telefax or email at least five days before; the second call shall be scheduled at least 24 hours prior the first.

Even in absence of a formal call, meetings in which the representatives of the Associated Organization, the President of the Board of Directors, the General Secretary, the Scientific Director and the President of the Board of Auditors of the association are present are considered valid.

The Board of Directors may meet utilising audio/video conference facilities or otherwise conference call facilities, subject to the

conditions that all attendees may be identified, that such identification of attendees is recorded in the minutes, that all attendees are permitted to follow the discussion, to take part in real-time in the discussion. In such case, the Meeting is deemed to be held in the place where the Chairman and the Minutes Secretary are present.

ARTICLE 8 - DELIBERATIONS OF THE ASSEMBLY

In first call, the Assembly is regularly constituted with the presence of the half plus one the religious representatives of the Associated Organizations.

In second call, it is regularly constituted regardless of the number of religious representatives.

Without prejudice to the cases in which these Articles of Association sets different majorities, the Assembly deliberates with the favourable votes of the majority of the present associates with right to vote.

ARTICLE 9 - POWERS OF THE ASSEMBLY

The Assembly has the power to:
- approve the general roadmaps and of association’s three-year period activities programs;
- approve the estimates and the annual appropriation account;
- change the Statute and decisions related to the dissolution of the association, after obtaining the assent of the Associated Organizations, as well as the formalities of credit assignment of the patrimony;
- decide regarding the proposals of the Board of Directors or reserved to the Assembly according to laws and rules.

ARTICLE 10 – THE PRESIDENT

The President is appointed by the Assembly among the legal representatives of the Associated Organizations or among the religious by them proposed, remains in charge for three years and is re-eligible.

The Assembly appoints among the legal representatives of the Associated Organizations or among the religious by them also proposed, the Deputy President that, in case of absence or temporary impediments of the President, assumes his/her functions.

Also the Deputy President remains in charge for three years and is re-eligible.

ARTICLE 11 – DUTIES OF THE PRESIDENT

The President has the social signature and the legal representation of the association.

To the same it is conferred the power to use the funds of the association to start, within the limits of the relative estimates, the programs approved by the Assembly according to the suggestion of the Board of Directors.

He/she calls and chairs the Assembly and the Board of Directors and, if the General Secretary has not been appointed, implements the decisions of the Board of Directors.

In case of need, he/she can adopt decisions on the subjects at the letters "c", "e", "g" of the following article 13 related to the competences of the Board of Directors, submitting them for approval to the same Board of Directors in the first useful meeting.

ARTICLE 12 – BOARD OF DIRECTORS

The Board of Directors is composed by two components of each Associated Organization appointed by the Assembly, among which the President and the Deputy President appointed according to article 10.

The Board of Directors can appoint, also outside its components, a General Secretary that remains in charge up to the end of three-year period mandate and is re-eligible.

To the sessions of the Council can participate, also, without right to vote:

- the General Secretary;
- the Scientific Director;
- the Scientific Coordinators of every Associated Organization;
- the President of the Board of Auditors.

The Board of Directors remains in charge for three years.
If during the three-year period the President or any other component of the Board of Directors leaves the office for resignations or any other cause, the Assembly will appoint a substitute according to the same formalities for the appointment of each of them and the new appointed will remain in charge up to the end of the three-year period in progress.

The Board of Directors meets ordinarily at least twice a year and every time the President deems it necessary or when it is requested by the religious representative of one of the Associated Organization.

The Board is called by registered mail letter sent to the Advisers at least five days prior the scheduled date for the call or by telegram, telefax or email sent at least three days before the meeting. The Board's meetings are valid in first call with the presence of half plus one the designated components with right to vote, in second call regardless of the number of the present advisers.

The presence of the majority and with the right of vote is necessary for the resolution of the Board to be validly passed. In the event of a tie, the person President holds the casting vote.

The Board of Directors may meet utilising audio/video conference facilities or otherwise conference call facilities, subject to the conditions that all attendees may be identified, that such identification of attendees is recorded in the minutes, that all attendees are permitted to follow the discussion, to take part in real-time in the discussion. In such case, the Meeting is deemed to be held in the place where the Chairman and the Minutes Secretary are present.

ARTICLE 13 – DUTIES OF THE BOARD OF DIRECTORS

The Board of Directors is entitled to manage the ordinary and extraordinary administration. In particular, it is up to it:

a) to prepare and to propose to the Assembly the general roadmaps and the yearly/multi-year programs of activities according to the research lines, under art. 4.

Estimates and budgets will have to be approved and deposited at registered seat thirty days prior the date scheduled for the first call of the Assembly called to approve them;

b) to approve rules for the implementation of the research activities and the rules and the administrative procedures for the accounting of the projects and the use of the resources;

c) to approve the programs and the projects of research set by the Scientific Director and by him/her agreed with the Responsibles of the Associated Centres and the single work groups or research laboratories, after obtaining the assent of the Scientific Technical Committee, and the related estimates, as well as to periodically verify the general progress of the programs;

d) to name the Scientific Director and the General Secretary;

e) to approve conventions and agreements of collaboration between the Association and institutes and organisms in the field of health and care field and of the research and human sciences applied to this field;

f) to found scholarships supporting grants in the frame of the resources to this assigned;

g) to accept legacies and donations assigned to the association;

h) to assume obligations however preventively approved by the Associated Organization.

The General Secretary is in charge of managing, in the respect of the competences of the Scientific Director, the association and to implement the decisions of the Board of Directors that, with the deliberation of nomination, confers him/her the necessary powers.

ARTICLE 14 – SCIENTIFIC TECHNICAL COMMITTEE

The Scientific Technical Committee is called and chaired by the Scientific Director of the association. Meetings are called at least once a year within November 30th, to express its opinion on the research programs and projects introduced by the Scientific Director.

Besides the Scientific Director, the Committee includes: a representative appointed by each Associated Organization as well as an external member appointed by the Board of Directors among tenured university professors in the Health Research and Social Sciences applied to the Health fields.
All the components of the Scientific Technical Committee shall be selected however among the tenured university professors or among leading figures of the cultural world and in the field of the scientific research for health, to whom are recognized qualities in line with the principles contained in the "Carta di Identità" (Identity Card) of the Hospital order of San Giovanni di Dio Fatebenefratelli. To the meeting can participate the President of the Board of Directors or an his/her delegate Adviser as well as the General Secretary.

The Scientific Technical Committee remains in charge period that can vary from three to five years and its members are re-eligible.

ARTICLE 15 – DUTIES OF THE SCIENTIFIC TECHNICAL COMMITTEE

The Scientific Technical Committee:

a) annually expresses its preventive opinion on research programs and projects to submit to the approval of the Board of Directors and the Assembly.

b) promotes initiatives in the field of the transfer of knowledge and technical-scientific updating, with particular respect to the personnel of the operational centres;

c) expresses, on application of the Scientific Director, its opinion on the research activities submitted by other organs of the association, as well as on the structure and on the contents of possible scientific publications, whose editing and the association takes care of.

ARTICLE 16 – SCIENTIFIC DIRECTOR

The Scientific Director is appointed by the Board of Directors for a period that can vary from three to five years and can be re-eligible.

Any person eligible to be member of the Scientific Committee can be appointed to the position of Scientific Director.

ARTICLE 17 – DUTIES OF THE SCIENTIFIC DIRECTOR

The Scientific Director takes on the general responsibility of the research activities promoted by the association.
To this purpose, the Scientific Director:

- elaborates proposals to submit to the Scientific Technical Committee;
- manages the relationships with other research and education institutions;
- monitors the implementation of programs and projects of basic and oriented research submitted to the operational centres;
- monitors the activities of education and updating developed by the operational centres;
- proposes the appointments of new researchers by mean of fixed-term research contracts;
- gathers and validates, by formulating the consequent proposals, applications for the acquisition of new technologies for the scientific research.

ARTICLE 18 – ETHICAL COMMITTEE

For the expected and necessary opinions regarding projects and research initiatives, the association can rely on its own ethical committee or, in absence of this, can use for the same objectives ethical committees of the Associated Organizations or those of analogous Organizatio.

ARTICLE 19 – THE BOARD OF AUDITORS

The Board of Auditors is composed by three regular members designated by the religious representatives of the Associated Organizations, and by two temporary members appointed by the Board of Directors.

The President of the association appoints the President of the Board of Auditors.

The Board of Auditors meets periodically to carry out the audit at least four times a year and remains in charge three years.

The President of the Board of Auditors, or other Auditor his/her delegate, participates to the sessions of the Assembly and of the Board of Directors.
The regular components of the Board of Auditors have the right to a complementary fee calculated under the D.P.R. 10th October 1994 n. 645 and its following changes or integrations.

ARTICLE 20 – COMPETENCES OF THE BOARD OF AUDITORS

The Board of Auditors:

- verifies the regularity of the accounting and the administrative course of the association by compiling special reports on the aforementioned bookkeeping documents at least fifteen days prior the date scheduled for the call of the Assembly;
- expresses opinions on the estimates and on the appropriation account;
- verifies the consistence of cash in hand at least every quarter.
The President of the Association can attend to the meetings of the Board of Auditors.

ARTICLE 21 – CHANGES TO THE STATUTE

Any change to this Statute shall be deliberated by the Assembly with favourable vote of the 2/3 of the representatives of the Associated Organizations after obtaining the assent of the respective deliberative organs of such Organization.

ARTICLE 22 – WIND-UP OF THE ASSOCIATION

The association dissolves:

a) for end of period;

b) for expressed favourable vote of 3/4 of the Associates by formal deliberation of the Assembly;

c) for the other causes according to the law.

In the chance that one of the causes of dissolution arises, the association, even if recognized as juridical person, will have to wind up and to liquidate its property. To such purpose, the Assembly will appoint one or more liquidators that will proceed according to what under articles 11 and following of the dispositions of the Civil Code.

Goods which might remain at the end of the liquidation will be devolved, optional subject to the Assembly as it follows:

to) to other Corporate Bodies or institutions belonging to the order of San Giovanni di Dio that pursue finality of general utility analogous to those proper of the association and which are characterized by the absence of profit-making aims;

b) to the in-partnership Corporate Bodies, in equal parts.

ARTICLE 23 – APPLICABLE LAW

For what has not been specified by the present Statute, reference is to be made to the dispositions of the Italian Civil Code and its related Laws.

GEBHARD ALOIS KNOPP in religion FRA RUDOLF
MARIA CHIARA BRUNO Notary

Directory n. *100663*_____Collection n. *33285*

DEED OF FOUNDATION
OF THE
"ASSOCIAZIONE FATEBENEFRATELLI PER LA
RICERCA BIOMEDICA E SANITARIA"

ITALIAN REPUBLIC

In the year NineteenNinetyFour on the day *twenty-two* of the month of *March* in Rome in my Office

22 March 1994

Before me, Dr. NICOLO' Bruno, a Public Notary in Rome with Office located in Lungotevere Sanzio n.9 enrolled in the Role of the Reunited Notarial Districts in Rome, Velletri and Civitavecchia[1],
appeared:

- REVEREND ADOLFO FABELLO, in religion Fra' Raymond, born in Bertiolo (UD) on ~~December~~[2] 5th 1942 and resident in Rome, via della Nocetta 263, religious
who declares to participate to this deed of foundation act in his quality of legal representative of the
"CASA GENERALIZIA DELL'ORDINE DI SAN GIOVANNI DI DIO, also known as FATEBENEFRATELLI", headquartered in Rome Via della Nocetta 263, Corporate body legally recognized, recorded in the register of the Juridical People of the Court in Rome with n. *667*
Fiscal code *01362340588*
hereby authorized following the decision of the Consiglio Generalizio of the aforesaid Corporate body on the day 10th March 1994, ~~that~~[3]

- REVEREND FABELLO Franco, in religion Fra' Marco, born in Bertiolo (UD) on June 8th 1944, resident in Brescia via Corsica 339, religious
who declares to intervene to this deed of foundation act in his quality of Special Attorney of the
"PROVINCIA LOMBARDO-VENETA DELL'ORDINE DI SAN GIOVANNI DI DIO", headquartered in Milan, via San Vittore n.12, Organization legally recognized, recorded in the Register of the Juridical People of the Court in Milan to the n.341
Fiscal code *01647730157*

constituted and hereby authorized by Power of Attorney executed before the notary public *Dr. Stefano Zanardi Notary in Milan on day 21st of March 1994 reg. 18921 […]*

The aforementioned Apperares, Italian citizens as from self declaration, whose identities me, the Notary, I am certain of, agree and stipulate the following:

Article 1

Between the "Casa Generalizia dell'ordine di San. Giovanni di Dio, also known as Fatebenefratelli" and the "Provincia Lombardo-Veneta dell'Ordina di S. Giovanni di Dio, Fatebenefratelli", a non-profit Association is constituted, named "ASSOCIAZIONE FATEBENEFRATELLI PER LA RICERCA BIOMEDICA E SANITARIA" (acronym A.F.A.R.)

Article 2

The headquarter of the Association has currently been fixed in Rome, via della Nocetta n. 263

Article 3

The purpose, the duration, the composition of the Organs, the winding up and anything regarding the association is specified in the Articles of Association composed by *21* articles, in plain text, read by me, the Notary, to the Appearers, and following, authenticated by the Appearers and myself and finally enclosed to the this act under the letter *B*, so to form integral and substantial part of it.

Article 4

The following persons have been appointed as members of the first Board of Directors:

Fratel Adolfo Fabello

Fratel Franco Fabello

Fratel Aldo Zambolin

and, respectively, the first as President, the second as Deputy President and as Secretary Treasurer the third.

The aforesaid positions will receive official ratification on the occasion of the first meeting of the Board of Directors and will remain in force up to the first Ordinary Meeting during which the components the Auditors' College will be nominated as set under article *18* of the enclosed Articles of Association.

Article 5

The financial year of the association closes on 31st December of every year.

The first financial year will be closed on December 31st 1994.

Article 6

To the President *Fra' Adolfo*[4] are conferred all the powers to bring to this deed of foundation and to the enclosed Articles of Association all those changes, additions and suppressions that were required by the competent Authorities to get, if the case, the acknowledgement of the legal entity of the association.

Article 7

To the charter members of the "Casa Generalizia dell'ordine di San Giovanni di Dio, also known as Fatebenefratelli" and of the "Provincia Lombardo-Veneta dell'Ordine di S. Giovanni di Dio, Fatebenefratelli" can joinn, with a simple request of accession, other Ecclesiastical Organization recognized of the order of San Giovanni di Dio working in Italy.

To such aim, to the charter members is reserved the faculty to designate, among the same recognized Organization, those held fitter.

Article 8

The costs of the this deed and its subsequent are charged to the association, constituted with the present deed of foundation. On demand, me, the Notary, I have received this act that I have read to the Appearers, who, by me questioned, have approved and confirmed it.

Writing partly on typewriter and partly by hand by trustworthy person in *five* pages of *two* sheets and undersigned by the Appearers and by me the Notary under the norm of the law.

---

[1] *Without the assistance of witnesses, having this the Appearers agreed between them and with my consensus explicitly authorised.*

[2] *December must be replaced with September*

[3] *Erased that*

[4] *Fabello*

A.Fa.R.
ASSOCIAZIONE FATEBENEFRATELLI
PER LA RICERCA BIOMEDICA E SANITARIA
C.F. 97107960581 - P.I. 05078881009

Costituita 22 marzo 1994
Riconoscimento M.S. del 20 ottobre 1998

Rome, December 29th 2008

Hereby to declare that AFAR (Associazione Fatebenefratelli per la Ricerca Biomedica e Sanitaria) has not changed in his purpose, character or organizational structure since the date of its not for profit designation letter.

Associazione Fatebenefratelli per la Ricerca
Biomedica e Sanitaria (A.Fa.R)
Sede Legale: Via della Nocetta, 263 - 00164 Roma

AFaR General Secretary
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