

Special Section: Brain Imaging Working Group Summaries for the European Joint Programme for Neurodegenerative Disease Research (JPND)

Harmonization of neuroimaging biomarkers for neurodegenerative diseases: A survey in the imaging community of perceived barriers and suggested actions

Jorge Jovicich^{a,*}, Frederik Barkhof^{b,c}, Claudio Babiloni^{d,e}, Karl Herholz^f, Christoph Mulert^g,
Bart N. M. van Berckel^h, Giovanni B. Frisoni^{i,j}, SRA-NED JPND Working Group¹

^aCenter for Mind/Brain Sciences, University of Trento, Trento, Italy

^bDepartment of Radiology and Nuclear Medicine, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, The Netherlands

^cInstitutes of Neurology and Healthcare Engineering, University College London, London, United Kingdom

^dDepartment of Physiology and Pharmacology “V. Erspamer”, Sapienza University of Rome, Rome, Italy

^eDepartment of Neuroscience, IRCCS-Hospital San Raffaele Pisana of Rome and Cassino, Rome and Cassino, Italy

^fDivision of Neuroscience & Experimental Psychology, University of Manchester, Manchester, United Kingdom

^gDepartment of Psychiatry and Psychotherapy, University Medical Center Hamburg Eppendorf, Hamburg, Germany

^hDepartment of Radiology & Nuclear Medicine, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, The Netherlands

ⁱLaboratory of Alzheimer's Neuroimaging and Epidemiology, IRCCS Fatebenefratelli, Brescia, Italy

^jMemory Clinic and LANVIE Laboratory of Neuroimaging of Aging, University Hospitals and University of Geneva, Geneva, Switzerland

Abstract

Introduction: Molecular, functional, and structural neuroimaging biomarkers are largely used to study neurodegenerative diseases, but their benefits to patients/science might be greatly enhanced by improving standardization and cross-validation. In this EU Joint Programme-Neurodegenerative Diseases Research-funded project, we surveyed the neuroimaging community to assess perceived barriers in multicentric neuroimaging harmonization and actions to overcome them.

Methods: An anonymous survey addressed researchers, clinicians, pharma industry, and professional associations, inquiring about both general and modality-specific harmonization barriers.

Results: Survey participants (459) represented an international (37 countries) multidisciplinary community. We identified two sets of funding actions, one proposing the creation of an updated hub of documents to help researchers plan and execute multicentric neuroimaging studies capitalizing from previous studies, and the other focused on modality-specific harmonization challenges in future neurodegenerative diseases clinical trials.

Discussion: This large survey of priorities and actions may help define harmonization calls launched by worldwide science funding agencies.

© 2018 The Authors. Published by Elsevier Inc. on behalf of the Alzheimer's Association. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Keywords:

Survey; Neurodegeneration; Biomarker; Multicentric; Multisite; Neuroimaging; Harmonization; Magnetic resonance imaging; MRI; Positron emission tomography; PET; Photon emission computed tomography; SPECT; Electroencephalography; EEG

¹Full list of participants listed in http://www.neurodegenerationresearch.eu/wp-content/uploads/2016/06/JPND_Project-Fact-Sheet_SRA-NED.pdf.

*Corresponding author. Tel: +39-0461-28-3064; Fax: +39-0461-28-3066.

E-mail address: jorge.jovicich@unitn.it

<https://doi.org/10.1016/j.dadm.2018.11.005>

2352-8729/© 2018 The Authors. Published by Elsevier Inc. on behalf of the Alzheimer's Association. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Early and accurate differential disease diagnosis, prognosis, progression tracking, and intervention assessment are still a challenge for the most prevalent neurodegenerative diseases (NDs) [1–3]. There is a consensus that molecular,

functional, and structural neuroimaging biomarkers from positron emission tomography (PET) and magnetic resonance imaging (MRI) may greatly help these clinical challenges by means of an improved standardization and cross-validation [4–11]. These developments would allow large-scale neuroimaging studies with higher statistical power to characterize ND. Although considerable progress has been made on the harmonized use of multicentric neuroimaging biomarkers, several challenges remain. Additional promising techniques (e.g., electroencephalography [EEG]; single photon emission computerized tomography [SPECT]) pose similar issues.

In this study (<http://www.sra-ned.org/>), we assess the current state of neuroimaging biomarker harmonization needs of MRI, PET, SPECT, and EEG in the context of large-scale multicenter neurodegenerative studies. To accomplish this goal, we surveyed the expert international community to identify (1) current barriers for a harmonized use of MRI/PET-SPECT/EEG biomarkers obtained from multicenter studies in NDs and (2) community-driven solutions to overcome these barriers.

2. Methods

2.1. Survey concept and structure

A survey was created aimed at understanding neuroimaging community thoughts on the most pressing barriers that currently hinder the harmonization of procedures and extraction of biomarkers derived from neuroimaging data (MRI, PET/SPECT, and EEG) collected in multicenter studies carried out in patients with neurodegenerative disorders. Three working groups were formed per imaging modality, each one lead by two people to cover clinical and methodological expertise in each modality (<http://www.sra-ned.org/>). In addition, an Advisory Reference Group oversaw the work.

The survey was structured in three parts: Part I: Background information about survey participants, who were asked to choose one neuroimaging modality from MRI, PET-SPECT, and EEG with dominant expertise. Part II: This section was specific to each neuroimaging modality while covering the following three general questions in the context of NDs: Are there high-level barriers to participate in multicenter neuroimaging ND studies in the chosen modality? What modality-specific biomarkers should be harmonized? How should these modality-specific biomarkers be harmonized? Part III: Final remarks, the same for all modalities, and aimed to collect comments about relevant issues not addressed by the survey.

2.2. Survey implementation and dissemination

The survey was implemented in Monkey Survey platform (<https://it.surveymonkey.com>). Participants were anonymous to encourage participation while allowing them to identify themselves. Dissemination of the survey was via e-mail to clinicians and researchers with a clinical (e.g.,

neurologist, neuroradiologist, nuclear medicine specialists, and so forth) and/or methodological (e.g., engineer, physicist, and so forth) background with experience in multicenter neuroimaging ND projects. Dissemination via e-mail was also made to relevant scientific field societies such as research/clinical associations, professional groups, and points of contact in the pharmaceutical and neuroimaging industry. Several associations accepted to disseminate the survey while not giving us the e-mail lists. This prevented an overall quantification of how many people received the survey invitation.

The complete survey with the list of associations contacted can be seen in the full SRA-NED Project Report (http://www.neurodegenerationresearch.eu/wp-content/uploads/2019/01/JPND-Brain-Imaging-Working-Group-Report_SRA-NED_FullReport.pdf).

3. Results

The survey was completed by 459 participants of the MRI/PET-SPECT/EEG community between February 1 and March 31, 2017 (MRI 53.6% of participants, EEG 30.3%, and PET-SPECT 16.1%). The participants were representative of a strong multidisciplinary community, dominated by research and academia whereas industry and participants from clinical settings were also included. Participants represented also an international community (Europe 75%; North, Central, South America 20%; Asia, Oceania, Africa 5%).

Here, we outline the main findings of the survey, the complete set of results can be found in the full SRA-NED Project Report (http://www.neurodegenerationresearch.eu/wp-content/uploads/2019/01/JPND-Brain-Imaging-Working-Group-Report_SRA-NED_FullReport.pdf). The survey provided information of perceived barriers that led to two broad classes of action recommendations, one that is independent of neuroimaging modality (outlined in Table 1), and then recommendations that are specific to each one of the three imaging modalities (outlined in Table 2).

Table 1
Summary of general high-level neuroimaging harmonization perceived barriers reported by the survey and actions proposed to address them

General high-level barriers	Actions to address barriers
• Insufficient information to participate in multicentric neuroimaging consortia • Insufficient funding or lack of access to expertise for neuroimaging harmonization • Difficulty in harmonizing recommendations for neuroimaging harmonization procedures • Lack of multidisciplinary education transversal to neuroimaging acquisition protocols, analysis to derive markers, clinical needs to validate markers	• Create an open-access web-based forum platform with updated information • Create a standardized registry to help plan and budget multicentric studies • Create an updated registry of neuroimaging harmonization findings • Continue to invest in multidisciplinary education in the context of neuroimaging biomarkers

Table 2

Summary of methodological barriers for the harmonization of multicentric neuroimaging protocols in the context of ND reported in the survey and actions proposed to address them

Neuroimaging modality	Perceived barriers	Actions to address barriers
MRI	- Unclear recommendations for acquisition and analyses details for multivendor protocols using state-of-the-art equipment - Unclear quality control guidelines and reference values in the context of different markers - Unclear recommendations for retrospective harmonization of existing data acquired with different protocols	- Harmonize multivendor state-of-the-art acquisition and quality assurance. In particular three-dimensional anatomic and quantitative tissue mapping (e.g., susceptibility, tissue relaxation, myelin, and so forth), advanced structural (diffusion), and functional (resting state) connectivity - Quantify reproducibility for different markers - Standardize quality assurance for different markers. Evaluate optimal markers for different ND types, stages, and experimental designs (cross-sectional or longitudinal) - Standardization of retrospective MRI data harmonization strategies
PET-SPECT	- Lack of harmonization for analysis tools and quantification (FDG-PET, amyloid PET, tau PET, and dopaminergic PET/SPECT) - Lack of standardization across amyloid PET tracers - Lack of public normative reference data, especially healthy volunteers - Lack of PET-SPECT comparisons (dopaminergic tracers)	- Harmonize multivendor image reconstruction parameters and quantification - Develop public databases of normal and ND patients (uniform with respect to acquisition and quantification) - Create centralized analysis platforms for widely available markers lacking standardization of analysis such as FDG and dopaminergic markers
EEG	- Lack of standardization of spectral source EEG analysis and high-resolution recordings - Lack of quality assurance standardization (ocular motion and cardiac artifacts) - Lack of clarity of the limits and opportunities of EEG biomarkers for NDs	- Harmonize multivendor state-of-the-art acquisition and quality assurance EEG protocols - Harmonize biomarker extraction using spectral or time-domain analysis: resting state (eyes open/closed) and event related (oddball, and so forth) - Quantify test-retest reliability from multivendor EEG data - Evaluate best biomarkers for different NDs and experimental designs (cross-sectional, longitudinal)

Abbreviations: EEG, electroencephalography; MRI, magnetic resonance imaging; ND, neurodegenerative diseases; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

The community that responded to the survey identified the following main barriers, which were common across the three neuroimaging modalities evaluated (Table 1): (1) lack of updated information and resources to effectively participate in multicenter ND studies (77% MRI, 61% EEG, and 75% PET-SPECT groups); (2) lack of guidelines for the harmonization of data acquisition using state-of-the-art equipment and protocols, biomarker extraction, and statistical modeling; (3) a general tendency of cost underestimation, in particular for software resources as well as for human resources with the relevant expertise, such as for the implementation of multicentric acquisition protocols and data analyses; (4) lack of harmonized recommendations resulting from multiple multicentric harmonization efforts.

To address these general barriers, we recommend that the EU Joint Programme-Neurodegenerative Diseases Research (JPND) agenda includes the following action (Table 1): establish an EU neuroimaging harmonization Working Group, considering MRI/PET-SPECT/EEG neuroimaging modalities, with advisors beyond EU, with commitments that include the following:

1. Develop and maintain an open-access web-based forum that can serve as updated centralized repository of information relevant to multicenter studies in NDs, generated by this group and from other initiatives. This resource should also enable a platform where

people can exchange information and discuss new literature findings and recommendations.

2. Develop and maintain updated consensus guidelines on the harmonization of neuroimaging MRI/PET-SPECT/EEG data acquisition and analysis in multicenter studies in NDs. Where applicable, these guidelines should relate acquisition strategies with different target-derived markers in the context of studying different NDs using different experimental designs (cross-sectional vs. longitudinal studies, observational vs. treatment effect studies, and so forth).
3. Develop and maintain standardized registry for planning and budgeting multicenter neuroimaging projects. This registry should include the comprehensive list of recommendations of aspects that are agreed to be typically essential parts of any successful multicenter study. Such guidelines could be helpful to both researchers preparing grant applications and funding agencies when reviewing project proposals.
4. Develop and maintain an updated registry of neuroimaging harmonization efforts for NDs that outlines key differences and common aspects of past/ongoing projects. Promote constructive synergies that help cross-reference recommendations and information from relevant multicentric neuroimaging biomarker harmonization projects in NDs.

- Promote periodic teaching activities through seminars/workshops/courses on topics relevant to the harmonized use of neuroimaging biomarkers in NDs. This activity could be synchronized with periodic national and international conference meetings to offer relevant satellite events.

With specific regards to MRI modality (Table 2), the survey reflected consensus on the need to harmonize multivendor state-of-the-art acquisition protocols (given the wider availability modern systems with strong image acceleration options) for high-spatial resolution anatomic MRI (including quantitative tissue mapping), prospective head motion correction tools, microstructure and connectivity characterizations from diffusion MRI, as well as high-temporal resolution functional and perfusion MRI neuroimaging. There is a particular need for characterizing test-retest reproducibility errors given the interest in longitudinal studies. In addition, there is a need to develop automated quantitative quality assurance methods specific for the various methodologies in the context of multicenter studies. There is also a need to develop methods that are able to harmonize existing data already acquired without standardized protocols, to make the most out of existing data and past investments.

With specific regards to PET-SPECT modalities (Table 2), the JPND agenda may fund the harmonization of image reconstruction parameters across PET and SPECT vendors as a first necessary step. The action may consider also creating public databases of normal and ND patients as well as creating centralized analysis platforms.

With specific regards to the EEG modality (Table 2), the JPND agenda may fund the harmonization of the recordings parameters and spectral or time-domain analyses of resting state eyes-closed and eyes-open EEG and event-related potentials (especially oddball paradigms), as well as the definition of the best EEG biomarkers for each data analysis technique and experimental/clinical condition.

4. Discussion

This survey supports the need for two types of funding actions. One type of action is general, aimed at creating an updated hub of information/updated documentation that can help researchers plan and execute multicentric neuroimaging studies capitalizing efficiently on lessons learned from previous relevant investments, particularly in neuroimaging modules of clinical trials in NDs. The other type of funding action is neuroimaging modality specific and may be composed of multiple actions focused to address the key challenges for the different modalities.

The actions here proposed are consistent with current EU legislation developments aimed at allowing secondary use of health data. Such legislation would also lend itself to the secondary use of multicenter neuroimaging data once these data

have been obtained within a common methodological framework. This therefore suggests that funding for the hereby proposed actions would come timely given the political agenda of health research legislation in the EU.

In conclusion, this JPND initiative produced the largest survey on the barriers and tentative solutions for the harmonized use of neuroimaging MRI/PET-SPECT/EEG techniques for multicentric clinical studies in NDs. The Working Group of this initiative transposed those solutions in a tentative agenda for JPND to overcome those barriers. This agenda is also consistent with current EU legislation developments relevant to the use of health data.

Acknowledgments

This work was supported by the EU Joint Programme of Neurodegenerative Disease Research (<http://www.neurodegenerationresearch.eu>). Our group thanks all participants of the survey as well as the leadership of the various associations who kindly accepted and facilitated the dissemination of the survey among its members.

RESEARCH IN CONTEXT

- Systematic review: Early and accurate differential diagnosis, progression tracking and intervention assessment are currently challenging for neurodegenerative diseases (ND). Although molecular, functional and structural neuroimaging biomarkers are largely used, there is still a need for multicentric harmonization and modality cross-validation of acquisition and analysis strategies.
- Interpretation: Our survey helped identify and prioritize perceived barriers for the harmonization of neuroimaging biomarkers in multicentric ND studies. The evaluation of the barriers allowed us to propose two set of actions to overcome them: one action proposes the creation of an updated hub of information/documents to help researchers plan and execute multicentric neuroimaging studies capitalizing from previous studies, and the other action focuses on modality-specific harmonization challenges in future ND clinical trials.
- Future directions: The priorities and proposed actions resulting from this survey may be considered by worldwide funding agencies interested the improvement of standardization and cross-validation of neuroimaging ND biomarkers. Such initiatives may contribute to ND clinical trials.

References

- [1] Kalia LV, Lang AE. Parkinson disease in 2015: evolving basic, pathological and clinical concepts in PD. *Nat Rev Neurol* 2016; 12:65–6.
- [2] Scheltens P, Blennow K, Breteler MM, de Strooper B, Frisoni GB, Salloway S, et al. Alzheimer's disease. *Lancet* 2016;388:505–17.
- [3] Tabrizi SJ, Scahill RI, Owen G, Durr A, Leavitt BR, Roos RA, et al., TRACK-HD Investigators. Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: analysis of 36-month observational data. *Lancet Neurol* 2013;12:637–49.
- [4] Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, Cummings J, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurol* 2007; 6:734–46.
- [5] Dubois B, Feldman HH, Jacova C, Hampel H, Molinuevo JL, Blennow K, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. *Lancet Neurol* 2014; 13:614–29. Erratum in: *Lancet Neurol*. 2014;13:757.
- [6] Frisoni GB, Fox NC, Jack CR Jr, Scheltens P, Thompson PM. The clinical use of structural MRI in Alzheimer disease. *Nat Rev Neurol* 2010; 6:67–77.
- [7] Jack CR Jr, Albert MS, Knopman DS, McKhann GM, Sperling RA, Carrillo MC, et al. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;7:257–62.
- [8] Risacher SL, Saykin AJ. Neuroimaging biomarkers of neurodegenerative diseases and dementia. *Semin Neurol* 2013;33:386–416.
- [9] Svenningsson P, Westman E, Ballard C, Aarsland D. Cognitive impairment in patients with Parkinson's disease: diagnosis, biomarkers, and treatment. *Lancet Neurol* 2012;11:697–707.
- [10] Teipel S, Drzezga A, Grothe MJ, Barthel H, Chételat G, Schuff N, et al. Multimodal imaging in Alzheimer's disease: validity and usefulness for early detection. *Lancet Neurol* 2015;14:1037–53.
- [11] Weir DW, Sturrock A, Leavitt BR. Development of biomarkers for Huntington's disease. *Lancet Neurol* 2011;10:573–90.