HARNESS:

HARMONIZING BRAIN IMAGING METHODS FOR VASCULAR CONTRIBUTIONS TO NEURODEGENERATION

Report of a JPND Working Group on Harmonisation and Alignment in Brain Imaging Methods

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Harmonizing Brain Imaging Methods for Vascular Contributions to Neurodegeneration (HARNESS) Initiative

Report to the JPND Working Groups for Harmonisation and Alignment in Brain Imaging Methods for Neurodegeneration

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Executive Summary

Vascular cognitive impairment (VCI) is the second most common cause of dementia, and the most frequent co-morbid copathology accompanying other causes of neurodegeneration. Recent neuroimaging research has substantially expanded the measurable manifestations of cerebrovascular disease and their cerebral consequences. Innovative neuroimaging methods have identified functional and structural cerebral consequences of cerebrovascular disease (e.g. using diffusion tensor and perfusion imaging), interactions with co-morbid pathologies (e.g. using amyloid-PET), and new lesion types (e.g. perivascular spaces). However, translating these innovations into multi-center research and clinic practice requires validation and standardization of acquisition and measurement.

To facilitate multicentre trials in small vessel disease, we assembled an international group of experts to form the Harmonising Brain Imaging Methods for Vascular Contributions to Neurodegeneration (HARNESS) initiative with the objectives of: 1) distributing MRI protocols suitable for assessing vascular contributions to neurodegeneration, 2) creating a repository of MR images of small vessel disease, 3) producing recommendations for quality control and reliability of measurement for multicenter studies, and 4) reviewing the status of development and standardization of emerging techniques. Grant-funded activities included surveys, teleconferences, and an in-person workshop.

Most expert members indicated support for standardized MR acquisition protocols, standards for implementing neuroimaging biomarkers in multicenter studies, a database for software analysis tools for quantitative imaging of cerebral small vessel disease, a repository of de-identified MR scans for training and validation of human readers, and a repository for software analysis tools. Working groups identified that atrophy, diffusion tensor imaging, and perivascular space imaging are at a relatively advanced stage of biomarker development, although more longitudinal data and multicenter data on reproducibility are needed. Measurements of perfusion, vascular reactivity, and blood-brain barrier permeability are promising but are at an earlier stage of development and will require further standardization for multi-center studies.

To disseminate tools for small vessel disease research we created the website www.harness-neuroimaging.org. The site contains sections for MRI acquisition protocols, an interactive database of MRI scans with varying degrees of small vessel disease, and tools for visual review and lesion classification including rating scales, guidelines, example images, and case report forms for research studies. We are in the late stages of creating an online searchable database of software programs for quantitative imaging analysis (e.g. for white matter hyperintensity volume) that should launch in 2018. The HARNESS website should serve as a resource for protocol implementation, training and validation of readers, and development of software algorithms, catalyzing more multicenter trials in the field of vascular contributions to cognitive decline and neurodegeneration.

Background

Vascular cognitive impairment is the second most common cause of dementia, and the most frequent co-morbid copathology accompanying other causes of neurodegeneration such as Alzheimer's disease. Neuropathology studies show that macroscopic infarcts, microscopic infarcts, and cerebral amyloid angiopathy are all associated with independent, additive risk for dementia, often in combination with other pathologies such as Alzheimer's disease. Importantly, these studies show that most of the vascular disease is clinically unrecognized; therefore, neuroimaging plays the key role in determining the vascular contributions to neurodegeneration during life. Our understanding of the manifestations of cerebrovascular disease and their consequences for the brain have substantially grown, and also become more complex, since these initial seminal studies. Innovative neuroimaging methods have identified functional and structural cerebral consequences of cerebrovascular disease (e.g. using DTI and perfusion imaging), interactions with co-morbid pathologies (e.g. using amyloid-PET), and new lesion types (e.g. perivascular spaces). The field has settled onconsensus terms and definitions for most lesion types[1]; however, harmonisation of acquisition and analysis methods is incomplete. There is now an opportunity to harmonise neuroimaging methods for vascular contributions to neurodegeneration to improve reproducibility of acquisition and reliability of assessment, enabling larger scale multi-centre studies and clinical trials.

Objectives as Defined in the JPND Application

1. Disseminate neuroimaging acquisition standards for collecting MR imaging data which are suitable for analysis of the principal manifestations of cerebrovascular disease and their impact on brain connectivity.
2. Develop a plan to create a password-protected web-based repository for completely deidentified subject MR exemplar data from multiple sites/vendors/field strengths demonstrating the cardinal manifestations of vascular disease. This repository will be accessed by image readers for the purpose of independently confirming reliability of measurements across research groups, and for derivation and validation of computerized algorithms for quantitative measurement (e.g. for segmenting WMH to determine location and overall volume) as well for comparing WMH algorithms against an independent standard.
3. Provide recommendations for reproducibility testing for markers of cerebral small vessel disease in multi-centre trials, including recommendations for determining withinsite and between-site variability.
4. Develop consensus recommendations for harmonisation of emerging neuroimaging methods relevant to quantifying vascular contributions to neurodegeneration, including for high field strength (7T), perfusion and vascular reactivity, and PET molecular imaging.

Revisions to Objectives

There were no changes to the existing objectives. To verify the usefulness of the planned activities for small vessel disease researchers, we surveyed the initiative membership on the utility of our objectives.

Methods

We convened a group of international experts. Participants were selected based on a history of publications on neuroimaging of small vessel disease in the context of stroke or cognitive impairment, with the additional goal of ensuring representation from multiple countries participating in the JPND as well as the United States and Asia. We also sought a balance of experts from the fields of imaging physics, biomedical engineering, neuroradiology, neurology, and psychiatry. The names of all participants and their institutions is provided in Appendix 1. We received input from 67 participants from 33 institutions in 13 countries, spanning 4 continents.

Participants were surveyed on needs for standardizing neuroimaging research on cerebral small vessel disease. Based on the survey responses, the working group structure was finalized. The Working Groups are listed in Table 2, and full details are in Appendix 2. Working group members were selected based on participant interest, balanced by a need to achieve sufficient size for each group. Each working group had 5-8 members. Working group Chairs were selected by the Executive.

Table 1. HARNESS Working Groups

Title	Objective
MR Repository	Plans for web-based repository of DICOM images
MR Software	Plans for web-based searchable database of analysis software
Quality Control	Define best practices for multi-center studies
Website	Design of HARNESS website
Diffusion Tensor Imaging (DTI)	Define current status and roadmap for future development.
Perivascular Spaces	Define current status and roadmap for future development.
Perfusion and Reactivity	Define current status and roadmap for future development.
Blood-brain Barrier	Define current status and roadmap for future development.
7T Vessel Imaging	Subsequently merged with similar Working Group in the JPND-funded EUFIND initiative.
PET & Molecular Imaging	Define current status and roadmap for future development.
Atrophy From Vascular Causes	Define current status and roadmap for future development.

Work proceeded via monthly teleconferences and in in-person meeting in Toronto in June 2016.

An Advisory Committee was created to attend the June meeting to provide feedback on the approach of the Initiative and to review draft outputs. The Advisory Committee membership was intended to represent the interest of key stakeholders in clinical trial planning and conduct (Dr. Mike Sharma, Population Health Research Institute, McMaster University, Canada), cohort studies in vascular cognitive impairment (Dr. Christopher Chen, National University of Singapore, Singapore), and government funding agencies (Dr. Rod Corriveau, NINDS, U.S.A.).

Main Findings and Outputs

To verify the HARNESS objectives, we began by surveying HARNESS initiative members on their importance, using a Likert scale with responses from 1 (not important) to 5 (critically important). Based on 28 responses, each of the HARNESS main objectives had mean scores of >4. Therefore, we continued with the Objectives as defined in the grant application.

There are two main outputs from the HARNESS initiative. First, the HARNESS neuroimaging website has been developed. Second, a manuscript is under preparation that

provides a roadmap for reproducibility and standardization of neuroimaging markers of cerebral small vessel disease.

HARNESS Website

The HARNESS website is available at www.harness-neuroimaging.org. The website provides tools for MRI acquisition and analysis for vascular contributions to neurodegeneration. There are four main sections.

MR Protocols contains complete MRI sequence parameters that have been developed and validated for use in multicenter studies of vascular cognitive impairment for the major scanner vendors (Siemens, Philips, and GE). Currently, the site houses links to the Canadian Dementia Imaging Protocol (PI Simon Duchesne, Canada). The MRI protocol for the INVESTIGATE@SVDS multicenter study is being prepared to be added to the site in January 2018. The NINDS VCID Biomarker Consortium MRI protocol is in the late stages of development and will be added to the site in early 2018.

MR Repository will contain links to an online database of MR DICOM files demonstrating a range of small vessel disease lesions, that can be viewed online or downloaded for analysis by researchers. These DICOM files are provided to the research community to facilitate training and reliability assessments of MRI readers, and to serve as a derivation or validation cohort for software for quantitative lesion analysis. To begin, the site will contain single center from 20 normal scans, 20 scans from patients with cerebral amyloid angiopathy (demonstrating microbleeds and hemorrhagic lesions), 20 from patients with minor ischemic stroke (demonstrating infarcts and WMH of presumed vascular origin), and 20 patients with Alzheimer's disease dementia, along with centrally interpreted lesion counts and manually segmented masks of WMH. Another six HARNESS researchers have indicated that they have ethical and legal approval to share completely de-identified MRI data with HARNESS.

Software Tools will contain a searchable database of software developed for automated processing of small vessel disease lesions or designed for use in brains affected by cerebral small vessel disease. The database will include links to the software developer's sites to access the software tools. Developers will be able to interact with the site to add and edit their entries. We have contracted a software developer to develop this database. The database will be launched in January 2018. From within the HARNESS group, we have identified 17 researchers with interest in contributing 70 software analysis tools to the site.

Radiology Review Tools contains rating scales, instruction manuals and guidelines, example images, and case report forms to aid visual assessment and classification of small vessel disease lesions by MR readers.

HARNESS manuscript

The HARNESS manuscript is in preparation for submission to a peer-reviewed scientific journal. This manuscript will provide a description of the objectives and methods of HARNESS, citing the website described above. It will provide an overview of the status of biomarker development for the main and more recently emerging neuroimaging markers of small vessel disease.

We adopted an intellectual framework for neuroimaging biomarker development that was adapted from consensus recommendations of the European Society of Radiology[2] and by a consensus group for development of imaging biomarkers for oncology[3]. A similar intellectual framework for biomarker development for Alzheimer's disease has recently been published[4]. Informed by these sources, we classified markers of cerebral small vessel disease according to biomarker development milestones of *proof of principle/mechanism,*

proof of concept, *proof of effectiveness*, *repeatability*, and *reproducibility*, along with evidence for validation in >2 studies of *longitudinal change*, *monitoring*, and *surrogate* for clinical outcomes.

Working groups were formed for each marker. These groups reviewed the literature to define the status of biomarker development for each marker. The full results will be published in the manuscript. In brief, we found that that lacunes, silent infarcts, WMH, microbleeds, and atrophy were the furthest advanced in their status as a qualified biomarker. For each of these markers there were data to establish proof of principle, concept and effectiveness, and longitudinal data as a monitoring biomarker. Markers of perivascular spaces and white matter connectivity on diffusion tensor imaging (DTI) were next most qualified, but longitudinal and monitoring data were just emerging. Markers of vascular reactivity and blood-brain barrier permeability were at the earliest stages, with data on proof of principle of proof of concept but few data on proof of effectiveness and mostly cross-sectional studies only.

Collaborations with Other International Initiatives

We identified synergies with the European Union Ultrahigh-Field Imaging Network for Neurodegenerative Diseases (EU-FIND; Lead Applicant Emrah Duzel), funded by the JPND Working Groups for Harmonisation and Alignment in Brain Imaging Methods for Neurodegeneration. EUFIND included a Vascular Lesions clinical topic subgroup. Dr. Geert Jan Biessels (UMC Utrecht) participated as a liaison between the EUFIND group and the HARNESS group, and reported on plans for 7T imaging validation at the HARNESS workshop.

We are collaborating closely with the Coordinating Center of the U.S. National Institute of Neurological Disorders and Stroke Mark VCID Consortium (https://markvcid.partners.org/), launched in 2017 to develop and validate biomarkers of cerebral small vessel disease. HARNESS Lead Applicant Dr. Smith is a named co-investigator on Mark VCID project and sits on coordinating center committees for neuroimaging protocols and data access, providing a liaison with HARNESS. Dr. Smith addressed the Mark VCID Consortium at their inaugural meeting at the International Stroke Conference on Feb 20, 2017, and will speak again on biomarker development at their upcoming conference on January 22, 2018. The Mark VCID project will use information and tools for multi-center studies developed by HARNESS. Mark VCID will share their MRI protocol for distribution o the HARNESS site once it is finalized (anticipated in 2018).

Conclusions and Future Directions

The HARNESS group has surveyed the status of biomarker development for vascular contributions to neurodegeneration, identifying gaps in current knowledge. This information is being used to develop a roadmap for biomarker development, which is being prepared for publication. The HARNESS website provides tools for acquisition and analysis of MRI data for cohort studies and clinical trials of vascular cognitive impairment. The site should help beginning researchers to design appropriate protocols, and experienced researchers to standardize their methods and approaches.

Cash and in-kind contributions from the Edinburgh Imaging (University of Edinburgh) and the University of Calgary (Katthy Taylor Chair in Vascular Dementia) will be used to sustain and further develop the HARNESS website (www.harness-neuroimaging.org). Plans for 2018 include adding new validated multi-center MRI protocols (*e.g.* from the Mark VCID

Biomarkers Consortium), publishing the searchable database of MRI analysis software, and adding new MRI DICOM datasets to the data repository.

References

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3. O'Connor JP, Aboagye EO, Adams JE, Aerts HJ, Barrington SF, Beer AJ, et al. Imaging biomarker roadmap for cancer studies. Nat Rev Clin Oncol. 2017;14(3):169-86. doi: 10.1038/nrclinonc.2016.162. PubMed PMID: 27725679.
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Appendix 1. Participants in HARNESS. This list includes participants in the working groups, attendees to the Toronto meeting, and participants who have provided feedback on the HARNESS outputs.

Name	Affiliation	Country	Attended Toronto Meeting
Perminder Sachdev	University of New South Wales	Australia	No
Wen Wei	University of New South Wales	Australia	No
Franz Fazekas	Medical University Graz	Austria	No
Simon Duchesne	Laval University	Canada	Yes
Louis Collins	McGill University	Canada	Yes
Mike Sharma	McMaster University	Canada	Yes
Bruce Pike	University of Calgary	Canada	Yes
Cheryl McCreary	University of Calgary	Canada	Yes
Eric Smith	University of Calgary	Canada	Yes
Richard Frayne	University of Calgary	Canada	Yes
Brad McIntosh	University of Toronto	Canada	Yes
Joel Ramirez	University of Toronto	Canada	Yes
Rick Swartz	University of Toronto	Canada	Yes
Sandra Black	University of Toronto	Canada	Yes
Vladimir Hachinksi	Western University	Canada	Yes
Leif Oostergaard	Aarhus University	Denmark	Yes
Eric Jouvent	Lariboisiere Hospital	France	Yes
Francois DeGuio	Lariboisiere Hospital	France	Yes
Hugues Chabriat	Lariboisiere Hospital	France	No
Bernard Mazoyer	University of Bordeaux	France	No
Carole Dufouil	University of Bordeaux	France	No
Christophe Tzourio	University of Bordeaux	France	No
Stephanie Debette	University of Bordeaux	France	No
Emrah Duzel	DZNE Magdeburg	Germany	No
Martin Dichgans	Ludwig Maximilians University	Germany	Yes
Jennifer Linn	University Hospital Carl Gustav Carus	Germany	No
Monique Breteler	University of Bonn	Germany	Yes
Tony Stoecker	University of Bonn	Germany	Yes
Valerie Lohner	University of Bonn	Germany	Yes
Marco Duering	University of Munich	Germany	Yes
Michael Ingrisch	University of Munich	Germany	No
Bonnie Lam	Chinese University Hong Kong	Hong Kong	Yes
Vincent Mok	Chinese University Hong Kong	Hong Kong	No
Vilmundur Gudnason	Icelandic Heart Association	Iceland	No
Leonardo Pantoni	University of Florence	Italy	Yes
Arfan Ikram	Erasmus University	Netherlands	Yes
Hieab Adams	Erasmus University	Netherlands	No
Marion Smits	Erasmus University	Netherlands	No
Meike Vernooij	Erasmus University	Netherlands	Yes

Rebecca Steketee	Erasmus University	Netherlands	No
Mark van Buchem	Leiden University Medical Centre	Netherlands	No
Senneke van Rooden	Leiden University Medical Centre	Netherlands	No
Thijs van Osch	Leiden University Medical Centre	Netherlands	Yes
Julie Staals	Maastricht University	Netherlands	No
Robert van Oostenbrugge	Maastricht University	Netherlands	No
Frank-Erik DeLeeuw	Radboud University	Netherlands	Yes
Geert Jan Biessels	University Medical Center Utrecht	Netherlands	Yes
Hugo Kuijf	University Medical Center Utrecht	Netherlands	Yes
Yael Reijmer	University Medical Center Utrecht	Netherlands	No
Christopher Chen	National University Singapore	Singapore	Yes
Paul Matthews	Imperial College London	United Kingdom	Yes
David Werring	University College London	United Kingdom	Yes
Dominic Job	University of Edinburgh	United Kingdom	Yes
Joanna Wardlaw	University of Edinburgh	United Kingdom	Yes
Lucia Ballerini	University of Edinburgh	United Kingdom	Yes
Michael Thrippleton	University of Edinburgh	United Kingdom	Yes
Steven Sourbron	University of Leeds	United Kingdom	No
Claudia Satizabal	Boston University	USA	Yes
Rafa (Jose) Romero	Boston University	USA	Yes
Sudha Seshadri	Boston University	USA	No
Anand Viswanathan	Massachusetts General Hospital	USA	Yes
Edip Gurol	Massachusetts General Hospital	USA	Yes
Natalia Rost	Massachusetts General Hospital	USA	Yes
Steve Greenberg	Massachusetts General Hospital	USA	Yes
Lenore Launer	National Institutes of Health	USA	Yes
Rod Corriveau	National Institutes of Health	USA	Yes
Charlie DeCarli	University of California Davis	USA	No

Appendix 2. Organization of the HARNESS Initiative.