SRA-NED:

HARMONIZATION OF ACQUISITION AND PROCESSING OF BRAIN IMAGING BIOMARKERS FOR NEURODEGENERATIVE DISEASES

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

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JPND research

HARMONIZATION OF ACQUISITION AND PROCESSING OF BRAIN IMAGING BIORMARKERS FOR NEURODEGENERATIVE DISEASES: A STRATEGIC RESEARCH AGENDA FOR BEST PRACTICE GUIDELINES (SRA-NED)

JPND 2016 Brain Imaging Working Groups

Contents

Executive Summary

This document is an activity report of the European Joint Programme of Neurodegenerative Diseases (JPND) 2016 Brain Imaging Working Group ***"Harmonization of acquisition and processing of brain imaging biormarkers for neurodegenerative diseases: a strategic research agenda for best practice guidelines (SRA-NED)"***.

This initiative was commissioned by the JPND to assess the current state of neuroimaging biomarker harmonization needs of magnetic resonance imaging (MRI), positron emission tomography (PET), single photon emission computerized tomography (SPECT), and electroencephalography (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 neurodegenerative diseases and (2) community driven solutions to overcome these barriers.

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 and South America 20%, and Asia, Oceania and Africa 5%). More details about the definition of the Survey can be found in Section 3, Appendix 2, and Appendix 3. All Survey results are reported in Section 4.

The main findings and recommendations resulting from this study are outlined as follows (see Section 5 for more details):

- The community that responded to the survey identified the following main barriers, which were also common across the neuroimaging modalities evaluated: (1) lack of updated information and resources to effectively participate in multicenter neurodegenerative 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 for data analyses; (4) lack of harmonized recommendations resulting from multiple multicentric harmonization efforts.
- To address these general barriers, we recommend that the JPND agenda includes the following action: establish a EU neuroimaging harmonization Working Group, considering MRI/PET-SPECT/EEG neuroimaging modalities, with advisors beyond EU, with commitments that include:
  (1) Develop and maintain an open-access web-based forum that can serve as updated centralized repository of information relevant to multicenter studies in neurodegenerative diseases, generated by this group as well as 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 acquisition and analyses strategies in multicenter studies in neurodegenerative diseases. Where applicable, these guidelines should relate acquisition strategies with different target derived markers in the context of studying different neurodegenerative diseases using different experimental designs (cross-sectional versus longitudinal studies, observational versus treatment effect studies, etc.).
  (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 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.

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

- With specific regards to MRI modality, the JPND agenda may fund the harmonization of multivendor state-of-the-art acquisition protocols for high-spatial resolution anatomical MRI (including quantitative tissue mapping), 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.
- With specific regards to PET-SPECT modalities, 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 neurodegenerative disease patients as well as creating centralized analysis platforms.
- With specific regards to the EEG modality, the JPND agenda may fund the harmonization of the recordings and spectral or time-domain analyses of resting state eyes-closed and –open EEG and event-related potentials (especially oddball paradigms), as well as the definition of the best biomarkers for each technique.

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 has 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 multi-centric clinical studies in neurodegenerative diseases. 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.

Research Outputs

At the time of the final report submission two research outputs have been generated from this work:

- Jovicich J, Barkhof F, Babiloni C, Herholz K, Mulert C, van Brckel BNM and Frisoni GB; Harmonization of Neuroimaging Biormarkers for Neurodegenerative Diseases: A Survey for Best Practice Guidelines, Alzheimer's Association International Conference, July 16-20, London 2017 (Developing Topic Abstract, P4-526).
- Jovicich J and Frisoni GB, European ADNI, World Wide ADNI Meeting, July 14, London, 2017.

To further increase the visibility of this work, we organized a meeting that brought together the JPND Brain Harmonization working groups and relevant journal editors attending the AAIC London 2017 meeting. Seven from the ten JPND groups could attend, as well as editors from the Journal of Alzheimer's and Dementia and Lancet Neurology. Discussions are ongoing for the preparation of a special issue that presents the whole body of work with summaries from the 10 working groups plus a higher-level paper that integrates and emphasizes the importance of the various harmonization aspects tackled by the different groups.

1. Introduction and background

Early and accurate differential disease diagnosis, prognosis, progression tracking, and intervention assessment are still a challenge for the most prevalent neurodegenerative diseases (NDs) such as Alzheimer's disease (AD), fronto temporal dementia (FTD), Parkinson's disease (PD) /Parkinson's disease dementia (PDD), Huntington's disease (HD), dementia with Lewy-bodies (DLB), Creutzfeldt-Jakob disease (CJD), progressive supranuclear palsy with corticobasal syndrome (PSP/CBS), multiple system atrophy (MSA), amyotrophic lateral sclerosis (ALS) (Scheltens et al., 2016; Kalia et al., 2016; Tabrizi et al., 2013).

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 (Dubois et al, 2007; Jack et al., 2011; Weir et al., 2011; Svenningsson et al, 2012; Risacher and Saykin, 2013; Dubois et al, 2014; Teipel 2015). These developments would allow large-scale neuroimaging studies with higher statistical power to characterize disease. Despite the fact that considerable progress has been made on the harmonized use of multicentric biomarkers, several challenges remain.

1.1 Big brain science challenges

The global dissemination of neuroimaging equipment together with the availability of sophisticated data analyses and distributed storage tools suggest that large amounts of useful data could be easily used to accelerate scientific discovery (Van Horn and Toga, 2014). The strong motivation behind multicenter neuroimaging studies is in fact their opportunity to accumulate large amounts of data that might increase the power for detecting disease effects, including for example a better differentiation across patient populations, a more sensitive characterization of their temporal evolution and treatment responses.

However, this gain in power offered by multicentric studies can be offset by increases in variability across scanners, data acquisition protocols, quality assurance protocols and data analyses strategies. Therefore, harmonization of these issues remains an important task for future clinical research to reduce sources of variability and increase detection accuracy. Recently, a large European Working Group committed to accelerate the use of AD biomarkers (the Geneva Roadmap for AD biomarker Development (Editorial Lancet Neurology, 2014) has highlighted the limited availability of best practice guidelines for biomarker collection and analysis. This severely limits the comparison of the results from different clinical trials and delays use of biomarkers in clinical research, drug discovery, and finally in routine care. It ultimately leads to uneven and suboptimal quality of care in the world and slows down processes of drug discovery.

Given the constant improvements of neuroimaging hardware, acquisition methods and analyses tools, the harmonization of neuroimaging data and analyses strategies represents an evolving challenge, a "moving target". Several international projects have previously addressed these challenges (Table 1). This list is not intended to be exhaustive or comprehensive. Projects like those listed have provided invaluable contributions to the standardization of neuroimaging data acquisition and analyses protocols in several brain diseases. However, because of developments in the field, very few of these harmonization studies can offer guidelines validated on state-of-the-art neuroimaging technology and analyses methods.

Table 1: Non-exhaustive list of neuroimaging harmonization projects in the context of neurodegenerative diseases

Project	**Neuroimaging modalities**	**Subject population**	**Publications include**
Alzheimer's Disease Neuroimaging Initiative (**ADNI**)	sMRI, dMRI, pMRI, rsfMRI, PET	Mild cognitive impairment, AD, normal control subjects	Weiner et al., 2017
Prediction of cognitive properties of new drug candidates for neurodegenerative diseases in early clinical development (**PharmaCog**)	Human: sMRI, dMRI, rsfMRI, EEG Animal: sMRI, dMRI, rsfMRI, EEG	Amnestic mild cognitive impairment, AD, normal control subjects. Animal models of AD.	Galluzi et al., 2016
European Consortium for ASL in Dementia (**ASL Network**)	pMRI	Mild cognitive impairment, AD, normal control subjects	Alsop et al., 2015
Network for Efficiency and Standardization of Dementia Diagnosis, (**NEST-DD**)	FDG PET	Mild cognitive impairment, AD, normal control subjects	Herholz, 2003
CATI Neuroimaging Platform	MRI, PET-SPECT	AD, Parkinson, Huntignton, ALS, Bipolar	Operto et al., 2016
Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing (**AIBL**)	MRI, PET	Mild cognitive impairment, AD, normal control subjects	Ellis et al., 2013
Huntington's Disease Research (**TRACK-HD**)	MRI	Huntinton's disease and healthy control subjects.	Tabrizi et al., 2011
Enhancing neuroimaging genetics through meta-analysis (**ENIGMA**)	sMRI, dMRI, EEG	Patient populations include Parkinson's, schizophrenia, bipolar.	Thompson et al., 2016
Quantitative Imaging Biomarkers Alliance (**QIBA**)	MRI, PET, SPECT among others	Including but not limited to neurodegenerative patients.	Sullivan et al., 2015
European Association of Nuclear Medicine Neuroimaging Committee – Dopamine Transporter initiative (**ENC-DAT**).	DAT SPECT	Healthy volunteers	Varrone et al., 2013
European Alzheimer Disease Consortium PET study group (**EADC**)	FDG-PET; amyloid PET	Mild cognitive impairment, AD, normal control subjects	Morbelli et al., 2013

1.2 MRI multicentric harmonization needs

MRI offers a wide spectrum of possibilities to study brain structure, function, perfusion and metabolism. Core neuroimaging MRI biomarkers for neurodegenerative diseases include: cortical and subcortical atrophy, in particular hippocampal atrophy. Promising candidate biomarkers include white matter vascular damage (FLAIR), cerebral microbleeds (T2* or susceptibility weighted imaging, SWI), brain structural connectivity (diffusion MRI: dMRI), resting state functional connectivity (rs-fMRI), and blood perfusion (arterial spin labelling: ASL MRI).

From all of these MRI methodologies, structural 3D T1-weighted MRI sequences (the most sensitive to gray matter atrophy) are the most advanced in terms of multicentric harmonization. The Alzheimer's disease Neuroimaging Initiative (ADNI) has been particularly influential and invested towards the acquisition harmonization and open-access documentation of MRI protocols across the most common platforms (ADNI protocols). Documented results (ADNI2 protocol) show the harmonization of structural MRI data (most common MRI platforms), resting state fMRI (rs-fMRI; Philips only), ASL (Siemens only) and diffusion MRI (GE only) imaging have been until recently limited to single MR vendors in ADNI2. Current ongoing efforts are developing the updated ADNI3 MRI protocol, which will update the protocol to include more advanced acquisitions now possible with modern MRI systems.

State-of-the-art clinical MRI systems from multiple vendors nowadays offer radiofrequency head coils with high number of channels (≥ 32) in combination with very fast and powerful magnetic gradients coils. This opens the possibility for the use of more advanced MRI protocols that exploit parallel imaging and/or simultaneous multislice strategies that accelerate acquisitions. This in turn opens up several possibilities, for example the evaluation of acquisition and analyses protocols with higher spatial resolution (e.g. higher resolution of the hippocampus subfield segmentation, higher resolution of microbleeding evaluation), multiple contrasts for improved tissue segmentation (e.g., 3D T1 with 3D T2 and 3D FLAIR), quantitative tissue mapping (e.g. tissue relaxation maps, myelin maps), as well as advanced rsfMRI and dMRI protocols as those used by the human connectome project (http://www.humanconnectomeproject.org/). Also, although recommendations for many of these protocols exist, the validation and comparison across state-of-the-art equipment with advanced hardware is still lacking.

1.3 PET-SPECT multicentric harmonization needs

Molecular neuroimaging with PET and SPECT enables the detection, quantification and topographic characterization of specific brain metabolites depending on the tracers used. Core PET neuroimaging biomarkers in neurodegenerative diseases include: cortical hypo-metabolism on ^{18}F-fluorodeoxyglucose (FDG) PET, increased uptake of amyloid ligands on PET, decreased striatal uptake of a presynaptic dopaminergic ligand on SPECT (^{123}I-Ioflupane). Recent studies also show that PET may be used to offer early detection of neuroinflammation processes (TSPO PET). For PET, harmonization of static neuroimage acquisition has been largely addressed by ADNI, international consortia and tracer manufacturers. However, quantification by regional analysis and dynamic scanning is still lacking standardization. There is also substantial regional variation in tracer availability and semi-quantification tools, in particular with respect to novel tracers. In what follows we outline some of the current harmonization challenges for the core PET neuroimaging biomarkers.

^{18}F-Fluorodeoxyglucose (FDG) PET is a marker of brain metabolic dysfunction. There is an urgent need of large-scale FDG PET studies due to several reasons. Despite its long use, since early-80s as a research tool and at least since mid-90s as a clinical tool, relatively few studies have been validated versus neuropathology or clinical confirmation on follow-up as a gold standard.

Further, with the exception of AD, available studies have been conducted in limited samples of subjects. Yet, it is by far the most used nuclear medicine tool and the most useful across conditions. A panel of experts from the European Association of Nuclear Medicine (EANM) and the European Academy of Neurology (EAN) is currently reviewing literature and writing recommendations on this front. This panel confirms the need of large-scale studies to validate the clinical utility and prognostic power of FDG PET.

Amyloid PET is a marker of β-amyloid deposition and related second-order physiological effects, such as regional cerebral blood flow (rCBF). There is a need of large-scale studies of Amyloid PET for several reasons. Firstly, it is yet unknown whether the three available amyloid PET radiopharmaceuticals on the market can be used interchangeably, especially for borderline scans (i.e., a scan might be in borderline with a tracer but clearly positive/negative with another one). Secondly, large-scale dynamic amyloid PET studies would also allow the exploration of the value of rCBF (derived by early scan acquisition) as an early marker of neurodegeneration and its relation with apparent amyloid deposition.

There is also a need for the harmonization of strategies for PET data quantification. Methods based on the standardized uptake value ratio (SUVr) need evaluation in large series and versus pathology (or expert readers as a surrogate) to validate their robustness in defining regions of interest (ROI). This is particularly relevant not only for cortical ROIs but also for the reference ROI used for the calculation of SUVr. Such considerations are crucial in follow-up studies, where apparent amyloid load may increase or decrease in a brain area depending on the reference ROI choice. Finally, advanced methods which avoid the need of a reference ROI need validation in larger studies.

Dopaminergic PET/SPECT tracers allow the study how pathology and treatment affect the dopaminergic system. From the acquisition point of view, there has been considerable progress in the standardization of dopaminergic PET/SPECT studies. Calibration coefficients among the main gamma cameras traded in Europe are available thanks to the work of the EANM and its Neuroimaging Committee. In addition, normal reference values in a relatively large sample of healthy subjects are available. The main issue for these methods remains the identification and comparability of semi-automated quantification tools and the definition of reconstruction parameters allowing comparability of data among centers. Complementary to these brain imaging techniques, cardiac 123I-metaIodobenzilguanidine (MIBG) imaging plays an increasingly relevant role for differential diagnosis between PD and atypical parkinsonism.

Finally, a long list of PET and SPECT biomarkers exist, targeting various neurotransmission systems, neuroinflammation and tau deposits. While several clinical research studies are ongoing, none has yet reached sufficient validation by multicenter studies.

1.4 EEG multicentric harmonization needs

EEG is a very promising neuroimaging tool that, complementary to MRI and PET, has been also used to study neurodegenerative diseases. Advantages of EEG include its very high temporal resolution (~ms), its sensitivity to neural activation changes without mediation of the hemodynamic response, its non-invasiveness and its low cost. Because of these features, EEG is a methodology widely available in clinical centers. EEG is especially suited to investigate the functioning and dynamics of gross neural transmission, and cortical neuronal synchronization and coupling across long-range neural networks when compared to other classical MRI and PET neuroimaging techniques (Teipel et al., 2016; Babiloni et al., 2016).

In the past years, several clinical studies in patients with neurodegenerative disorders, especially AD, PD, and dementia with Lewy Bodies (DLB) have shown that EEG biomarkers are promising candidates (Schomer and Lopes da Silva, 2011; Babiloni et al., 2017). Two concrete applications of EEG biomarkers in the clinical diagnostic routine involving patients with neurodegenerative disorders have been reported: detection of abnormal EEG slow-frequency waveforms in patients suspected to suffer from DLB (McKeith et al., 2005) and detection of triphasic EEG waveforms in patients suspected to suffer from a sporadic variant of CJD (Zerr et al., 2009).

However, larger-scale studies are still needed for further validation and for the confirmation of EEG's utility in clinical neurodegenerative disease research and medical practice. In particular, it is of interest to better understand how to complement the information obtained from EEG signatures with those obtained by MRI and PET for a more effective and comprehensive characterization of neurodegenerative diseases. For example, it would be of interest to explore the value of using EEG markers as a first-level diagnostic index for an initial selection of the people to undergo to second-level more invasive and relatively expensive diagnostic procedures such as MRI and PET neuroimaging.

1.5 Summary

Current challenges in the characterization of neurodegenerative diseases may be addressed by larger-scale neuroimaging studies, in particular with MRI, PET-SPECT and EEG modalities. To achieve the goal of increased statistical power, such multicentric studies require the harmonization of acquisition and analysis strategies. Even though some guidelines from previous harmonization efforts exist, it is possible to define updated needs based on recent hardware/methodological developments. However, the information about current needs may be incomplete and therefore misleading. In addition, even though some of the harmonization needs may be clear, it is less clear which are key practical barriers that make difficult the effective implementation of harmonization efforts.

It would be useful to obtain an updated understanding, from the wider neuroimaging community working in neurodegenerative studies, of what are nowadays the most pressing barriers for harmonizing large-scale studies when using current technological standards of neuroimaging equipment. Further, even though each of the MRI/PET-SPECT/EEG neuroimaging modalities may contribute with complementary information in neurodegenerative disease studies, the markers from these modalities are at remarkably heterogeneous development stages.

2. Objectives

This project aims to identify (1) community-agreed barriers challenging the large scale harmonized use of neuroimaging MRI/PET-SPECT/EEG biomarkers in neurodegenerative diseases and (2) possible solutions to overcome these barriers, in order to accelerate the use of those markers in clinical context.

The first goal was firstly addressed by conducting a detailed survey targeted to experts in the neuroimaging MRI/PET-SPECT/EEG community to detect main problems associated with the level of calibration, recording, and data analysis protocols. Secondly, from the information gathered in the survey we developed recommendations to address the most critical barriers for neuroimaging harmonization of calibration, recording, and data analysis protocols. These recommendations are expected to help funding agencies to identify topics and actions deserving funding with the ultimate

aim of overcoming those barriers and developing best practices to be followed for the elaboration of biomarkers in multicenter studies carried out in neurodegenerative diseases.

This study is unique in that it integrates in a single framework harmonized procedures for a number of neuroimaging modalities that so far have been addressed separately and are at very different stages of development. Finding a common language for all modalities may help foster multimodality explorations.

3. Methodology

3.1 Working group

The Working Group of the present project was organized as follows: a PI (G. Frisoni) and co-PI (J. Jovicich) oversaw three working subgroups (WGs) of international experts focused on three neuroimaging modalities: MRI (13 people), PET-SPECT (11 people) and EEG (7 people). Each of these WGs was in turn led by two people, one with a more methodological experience and the other with a more clinical oriented experience in the corresponding neuroimaging modality. This organization was thought to ensure a balanced integration from both methodological and clinical perspectives when considering harmonization issues. The group WG leaders were:

- MRI: Fred Barkhof (clinical co-lead), Jorge Jovicich (methodological co-lead)
- PET-SPECT: Karl Herholz (clinical co-lead), Bart van Berckel (methodological co-lead)
- EEG: Claudio Babiloni (clinical co-lead), Christian Mulert (methodological co-lead)

In addition, there was also an international Advisory Reference Group formed by three types of external members: i) individual key opinion leaders in the broad international field of brain imaging for neurodegenerative diseases and survey experts, ii) international community experts, groups and associations working in the broad field of brain imaging for neurodegenerative diseases, and iii) experts working in pharmaceutical or neuroimaging systems industry.

This work was largely contributed by people who provided an administrative and technical support throughout the project. These people included: Irena Jatro (project management), Rosita Haddad (workshop logistics, website, etc.), Paolo Fedi (website design & implementation), Margherita Mauri & Libera Cavaliere (administrative support).

3.2 Project webpage

Given the international distribution of project members, it was important to set up rapidly a centralized webpage for our project (http://www.sra-ned.org/). This website helped on two main fronts: i) it allowed a single place where all project-relevant information could be posted (project goals, project members and contact information, survey and workshop details), both to the public and internally with restricted access, ii) this webpage was also important for visibility purposes because it represented the presentation card when distributing survey invitations.

3.3 Survey

3.3.1 Survey concept & structure

As mentioned above, the survey was 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.

Given the number of aspects involved (e.g., specific neurodegenerative disease, biomarker informative value, neuroimaging modality), the survey served also to address a secondary goal: structure the relevant information in a way that could help reduce the dimensionality of the problem. The survey was structured to have the following main parts, each of which had a series of specific questions to collect information:

- Part I: Background information about survey participants. In this part participants were asked to choose the one neuroimaging modality from MRI, PET-SPECT and EEG in which they considered they had the most expertise. After making this choice, Part II of the survey followed with a modality-specific questionnaire. Assuming an expertise predominant with one imaging modality, the option to choose more than one modality (e.g. MRI and PET/SPECT) was not provided.
- Part II: This section was specific to each neuroimaging modality while covering the following three general questions in the context of neurodegenerative diseases (ND):
  - Are there high-level barriers to participate in multicenter neuroimaging studies in the chosen modality?
  - What modality-specific biomarkers should be harmonized?
  - How should these modality-specific biomarkers be harmonized?
- Part III**:** Final remarks. This part was the same for all modalities and aimed to collect comments about relevant issues not addressed by the survey

The content of the survey was developed through discussions amongst the WG leaders and a survey advisor (Sieske Sikkes) to find a compromise between clarity of open and multiple choice questions that addressed the goals of the survey, limited length that would allow for completion of the survey in about 10 minutes, and the time constraints of the project. Feedback from the whole group was obtained before the final survey launch.

3.3.2 Survey implementation

The most important aspects of the survey are reported as follows: (1) implementation on Monkey Survey (https://it.surveymonkey.com) because of its ease of use and low cost for features used, (2) anonymity of participants in order to encourage participation without compromising privacy, (3) dissemination via email to clinicians and researchers with a clinical (e.g., neurologist, neuroradiologist, nuclear medicine specialists, etc.) and/or methodological (e.g., engineer, physicist, etc.) background with experience in multicenter neuroimaging ND projects, (4) dissemination via email to relevant scientific field societies such as research/clinical associations, professional groups, and points of contact in the pharmaceutical and neuroimaging industry.

The survey link was included in the http://www.sra-ned.org/ website and was tested within group participants for last feedback on editorial/functionality plus also for estimating completion time.

3.3.3 Survey dissemination

The survey was first launched to the public on February 1st, 2017 with invitations to over 400 people. Preliminary data was collected for discussion at the Geneva Working Group Workshop on March 2nd-3rd, 2017 (see Section 3.4 for details). One of the findings of the Workshop was that the survey had not been disseminated to all relevant groups and associations. It was therefore decided to maintain the survey open until March 31st, 2017 and further disseminate it to an extended group of

associations. Appendix II provides the final list of professional groups and associations that were invited to participate in the survey. Appendix III reports the layout of the final version of the survey.

3.3.4 Survey data analysis

The data from the survey are descriptive. The survey presented participants with two types of questions: multiple choice or open text. The results from the multiple choice questions are summarized by indicating the percent response count relative to the total number of people answering the question, showing also the total response count for each option. The results from the open questions were examined and summarized by the WG leaders with the goal of capturing what were considered to be points not already raised by other parts of the survey.

3.4 Workshop

A two-day Workshop was organized and conducted in Geneva, Switzerland (Campus BioTech) on March 2nd-3rd, 2017. The Workshop had two main goals. The first one was to summarize and discuss the preliminary results of the survey. The second goal was to discuss the best way to represent the survey findings in the SRA-NED document, which is the main deliverable of this project, with recommendations of actions that can address the main barriers identified by the survey.

The Workshop was attended by 28 participants representing the three WGs (MRI: 9; EEG: 8; PET/SPECT: 4) as well as Giovanni Frisoni's research group (4) and administrative support staff. The Workshop agenda was defined around the workshop goals. Briefly, Day 1 of the workshop was used to summarize and review the main findings of the survey with morning presentations, followed by afternoon parallel sessions within each working group to discuss the main recommendations that could address the survey findings. Day 2 was used to present the main recommendations from each of the working groups and discuss their integration for the final SRA. Coffee breaks, lunches, and a delightful social dinner on Day 1 gave ample opportunities for the participants to meet and interact. Indeed, all was very well organized ensuring a productive flow of fruitful discussion.

The survey identified a series of common high-level barriers across the neuroimaging modalities of interest (MRI, PET/SPECT, EEG), as well as more specific barriers. Results were mentioned in a preliminary draft of the Strategic Research Agenda with recommendations addressed to remove the identified barriers. Finally, participants scheduled the next steps (actions and deadlines) to be followed in the next months of the project.

All relevant information about the workshop is available on the website http://www.sra-ned.org/ (Geneva Workshop Summary).

3.5 JPND Brain Imaging Groups meet Editors meeting

On 17 July 2017, within the framework of the AAIC 2017 Conference held in London, we organized a one-hour meeting between the "*JPND Working Groups for Harmonisation and Alignment in Brain Imaging Methods for Neurodegeneration"* (JPND 2016 call) and relevant journal editors. The main goal of the meeting was to take advantage of AAIC 2017 attendance to have the JPND harmonization working groups present their main findings to editors for consideration of potential publications.

All JPND groups were invited, 7 out of 10 could attend. A number of relevant journals were invited, but only the Editors from Lancet Neurology and the Journal of Alzheimer's and Dementia (JAD) could attend. The meeting agenda was as follows:

- Welcome and meeting goals
- Short presentations from JPND WG attending AAIC
- Discussion with Editors

Preliminary outcomes: results from the meeting were very encouraging. After the presentations, we briefly discussed with the present Editors possible courses of actions:

- The whole body of work from the ten JPND working groups may receive more attention from funding agencies if presented together, maybe as a collection of position papers plus a higher-level paper that integrates them.
- JAD editors showed strong interest to have the 10 papers in their new journal, Diagnostic, Assessments & Disease Monitoring (no impact factor now, first issues from 2015), accompanied by a single paper that puts outlines the collective body of work to be published at the main JAD journal, which would point to each of the ten papers.
- Lancet Neurology expressed interest to have an editorial that points to the JAD publications.

The meeting outcomes and summary slides were shared across all 10 JPND groups, including those groups that could not attend. The publication strategy was well received by the whole group. We will continue with this initiative after the submission of this report.

4. Survey results

The final layout of the survey can be seen in Appendix III. In the next sections we summarize the main findings obtained from the survey.

4.1 Participants background

A total of 459 participants completed the survey which was open during the period February 1st - March 31st, 2017. Participants received survey invitation mostly from direct email from the members of the SRA-NED group (70.4%) or from colleagues (20%). A few participants received the invitation from EU Neuroimaging networks (5.2%) or from other associations (4.4%).

The survey participants represent a rich multidisciplinary community (Table Q2) dominated by research and academia but also including industry and clinical settings (Table Q3) from different parts of the world (Figure Q4, Table Q4).

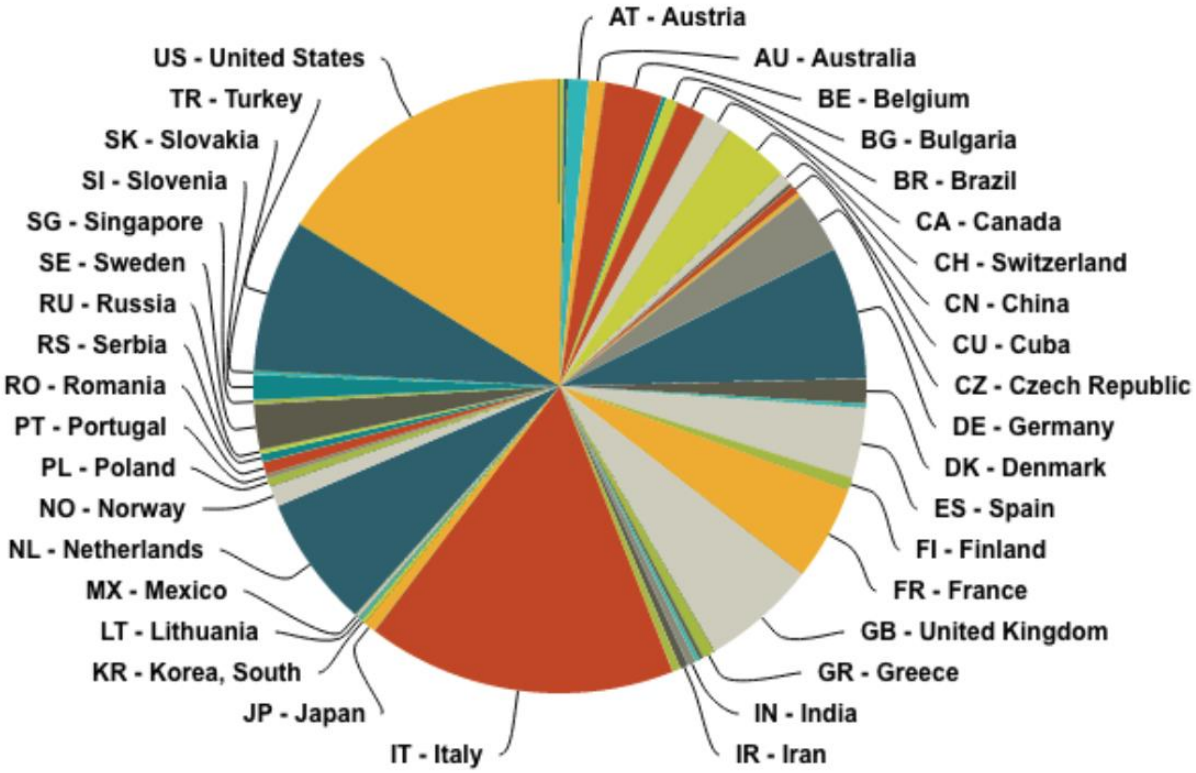
Table Q2: Distribution of survey participants by professional role, in decreasing order of percent response relative to the total number of responders (459). A total of 119 people chose to describe their professional role as "other". These descriptions had 92 people from other basic training areas (e.g. biology, neurophysiology, data analysts, informatics), as well as a variety of other roles including 9 senior leadership roles (e.g., head of consortium for ND, center directors, imaging center directors, clinical trial directors, research officers), junior academic roles (5 PhD students, 2 postdocs), technician roles (11).

Answer Options	Response Percent	Response Count
Neurologist	26,8%	123
Other	25,9%	119
Physicist	15,0%	69
Engineer	9,6%	44
Psychologist	6,5%	30
Nuclear medicine physician	5,7%	26
Radiologist	5,4%	25
Psychiatrist	4,1%	19
Geriatrician	0,9%	4

Table Q3: Distribution of survey participants by the type of institution to which they have their primary affiliation, in decreasing order of percent response relative to the total number of responders (459). Multiple options were possible. The category "other" included people from government (4) and non-government organizations (5), as well as private clinical groups (6).

Answer Options	Response Percent	Response Count
University	61,2%	281
Research institute	29,0%	133
Teaching hospital	22,0%	101
General hospital	9,4%	43
Specialized clinic	7,8%	36
Industry	7,4%	34
Other	4,1%	19
General practice	1,3%	6

Figure Q4: Distribution of survey participants by country (see also Table Q4).



Expertise of the participants was highest for MRI (53.6%), followed by EEG (30.3%) and PET-SPECT (16.1%).

The large majority of the participants were involved in research (94%), they were currently active mostly in observational research (63.3%) and/or clinical trials (47.7%) (Table Q6). The disease interest in the participants was distributed across various different ND, with particular interest in AD (73.3%), healthy ageing (46.6%), PD (43.9%) and frontotemporal dementia, FTD (35.1%) (Table Q7).

Table Q6: Distribution of survey participants by type of multicenter neuroimaging research studies. A total of 442 participants responded, multiple options were possible.

Answer Options	Response Percent	Response Count
Observational	63,3%	280
Clinical trials	47,7%	211
Non-pharmacological interventions	34,6%	153
Other	19,9%	88
None	6,1%	27

Table Q4: Distribution of survey participants by continent and country

Answer Options	Response Percent	Response Count (Total 459)
AFRICA (1)		
BF - Burkina Faso	0.2%	1
ASIA (13)		
CN - China	0.7%	3
IL - Israel	0.2%	1
IN - India	0.4%	2
IR - Iran	0.4%	2
JP - Japan	0.7%	3
KR - Korea, South	0.2%	1
SG - Singapore	0.2%	1
EUROPE (349)		
AD - Andorra	0.2%	1
AI - Anguilla	0.2%	1
AT - Austria	1.1%	5
BE - Belgium	3.1%	14
BG - Bulgaria	0.7%	3
CH - Switzerland	3.5%	16
CY - Cyprus	0.2%	1
CZ - Czech Republic	3.3%	15
DE - Germany	7.0%	32
DK - Denmark	1.3%	6
EE - Estonia	0.2%	1
ES - Spain	3.7%	17
FI - Finland	0.7%	3
FR - France	5.0%	23
GB - United Kingdom	6.1%	28
GR - Greece	0.7%	3
HR - Croatia	0.2%	1
IS - Iceland	0.4%	2
IT - Italy	16.3%	75
LT - Lithuania	0.2%	1
NL - Netherlands	7.0%	32
NO - Norway	1.1%	5
PL - Poland	0.4%	2
PT - Portugal	0.2%	1
RO - Romania	0.7%	3
RS - Serbia	0.4%	2
RU - Russia	0.2%	1
SE - Sweden	2.4%	11
SI - Slovenia	1.3%	6
SK - Slovakia	0.2%	1
TR - Turkey	8.1%	37
NORTH AMERICA (84)		
CA - Canada	1.5%	7
CU - Cuba	0.4%	2
MX - Mexico	0.2%	1
US - United States	16.1%	74
SOUTH AMERICA (8)		
BR - Brazil	1.5%	7
CO - Colombia	0.2%	1
OCEANIA (4)		
AU - Australia	0.9%	4

Table Q7: Distribution of neurodegenerative disease interest in the survey participants. Response percent was calculated relative to the 442 participants who responded, multiple answers were allowed. The option of "other" diseases included traumatic brain injury, depression, schizophrenia, multiple sclerosis, vascular dementia, autism, cancer, HIV related dementia, epilepsy, ataxia, progressive aphasia, Down syndrome, developmental dyslexia, pain.

Answer Options	Response Percent	Response Count
Alzheimer's Disease	73,3%	324
Healthy aging	46,6%	206
Parkinson's Disease /Parkinson's Disease Dementia	43,9%	194
Fronto temporal dementia	35,1%	155
Dementia with Lewy Bodies	25,1%	111
Amyotrophic Lateral Sclerosis	17,0%	75
Huntington's Disease	15,2%	67
Progressive supranuclear palsy with corticobasal syndrome	13,6%	60
Multiple System Atrophy	13,6%	60
Other	11,8%	52
Creutzfeldt-Jakob disease	8,8%	39

4.2 Neuroimaging modality specific responses

In the following sections we summarize the survey findings for each one of the three neuroimaging modalities (MRI, PET-SPECT, EEG). As outlined in the survey description, each modality consists of three parts, one for identifying high-level barriers for effectively participating in multicenter studies, one for prioritizing biomarkers derived by each modality, and finally one for defining methodological barriers for biomarker harmonization within each modality.

4.2.1 MRI

MRI Summary: High level barriers for effectively participating in multisite MRI ND studies (Q8-Q12)

The goal of this section of the survey was to identify practical high-level barriers that limit the effective participation of centers/groups in large-scale multicenter MRI neuroimaging ND studies.

- **Q8**: The majority of the MRI participants (Q8, 76.6% from a total of 177 participants) agreed that there are barriers to join multicenter MRI studies of ND.
- **Q9**: MRI participants were asked to rate the urgency level (urgent problem, non-urgent problem, not a problem) of a number of potential barriers that may prevent the effective participation in multisite MRI ND studies. The main results were:
    - 154 people answered. None of the potential barriers proposed was regarded by a net majority of participants as not being a problem.

- To rank the degree of severity of the barriers we computed for each barrier the total percent of people voting for it being an urgent or non-urgent problem. Table Q9 presents the results with the barriers ordered from highest to lowest degree of importance.
- The outstanding most urgent problem was related to lack of funding (96%).
- Interestingly, access to MRI facilities or patient populations was ranked as the least serious problems (approximately 40% of people regarded them as not a problem).

- **Q10**: Survey participants were invited to list additional high-level barriers to participate in multicenter studies. There were 68 answers, most of which actually highlighted aspects related to the barriers already listed in Table Q9. Most notably, there were multiple references to insufficient funding for human resources involved in acquisition harmonization of multicenter MRI studies, multicenter work coordination and data analysis, as well as for scanning and informatics infrastructure costs. Another barrier mentioned was related to the unclear benefits in participating in such studies, especially because some institutions typically give poor local recognition to participation in collaborative studies where the institution is not a leading partner. Other benefit issue included often unclear authorship roles as well as unclear credits for non-academic staff, in particular medical staff that is critical for patient recruitment.

Q11: A series of possible recommendations were proposed as possible actions to address high-level barriers to join multicenter MRI studies. 144 people answered giving very high consensus (>70%) in favor of all of them (Table Q11), with the only exception being the option of having central facilities for MRI data acquisition (51.5% yes).

Q12: Survey participants were invited to list additional suggestions for addressing high-level barriers that prevent participation in multicenter MRI studies. The summary of the 29 responses is as follows:

- Budget planning: include formation and training of personnel involved in data acquisition and analysis; recognition that data analysis costs tend to be higher than data acquisition
- Create incentives for increased standardization of routine MRI clinical protocols towards reducing the gap with research protocols.
- Motivate people with the relevant technical/scientific expertise to be actively involved early on in the planning of such projects.
- Create research career incentives that promote data integration
- In the case of public forums, consider challenges like: keeping a proper engagement level (credit), ensuring long-term sustainability for documentation, work on visibility

Table Q9: Urgency scores for barriers that may prevent the effective participation of a center/group in a multicenter MRI neurodegenerative study. A total of 154 people responded to the question.

Answer Options	Response Count	% Not a problem	% Non urgent problem	% Urgent problem	sum urgent +non-urgent
Insufficient funding	151	3,97	25,83	70,20	96,03
Insufficient access to information about the possibility of participating in multicenter studies	150	11,33	49,33	39,33	88,67
Bureaucratic hurdles (data protection/privacy, anonymization, unclear legal situation regarding data transfer with/without patient consent etc.)	149	16,11	40,27	43,62	83,89
Insufficient standard operating procedures for neuroimaging data analysis	151	16,56	37,75	45,70	83,44
Insufficient standard operating procedures for neuroimaging data acquisition	153	23,53	24,18	52,29	76,47
Insufficient access to an IT infrastructure that facilitates the integration and management of the project (data storage, secure data transfer etc.)	150	24,00	38,00	38,00	76,00
Insufficient access to expertise and resources for the optimization of a local IT and informatics infrastructure	147	27,21	40,82	31,97	72,79
Insufficient access to expertise and resources for the choice of and optimization of image acquisition protocols	151	27,81	32,45	39,74	72,19
Insufficient access to expertise and resources for the optimization of image analysis protocols	153	29,41	28,10	42,48	70,59
Insufficient access to administrative resources (e.g., support for ethical committee, recruiting, etc.)	148	31,76	39,86	28,38	68,24
Insufficient support for statistical analysis	149	32,89	40,27	26,85	67,11
Insufficient access to clinical resources to interact with patients	145	37,24	33,79	28,97	62,76
Insufficient access to expertise and resources for the interpretation of results	149	38,26	44,30	17,45	61,74
Insufficient access to patient population	145	40,00	24,83	35,17	60,00
Insufficient access to imaging facilities	147	40,82	38,78	20,41	59,18

Table Q11: Actions that may help addressing high-level barriers preventing effective participation in multicenter MRI ND studies, ranked from highest to lowest votes.

Answer Options	% Yes	Response Count
Establishing common ethical guidelines on required patient consent for data sharing and rules for making use of publicly available data.	89,0	136
Production of an open access WEB-based knowledge platform with documentation about biomarkers for specific modalities as well as other general issues that need special consideration in multi-centric longitudinal studies on neurodegenerative disorders.	87,1	132
Central facilities for data upload and storage.	82,4	136
Central facilities for data analysis.	80,5	133
Institution of a public web-based forum in which clinical and basic researchers can communicate with their peers to discuss and exchange updated information relevant to multi-centric longitudinal studies on neurodegenerative disorders.	77,4	133
Central facilities for data-acquisition.	51,5	134

MRI-Summary: Biomarker Priorities (Q23-A25)

The goal of this section was to identify the most useful MRI biomarkers to be used in future multicenter longitudinal ND studies

- **Q23**: There was consensus that there is a need to prioritize MRI biomarkers (81.9%, from a total of 199 participants)
- **Q24:** Participants were asked to give a clinical priority (high, medium, low) to a list of generic MRI data acquisition methods for biomarker determination (atrophy from structural T1, cerebral microbleeds from T2* or SWI, white matter vascular damage from FLAIR, functional connectivity from resting state functional MRI, microsctructure and structural connectivity from diffusion MRI, cerebral perfusion from ASL) to a number of ND. A total of 127 responded, the results are shown in Table Q24. In summary:
    - **AD biomarkers:** ≥70% (113 responses) gave high/medium priority on all proposed MRI methods, with the highest priority for brain atrophy measures from structural T1 MRI (96%).
    - **PD/PDD biomarkers:** ≥ 70% (75 responses) gave high/medium priority to diffusion MRI (84%), fMRI (83%), structural T1 (80%) and FLAIR (72%).
    - **FTD biomarkers:** ≥ 70% (77 responses) gave high/medium priority to structural MRI (99%), diffusion MRI (86%), fMRI (80%) and FLAIR (70%).
    - **HD biomarkers**: ≥ 70% (60 responses) gave high/medium priority to structural T1 MRI (80%) and diffusion MRI (71%).
    - **CJD biomarkers:** ≥ 70% (52 responses) gave high/medium priority to diffusion MRI (73%).
    - **PSP/CBS biomarkers**: ≥ 70% ((56 responses) gave high/medium priority to structural T1 (89%) and diffusion MRI (73%).

- **ALS biomarkers:** ≥ 70% (63 responses) gave high/medium priority to diffusion MRI (76%).

These results show that structural T1, FLAIR, rsfMRI, diffusion MRI sequences are important to harmonize for the use of biomarker estimations. In this survey, perfusion MRI with arterial spin labeling was less frequently considered a priority, except for AD.

- **Q25:** Survey participants were invited to suggest other MRI pathology biomarkers relevant to ND disorders. 24 people responded. In summary, the MRI methods recommended which were not related to those already discussed in Q24 were:
  - Magnetic resonance spectroscopy
  - Quantitative tissue MRI mapping: magnetic susceptibility, tissue relaxation times (T1, etc.)
  - Myelin mapping

Table Q24: Clinical priority (high, medium, low) for potential MRI biomarkers for the relevant neurodegenerative diseases (127 people responded). AD: Alzheimer's disease. PD/PDD: Parkinson's disease / Parkinson's disease dementia. FTD: Fronto-temporal Dementia. HD: Huntington's disease. CJD: Creutzfeldt-Jakob disease. PSP/CBS: Progressive supranuclear palsy / Corticobasal syndrome. ALS: Amyotrophic Lateral Sclerosis.

MRI AD biomarkers	High priority (%)	Medium priority (%)	Low priority (%)	High+ medium (%)	Response Count
Brain atrophy from T1 MRI	81,42	15,04	3,54	96,46	113
White matter vascular damage from FLAIR MRI	51,92	36,54	11,54	88,46	104
Cerebral microbleeds on T2* or SWI MRI	46,53	40,59	12,87	87,13	101
Microstructure and structural connectivity from diffusion MRI	48,04	38,24	13,73	86,27	102
Cerebral perfusion from arterial spin labeling	49,50	30,69	19,80	80,20	101
Functional connectivity from resting state BOLD fMRI	44,66	33,98	21,36	78,64	103

MRI PD/PDD biomarkers	High priority (%)	Medium priority (%)	Low priority (%)	High+ medium (%)	Response Count
Microstructure and structural connectivity from diffusion MRI	42,67	41,33	16,00	84,00	75
Functional connectivity from resting state BOLD fMRI	41,56	41,56	16,88	83,12	77
Brain atrophy from T1 MRI	41,46	39,02	19,51	80,49	82
White matter vascular damage from FLAIR MRI	23,53	48,53	27,94	72,06	68
Cerebral perfusion from arterial spin labeling	20,83	41,67	37,50	62,50	72
Cerebral microbleeds on T2* or SWI MRI	29,33	26,67	44,00	56,00	75

MRI FTD biomarkers	High priority (%)	Medium priority (%)	Low priority (%)	High+ medium (%)	Response Count
Brain atrophy from T1 MRI	83,12	15,58	1,30	98,70	77
Microstructure and structural connectivity from diffusion MRI	37,14	48,57	14,29	85,71	70
Functional connectivity from resting state BOLD fMRI	42,25	38,03	19,72	80,28	71
White matter vascular damage from FLAIR MRI	15,15	54,55	30,30	69,70	66
Cerebral perfusion from arterial spin labeling	40,00	27,14	32,86	67,14	70
Cerebral microbleeds on T2* or SWI MRI	8,82	38,24	52,94	47,06	68

MRI HD biomarkers	High priority (%)	Medium priority (%)	Low priority (%)	High+ medium (%)	Response Count
Brain atrophy from T1 MRI	41,67	38,33	20,00	80,00	60
Microstructure and structural connectivity from diffusion MRI	30,91	40,00	29,09	70,91	55

Functional connectivity from resting state BOLD fMRI	16,07	46,43	37,50	62,50	56
Cerebral perfusion from arterial spin labeling	10,91	32,73	56,36	43,64	55
White matter vascular damage from FLAIR MRI	9,43	26,42	64,15	35,85	53
Cerebral microbleeds on T2* or SWI MRI	7,14	17,86	75,00	25,00	56

MRI CJD biomarkers	High priority (%)	Medium priority (%)	Low priority (%)	High+ medium (%)	Response Count
Microstructure and structural connectivity from diffusion MRI	41,67	31,25	27,08	72,92	48
Brain atrophy from T1 MRI	23,08	25,00	51,92	48,08	52
White matter vascular damage from FLAIR MRI	18,75	29,17	52,08	47,92	48
Cerebral perfusion from arterial spin labeling	10,42	29,17	60,42	39,58	48
Functional connectivity from resting state BOLD fMRI	12,50	27,08	60,42	39,58	48
Cerebral microbleeds on T2* or SWI MRI	12,50	20,83	66,67	33,33	48

MRI PSP/CBS biomarkers	High priority (%)	Medium priority (%)	Low priority (%)	High+ medium (%)	Response Count
Brain atrophy from T1 MRI	64,29	25,00	10,71	89,29	56
Microstructure and structural connectivity from diffusion MRI	32,65	40,82	26,53	73,47	49
Functional connectivity from resting state BOLD fMRI	25,49	47,06	27,45	72,55	51
Cerebral perfusion from arterial spin labeling	12,00	42,00	46,00	54,00	50
White matter vascular damage from FLAIR MRI	12,77	40,43	46,81	53,19	47
Cerebral microbleeds on T2* or SWI MRI	9,80	27,45	62,75	37,25	51

MRI ALS biomarkers	High priority (%)	Medium priority (%)	Low priority (%)	High+ medium (%)	Response Count
Microstructure and structural connectivity from diffusion MRI	46,55	29,31	24,14	75,86	58
Functional connectivity from resting state BOLD fMRI	23,73	37,29	38,98	61,02	59
Brain atrophy from T1 MRI	30,16	30,16	39,68	60,32	63
White matter vascular damage from FLAIR MRI	15,79	21,05	63,16	36,84	57
Cerebral perfusion from arterial spin labeling	5,56	27,78	66,67	33,33	54
Cerebral microbleeds on T2* or SWI MRI	7,27	16,36	76,36	23,64	55

MRI Summary: Protocol Harmonization (Q32-Q40)

The goal of this section is to identify specific harmonization needs for different MRI pathology biomarkers. This is done by considering first general issues (regardless of specific MRI sequence) and then focusing on specific harmonization issues in each one of the MRI protocols discussed in the biomarker section (atrophy from structural T1, cerebral microbleeds from T2* or SWI, white matter vascular damage from FLAIR, functional connectivity from resting state functional MRI, microsctructure and structural connectivity from diffusion MRI, cerebral perfusion from ASL).

- **Q32:** The survey evaluated the importance of general methodological barriers for the harmonization of MRI biomarkers in multicenter studies. A number of suggestions were made and survey participants had to vote with a yes/no to indicate their agreement with the proposed factors being a barrier (Table Q32). Clearly all of the proposed factors can influence the multicenter studies. The spirit of the question was to ask for the specific factors that survey participants have faced as being most problematic according to their recent experiences.

  All proposed barriers received a positive vote by the majority of responders (≥54%, 163 responses). The highest votes went for lack of clarification in the data analysis details (including factors such as software tools, software version, processing pipeline steps).

Table Q32: General methodological barriers for the harmonization of MRI biomarkers. The barriers are listed in decreasing order of survey votes (163 participants).

Answer Options	Response Percent	Response Count
Unclear analysis details (software, version, steps, etc.)	63,8%	104
Unclear MRI protocol based on time constraints and population	59,5%	97
Unclear QC guidelines during acquisition to decide on repeated scans/exclusions	57,1%	93
Lack of central quality control post acquisition	54,6%	89
Unclear target measures, data analysis and acquisition	54,0%	88
Other	6,7%	11

- **Q33:** Survey participants were asked to list methodological barriers for multicenter brain atrophy from structural T1. 163 people responded to an evaluation of potential barriers relevant to the harmonization of structural T1 MRI for atrophy biomarkers (Table Q33). Multivendor harmonization of multispectral protocols (50%) and prospective head motion correction methods (47%) were the highest ranked problems. Additional barriers listed as "other" included the harmonization of multivendor tissue quantitative mapping techniques.

Table Q33: Structural T1 MRI issues for multisite harmonization of ND biomarkers. The barriers are listed in decreasing order of survey votes (163 participants).

Answer Options	Response Percent	Response Count
Multivendor multispectral MR protocols effects on brain morphometry	50,3%	82
Multivendor online head motion correction effects on brain morphometry	47,2%	77
Histology validation studies of automated and manual segmentation methods	36,8%	60
Retrospective measures of head motion and their effects on the final metrics	36,2%	59
Evaluating shape analysis tools based on free and paid-for software tools	33,7%	55
Other	14,7%	24

- **Q34:** Survey participants were asked to list methodological barriers for multicenter cerebral microbleeds on T2* or SWI MRI. 28 people responded to this open text question. In summary, the main concerns were:
    - Lack of multivendor calibrated acquisition protocols for 3D Quantitative susceptibility Mapping (QSM)
    - Lack of multicenter quality assurance criteria for QSM
    - Lack of standardization and access to automated analysis pipelines for QSM
    - Lack of histology validation of in-vivo QSM findings

- **Q35:** Survey participants were asked to list methodological barriers for multicenter white matter vascular damage from FLAIR. 28 people responded to this open text question. In summary, the main concerns were:

- Lack of multivendor calibrated of FLAIR acquisition protocols for state-of-the art scanners, in particular comparisons between 3D and 2D FLAIR protocols
- Lack of multicenter quality assurance criteria for FLAIR
- Lack of robust automated lesion segmentation and quantification tools

- **Q36**: Survey participants were asked to list methodological barriers for multicenter functional connectivity from task-free fMRI. 59 people responded to this open text question. In summary, the main concerns were:
  - Lack of standardization of experimental conditions across centers (instructions to subject, lights in magnet room)
  - Lack of harmonization and lack of reliability measures from multivendor state-of-the art protocols that use simultaneous multislice acquisitions for fast fMRI.
  - Lack of standardized preprocessing (notably head motion correction) and functional connectivity analysis approaches (seed based, ICA, graph theory, frequency analysis).
  - In particular, lack of guidelines about which acquisition sequences are needed in the context of specific outcome functional connectivity metrics might be most sensitive to particular ND and context (e.g., diagnosis, prognosis, disease stage)

- **Q37:** Survey participants were asked to list methodological barriers for multicenter microstructure and structural diffusion MRI. 50 people responded to this open text question. In summary, the main concerns were:
  - Lack of harmonization and lack of reliability measures from multivendor state-of-the art protocols that use simultaneous multislice acquisitions for diffusion MRI (e.g. multi-shell protocols).
  - Lack of standardized preprocessing, in particular QA for geometric distortion, Eddy currents and head motion correction (eg., consensus criteria for discarding acquisitions due to excessive motion).
  - Lack of a user-friendly DTI phantom that can be used to calibrate tractography and advanced diffusion schemes across sites.
  - Lack of guidelines about which MRI acquisition schemes are needed in the context of specific outcome measures (scalar maps, tractography, etc), specific brain areas and optimal sensitivity to particular NDs in different contexts (e.g., diagnosis, prognosis, disease stage).
  - Lack of solid diffusion models that can be used for in-vivo MRI supported by histology.

- **Q38:** Survey participants were asked to list methodological barriers for multicenter cerebral perfusion from arterial spin labeling MRI. 42 people responded to this open question. In summary, the main concerns were:
  - Lack of harmonization and lack of reliability measures from multivendor state-of-the art protocols that use simultaneous multislice acquisitions for ASL MRI, in particular pseudo-continuous ASL and multi-delay ASL.
  - Several responders raised the issue that a current barrier is that not all MRI vendors offer the 3D PCASL sequence, which has been demonstrated to be the most sensitive perfusion sequence (white paper).
  - Lack of a validated standardized perfusion phantom that can be used to calibrate perfusion quantification across sites.

- Lack of quality control criteria for multicenter implementations (e.g. labeling efficiency)

- **Q39**: Survey participants were asked to list other MRI biomarkers with barriers for their multicenter harmonization. 30 people responded to this open question. In summary, the suggestions included:
  - Magnetic resonance spectroscopy could offer important biomarkers about tissue biochemistry and metabolism. An important barrier is the harmonization across multiple vendors on state-of-the-art systems.
  - Quantitative tissue mapping (T1, T2, and proton density) may offer interesting microstructural characterization of ND diseases. A current barrier is lack of harmonization of multivendor acquisition protocols and characterization of reliability in state-of-the-art MR systems.
  - Task-based fMRI may offer a better controlled environment than task-free fMRI. More work is needed to identify ND disease specific tasks that can be used as fMRI markers, with their reliability.
  - Quantitative magnetization transfer MRI could offer microstructural brain tissue characterization sensitive to early-phase disease stages, in particular for HD and PD. (https://www.ncbi.nlm.nih.gov/pubmed/25891828). Current barriers include harmonization of multivendor acquisition and analysis protocols and characterization of reliability in state-of-the-art MR systems.
  - Multimodal neuroimaging: composite measures derived from atrophy, structural and functional network modeling as well as metrics derived from simultaneous EEG/fMRI. There is currently a lack of standardization in data fusion methodologies.
  - Multivariate analysis that characterize neurodegenerative disease topography instead of region-specific markers (e.g. hippocampus volume with structural MRI). A current barrier is that the distinct ND disease topographies are not well investigated for most imaging modalities mentioned, with the partial exception of structural MRI.

- **Q40**: Survey participants were asked to propose facilitators for multicenter MRI harmonization. 41 people responded to this open question. To summarize the suggestions we classified them in the following broad categories:
  - MRI acquisition facilitators
    - Develop public, validated multi-vendor standardized MRI acquisition protocols and recommendations for different updated scanner models.
    - Establish a more open and integrated MRI sequence information exchange across MRI vendors that facilitates protocol harmonization.
    - Encourage acquisition protocol harmonization (least common denominator) while pushing for testing novel data/analysis.
  - MRI analysis facilitators
    - Develop consensus on automated quality control metrics of multivendor MRI data for different analysis needs.
    - Development of standardized dedicated phantoms that can be used for multicenter harmonization evaluation
    - Establish publicly shared validated and documented analysis pipelines.
    - Establish quantitative reference values that can be used to evaluate degree of multivendor harmonization
    - Encourage harmonization of data post-acquisition to exploit retrospective data.

- MRI data sharing facilitators
  - Allowing the use of imaging data beyond the reason for research purpose , to allow meta analytical assessment s for cross-site comparisons
  - Sense of security about retained publication ownership of hard-fought MRI and clinical data
- Documentation facilitators
  - Establish well documented and updated standard operating procedures for data acquisition, sharing and analysis.
- Funding
  - Ensure funding and proper credits criteria to support and motivate core group of researchers that work on the technical aspects of MRI harmonization and reliability estimation. There should be sufficient overlap in the capacities of this core group to minimize criticality of a single person to the whole project.
  - Ensure sufficient funding is allocated for training staff that will be involved in data acquisition and analysis.

4.2.2 PET-SPECT

PET-SPECT Summary: High level barriers for effectively participating in multisite PET-SPECT ND studies (Q13-Q17)

The goal of this section of the survey was to identify practical high-level barriers that limit the effective participation of centers/groups in large-scale multicenter PET-SPECT ND studies.

- **Q13:** The majority of the PET/SPECT participants (Q13, 75.4% from a total of 69 participants) agreed in that there are barriers to join multicenter PET/SPECT studies of ND.
- **Q14:** PET/SPECT participants were asked to rate the urgency level (urgent problem, non-urgent problem, not a problem) of a number of potential barriers that may prevent the effective participation in multisite PET/SPECT ND studies. The main results were:
  - 42 people answered. None of the potential barriers proposed was regarded by a net majority of participants as not being a problem.
  - To rank the degree of severity of the barriers we computed for each barrier the total percent of people voting for it being an urgent or non-urgent problem. Table Q14 presents the results with the barriers ordered from highest to lowest degree of importance.
  - The main problems were related to lack of funding (100%) and to insufficient standard operating procedures for neuroimaging data analysis (87%).
  - Access to PET/SPECT imaging facilities and to clinical resources to interact with patients were ranked as the least serious problems (respectively 47.5% and 36.84% of people regarded them as not a problem).
- **Q15:** Survey participants were invited to list additional high-level barriers to participate in multicenter studies. There were 22 answers. Most notably, there were multiple references to lack of standardization of protocols and limited availability of novel PET tracers. Another barrier mentioned was insufficient funding for IT infrastructure, data analysis, data management, working meetings, etc.
- **Q16:** A series of possible recommendations were proposed as possible actions to address high-level barriers to join multicenter PET/SPECT studies. 38 people answered giving very high consensus (>75%) in favor of most of them (Table Q16), with a little less consensus for central facilities for PET/SPECT data acquisition (54.84% yes).

Table Q14: Urgency scores for barriers that may prevent the effective participation of a center/group in a multicenter PET/SPECT neurodegenerative study. A total of 42 people responded to the question.

Answer Options	Response Count	% Not a problem	% Non-urgent problem	% Urgent problem	Sum urgent +non-urgent
Insufficient funding	40	0.00	37.50	62.50	100.00
Insufficient access to information about the possibility of participating in multicenter studies	39	12.82	38.46	48.72	87.18
Insufficient standard operating procedures for neuroimaging data analysis	40	15.00	27.50	57.50	85.00
Bureaucratic hurdles (data protection/privacy, anonymization, unclear legal situation regarding data transfer with/without patient consent etc.)	39	15.38	38.46	46.15	84.62
Insufficient access to an IT infrastructure that facilitates the integration and management of the project (data storage, secure data transfer etc.)	40	17.50	52.50	30.00	82.50
Insufficient access to expertise and resources for the optimization of a local IT and informatics infrastructure	38	18.42	55.26	26.32	81.58
Insufficient access to administrative resources (e.g., support for ethical committee, recruiting, etc.)	39	20.51	41.03	38.46	79.49
Insufficient support for statistical analysis	38	21.05	36.84	42.11	78.95
Insufficient standard operating procedures for neuroimaging data acquisition	39	23.08	38.46	38.46	76.92
Insufficient access to expertise and resources for the optimization of image analysis protocols	39	25.64	28.21	46.15	74.36
Insufficient access to patient population	40	32.50	37.50	30.00	67.50
Insufficient access to expertise and resources for the choice of and optimization of image acquisition protocols	40	32.50	30.00	37.50	67.50
Insufficient access to expertise and resources for the interpretation of results	39	33.33	46.15	20.51	66.67
Insufficient access to clinical resources to interact with patients	38	36.84	44.74	18.42	63.16
Insufficient access to imaging facilities	40	47.50	30.00	22.50	52.50

Table Q16: Actions that may help addressing high-level barriers preventing effective participation in multicenter PET/SPECT ND studies, ranked from highest to lowest votes.

Answer Options	% Yes	Response Count
Establishing common ethical guidelines on required patient consent for data sharing and rules for making use of publicly available data	85.71	35
Production of an open access WEB-based knowledge platform with documentation about biomarkers for specific modalities as well as other general issues that need special consideration in multi-centric longitudinal studies on neurodegenerative disorders	83.33	36
Central facilities for data upload and storage	81.82	33
Institution of a public web-based forum in which clinical and basic researchers can communicate with their peers to discuss and exchange updated information relevant to multi-centric longitudinal studies on neurodegenerative disorders	78.38	37
Central facilities for data analysis	76.47	34
Central facilities for data-acquisition	54.84	31

- **Q17:** Survey participants were invited to list additional suggestions for addressing high-level barriers that prevent participation in multicenter PET/SPECT studies. The summary of the 12 responses is as follows:
    - Closer co-operation between hospitals, universities, funders, charities and industry to develop and apply common guidelines
    - Standardization of medical instrumentation and definitions of different biomarkers
    - A central European based committee of independent experts to comment on proposed studies

PET-SPECT Summary: Biomarker Priorities (Q26-Q28)

The goal of this section was to identify the most useful PET-SPECT biomarkers to be used in future multicenter longitudinal ND studies

- **Q26:** There was consensus that there is a need to prioritize PET/SPECT biomarkers (86%, from a total of 57 participants)

- **Q27:** Participants were asked to give a clinical priority (high, medium, low) to a list of generic PET/SPECT data acquisition methods for biomarker determination (FDG PET–glucose, Amyloid PET, Tau PET, Dopaminergic PET/SPECT) to a number of ND. A total of 39 responded, the results are shown in Table Q27. In summary:
    - **AD biomarkers:** ≥90% gave high/medium priority to amyloid PET, tau PET and FDG PET, with amyloid PET (97.37%) ranking first. Dopaminergic PET/SPECT was on the contrary given much less priority (24%).
    - **PD biomarkers:** ≥ 70% gave high/medium priority to dopaminergic PET/SPECT (96.67%) and FDG PET–glucose (70.37%). Tau PET (45%) and amyloid PET (27.27) were given less priority.
    - **DLB biomarkers:** ≥90% gave high/medium priority to dopaminergic PET/SPECT (95%) and FDG PET–glucose (90%). High scores were given also to amyloid PET (71.43) and Tau PET (65%).
    - **FTD biomarkers:** ≥ 75% gave high/medium priority to FDG PET–glucose (100%), Tau PET (83.33%) and amyloid PET (75%)

- **HD biomarkers**: ≥ 55% gave high/medium priority to FDG PET–glucose (58.82%), while less priority was given to Tau PET (40%), dopaminergic PET/SPECT (35.71%) and amyloid PET (13.33%).
- **CJ biomarkers:** ≥ 50% gave high/medium priority to FDG PET–glucose (52.94%). Less priority was given to Tau PET (21.43%), amyloid PET (12.50%) and dopaminergic PET/SPECT (15.38%).
- **PSP/CBS biomarkers**: ≥ 80% gave high/medium priority to FDG PET–glucose (86.96%) and Tau PET (81.82%). Dopaminergic PET/SPECT was indicated by 66.7%.
- **ALS biomarkers:** ≥ 80% gave high/medium priority to FDG PET–glucose (81.25%). Much less priority was given to TAU PET (35.71), amyloid PET (20%) and dopaminergic PET/SPECT (15.38%).

These results show that FDG-PET is in the front line for all ND as it is regarded similarly as a 'wide-spectrum antibiotics' and because of relatively lower cost and larger availability as compared to the other modalities. Moreover, the clinical experience is far longer and larger with FDG PET. Even in the AD field, FDG PET has same relevance as amyloid PET. Acquisition and reconstruction parameters may vary among centers but the main issue is reporting and the identification of semi-quantitative tools to assist interpretation that could allow data sharing among centers. The role of amyloid PET seems more confined to AD and FTD, and to DLB where it can add information of coexistence of AD pathology. Issues with amyPET concern the use of different radiopharmaceuticals that might generate non-comparable dataset. As for FDG PET, for amyPET also the choice of semi-quantification tools should be better defined with the aim to allow data sharing. The Centiloid project is a possible solution for PET data sharing but semi-quantification tools need to be validated versus expert reading (or versus pathology, if possible). Also, further research is needed to understand the meaning of 'borderline' scans. Dopaminergic imaging is thought to be a first-line need in PD and DLB with some load also in HD. While PET radiopharmaceuticals are generally not available on the market, the vast majority of studies has to date been performed with FP-CIT or beta-CIT. A considerable effort has been made by the EANM that in the last years has led to availability of a relatively large group (about 150 subjects) of healthy European controls but overall of recovery coefficients for virtually all gamma camera commercially available in Europe (not SPECT-CT, however). These recovery coefficients do allow data sharing among centers. Furthermore, reference normal values are available with at least three semi-quantification tools. Tau PET is an emerging modality but much lesser developed and clarified. First, it remains unknown what kind of Tau molecule the various available radiopharmaceuticals are specific to (e.g., 3-R or 4-R, or both). In addition, Tau PET radiopharmaceuticals still need approval by the European Medicines Agency (EMA) for clinical use. Therefore, these Tau tracers need to be considered as research tools only and undergo the required steps to define their affinity profile, proper quantification approaches and subsequent validation for clinical use. This also clearly emerges from table 43 observations (see below).

- **Q28:** Survey participants were invited to suggest other PET/SPECT pathology biomarkers relevant to ND disorders. 9 people responded. In summary, the PET/SPECT methods recommended which were not related to those already discussed in Q28 were:
  - ^{123}I-MIBG imaging in RBD, PD, DLB
  - Imaging of neuroinflammation and microglia (TSPO)
  - PDE10 imaging
  - Alpha-synuclein tracers

As stated in the introduction, for cardiac I-123 MIBG imaging there is a large body of evidence in PD, DLB and their differentiation versus either AD or atypical Parkinsonism.

Microglia imaging is an area of intense research interest, while there is still a need for tracer and methods development. Other ligands are far from being proximal to the market.

Table Q27: Clinical priority (high, medium, low) for potential PET/SPECT biomarkers for the relevant neurodegenerative diseases (39 people responded). AD: Alzheimer's disease. PD/PDD: Parkinson's disease/Parkinson's disease dementia. FTD: Fronto-temporal Dementia. HD: Huntington's disease. CJD: Creutzfeldt-Jakob disease. PSP/CBS: Progressive supranuclear palsy and corticobasal syndrome. ALS: Amyotrophic Lateral Sclerosis.

PET/SPECT AD biomarkers	High priority (%)	Medium priority (%)	Low priority (%)	High + Medium (%)	Response Count
Amyloid PET	86.84	10.53	2.63	97.37	38
Tau PET	77.78	19.44	2.78	97.22	36
FDG PET – glucose	65.79	28.95	5.26	94.74	38
Dopaminergic PET/SPECT	16.00	8.00	76.00	24.00	25

PET/SPECT PD biomarkers	High priority (%)	Medium priority (%)	Low priority (%)	High + Medium (%)	Response Count
Dopaminergic PET/SPECT	83.33	13.33	3.33	96.67	30
FDG PET – glucose	29.63	40.74	29.63	70.37	27
Tau PET	20.00	25.00	55.00	45.00	20
Amyloid PET	0.00	27.27	72.73	27.27	22

PET/SPECT DLB biomarkers	High priority (%)	Medium priority (%)	Low priority (%)	High + Medium (%)	Response Count
Dopaminergic PET / SPECT	61.90	33.33	4.76	95.24	21
FDG PET – glucose	63.33	26.67	10.00	90.00	30
Amyloid PET	33.33	38.10	28.57	71.43	21
Tau PET	25.00	40.00	35.00	65.00	20

PET/SPECT FTD biomarkers	High priority (%)	Medium priority (%)	Low priority (%)	High + Medium (%)	Response Count
FDG PET – glucose	75.86	24.14	0.00	100.00	29
Tau PET	62.50	20.83	16.67	83.33	24
Amyloid PET	37.50	37.50	25.00	75.00	24
Dopaminergic PET / SPECT	11.11	27.78	61.11	38.89	18

PET/SPECT HD biomarkers	High priority (%)	Medium priority	Low priority (%)	High + Medium (%)	Response Count

		(%)			
FDG PET – glucose	23.53	35.29	41.18	58.82	17
Tau PET	6.67	33.33	60.00	40.00	15
Dopaminergic PET / SPECT	28.57	7.14	64.29	35.71	14
Amyloid PET	0.00	13.33	86.67	13.33	15

PET/SPECT CJD biomarkers	High priority (%)	Medium priority (%)	Low priority (%)	High + Medium (%)	Response Count
FDG PET – glucose	23.53	29.41	47.06	52.94	17
Tau PET	14.29	7.14	78.57	21.43	14
Amyloid PET	0.00	12.50	87.50	12.50	16
Dopaminergic PET / SPECT	0.00	15.38	84.62	15.38	13

PET/SPECT PSP/CBS biomarkers	High priority (%)	Medium priority (%)	Low priority (%)	High + Medium (%)	Response Count
FDG PET – glucose	60.87	26.09	13.04	86.96	23
Tau PET	68.18	13.64	18.18	81.82	22
Dopaminergic PET / SPECT	42.86	23.81	33.33	66.67	21
Amyloid PET	15.79	31.58	52.63	47.37	19

PET/SPECT ALS biomarkers	High priority (%)	Medium priority (%)	Low priority (%)	High + Medium (%)	Response Count
FDG PET – glucose	31.25	50.00	18.75	81.25	16
Tau PET	14.29	21.43	64.29	35.71	14
Amyloid PET	6.67	13.33	80.00	20.00	15
Dopaminergic PET / SPECT	0.00	15.38	84.62	15.38	13

PET-SPECT Summary: Protocol Harmonization (Q41-Q46)

The goal of this section is to identify specific harmonization needs for different PET-SPECT pathology biomarkers.

- **Q41:** Survey participants were asked to list methodological barriers relevant for the harmonization of biomarkers derived from FDG-PET. 52 people responded (Table Q41). Analysis tools (69.2%) and missing public brain bank of FDG-PET healthy controls coming from several centers (67.3%) were the highest ranked problems.

Table 41 Methodological barriers relevant for the harmonization of biomarkers derived from FDG-PET. The barriers are listed in decreasing order of survey votes (52 participants).

Answer Options	Response Percent	Response Count
Analysis tools	69.2%	36
Missing public brain bank of FDG-PET healthy controls coming from several centers	67.3%	35
Definition of normal controls	63.5%	33
Harmonization in the reference region selection	61.5%	32
Image reconstruction protocol: iterative/FBP	57.7%	30
Acquisition duration and time-interval between injection and acquisition	50.0%	26
Patient injection protocol: eyes open versus eyes closed during experiment	48.1%	25
Semi quantification tools	46.2%	24
Head movement artifacts correction	42.3%	22
Image co-registrations between CT and PET scans	25.0%	13
Other	25.0%	13

- **Q42:** Survey participants were asked to list methodological barriers relevant the harmonization of biomarkers derived from amyloid PET. 52 people responded (Table 42). Standardization across tracers (63.5%) and ROI selection for SUVr computation (61.5%) were the highest ranked problems.

Table 42 Methodological barriers relevant for the harmonization of biomarkers derived from amyloid PET. The barriers are listed in decreasing order of survey votes (52 participants).

Answer Options	Response Percent	Response Count
Standardization across tracers	63.5%	33
ROI selection for SUVr computation (atlas, MRI-based, etc.)	61.5%	32
Handling of atrophy hampering interpretation of cortical tracer uptake	57.7%	30
Reference region	53.8%	28
Reconstruction protocol: iterative/FBP	53.8%	28
Harmonization of criteria used for visual readings across vendors and nuclear medicine physicians.	51.9%	27
Use of kinetic parameters (distribution volumes, binding potentials)	46.2%	24
Acquisition time points	42.3%	22
Analytical strategies proposed by the different vendors	40.4%	21
Movement artifacts	34.6%	18
Other	23.1%	12
Need for other metrics	19.2%	10

- **Q43:** Survey participants were asked to list methodological barriers relevant the harmonization of biomarkers derived from Tau PET. 52 people responded. Quantification (73.1%) and affinity profile of different tracers for different isoforms (63.5%) were the highest ranked problems.

Table 43 Methodological barriers relevant for the harmonization of biomarkers derived from Tau PET. The barriers are listed in decreasing order of survey votes (52 participants).

Answer Options	Response Percent	Response Count
Quantification	73.1%	38
Affinity profile of different tracers for different isoforms	63.5%	33
Unspecific tracer uptake in basal ganglia/brainstem Reference region	61.5%	32
Tracer uptake in healthy controls (mesial temporal)	55.8%	29
Other	26.9%	14

- **Q44:** Survey participants were asked to list methodological barriers relevant the harmonization of biomarkers derived from dopaminergic PET/SPECT. 52 people responded.

Table 44 Methodological barriers relevant for the harmonization of biomarkers derived from dopaminergic PET/SPECT. The barriers are listed in decreasing order of survey votes (52 participants). Analysis tools (69.2%) and comparability of PET and SPECT approaches (67.3%) were the highest ranked problems.

Answer Options	Response Percent	Response Count
Analysis tools: Visual vs. semi-quantitative	69.2%	36
Comparability of PET and SPECT approaches	67.3%	35
Missing public brain bank of Dopaminergic PET/SPECT healthy controls coming from several centers	48.1%	25
Reconstruction protocol: iterative/FBP	44.2%	23
Other	21.2%	11

- **Q45:** Survey participants were asked to list additional PET/SPECT biomarkers considered important to include with barriers for their harmonization. The summary of the 7 responses is as follows:
    - Alpha-Methyl-Tyrosine
    - Flumazenil
    - 123I-MIBG (need for harmonization of the acquisition protocol and analytical approach)
    - Tracers of neuroinflammation, including PK-11195, DPA-714 and other second generation TSPO tracers
    - Cerebral blood flow measurements

- **Q46:** Survey participants were asked to propose facilitators for multicenter PET/SPECT harmonization. 16 people responded to this open question. To summarize the suggestions we classified them in the following broad categories:
    - Interdisciplinary and multicenter collaboration
    - Central dissemination of technology and centrally driven guidelines
    - Funding for researcher-driven research
    - Agreement on the optimal protocol and data analysis procedure, also mentioning the contribution that MRI harmonization can give to standardized PET analysis
    - Harmonization of scanners and preprocessing steps
    - Joint training programs for multimodal imaging
    - Image quality standards

- Industrial support

4.2.3 EEG

EEG Summary: High-level barriers for effectively participating in multisite EEG ND studies (Q18-Q22)

The goal of this section of the survey was to identify practical high-level barriers that limit the effective participation of centers/groups in large-scale multicenter EEG ND studies.

- **Q18:** The majority of the EEG participants (Q18, 60.8% from a total of 130 participants) agreed in that there are barriers to join multicenter EEG studies of ND.

- **Q19:** EEG participants were asked to rate the urgency level (urgent problem, non-urgent problem, not a problem) of a number of potential barriers that may prevent the effective participation in multisite EEG ND studies. The main results were:
  - 67 people answered. None of the potential barriers proposed was regarded by a net majority of participants as not being a problem.
  - To rank the degree of severity of the barriers, we computed for each barrier the total percent of people voting for it being an urgent or non-urgent problem. Table Q19 presents the results with the barriers ordered from highest to lowest degree of importance.
  - The outstanding most urgent problem was related to lack of funding (98.46%).
  - Interestingly, access to EEG imaging facilities or to clinical resources to interact with patients were ranked as the least serious problems (respectively 43.55% and 36.67% of people regarded them as not a problem).

- **Q20:** Survey participants were invited to list additional high-level barriers to participate in multicenter studies. There were 26 answers. Most notably, there were multiple references to lack of standardisation. Another barrier mentioned was the lack of interaction between industry and university, and the fact that EEG neurodegenerative studies are not published in regular neuropsychiatry journals and neither mentioned in the regulatory guidelines (there is less believe on the potential of EEG).

- **Q21:** A series of possible recommendations were proposed as possible actions to address high-level barriers to join multicenter EEG studies. In total, 66 people answered giving very high consensus (>80%) in favor of most of them (Table Q21), with a little less consensus for central facilities for EEG data acquisition (58.18% yes).

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Table Q19 Urgency scores for barriers that may prevent the effective participation in a multicenter EEG neurodegenerative study. A total of 67 people responded to the question

Answer Options	Response Count	% Not a problem	% Non-urgent problem	% Urgent problem	sum urgent+ non urgent
Insufficient funding	65	1.54	24.62	73.85	98.46
Insufficient access to information about the possibility of participating in multicenter studies	61	6.56	49.18	44.26	93.44
Insufficient standard operating procedures for neuroimaging data analysis	62	16.13	33.87	50.00	83.87
Insufficient access to an IT infrastructure that facilitates the integration and management of the project (data storage, secure data transfer etc.)	61	19.67	42.62	37.70	80.33
Insufficient standard operating procedures for neuroimaging data acquisition	62	22.58	29.03	48.39	77.42
Insufficient access to expertise and resources for the optimization of a local IT and informatics infrastructure	60	23.33	50.00	26.67	76.67
Bureaucratic hurdles (data protection/privacy, anonymisation, unclear legal situation regarding data transfer with/without patient consent etc.)	63	23.81	42.86	33.33	76.19
Insufficient access to expertise and resources for the optimization of image analysis protocols	60	25.00	33.33	41.67	75.00
Insufficient support for statistical analysis	62	30.65	37.10	32.26	69.35
Insufficient access to expertise and resources for the interpretation of results	63	31.75	42.86	25.40	68.25
Insufficient access to expertise and resources for the choice of and optimization of image acquisition protocols	59	32.20	32.20	35.59	67.80
Insufficient access to patient population	62	32.26	33.87	33.87	67.74
Insufficient access to administrative resources (e.g., support for ethical committee, recruiting, etc.)	63	33.33	41.27	25.40	66.67
Insufficient access to clinical resources to interact with patients	60	36.67	33.33	30.00	63.33
Insufficient access to imaging facilities	62	43.55	32.26	24.19	56.45

Table Q21 Actions that may help addressing high-level barriers preventing effective participation in multicenter EEG ND studies, ranked from highest to lowest votes.

Answer Options	% Yes	Response Count
Production of an open access WEB-based knowledge platform with documentation about biomarkers for specific modalities as well as other general issues that need special consideration in multi-centric longitudinal studies on neurodegenerative disorders	98.41	63
Institution of a public web-based forum in which clinical and basic researchers can communicate with their peers to discuss and exchange updated information relevant to multi-centric longitudinal studies on neurodegenerative disorders.	84.13	63
Central facilities for data upload and storage	83.93	56
Establishing common ethical guidelines on required patient consent for data sharing and rules for making use of publicly available data	83.87	62
Central facilities for data analysis	80.36	56
Central facilities for data-acquisition	58.18	55

- **Q22:** Survey participants were invited to list additional suggestions for addressing high-level barriers that prevent participation in multicenter EEG studies. The summary of the 19 responses is as follows:
    - Standardised procedures for data acquisition;
    - Wider access to clinical data (open-access, data sharing, etc.);
    - A common protocol for data acquisition.

EEG Summary: Biomarker Priorities (Q29-Q31)

The goal of this section was to identify the most useful EEG biomarkers to be used in future multicenter longitudinal ND studies

- **Q29:** There was consensus that there is a need to prioritize EEG biomarkers (86.2%, from a total of 116 participants)

- **Q30:** Participants were asked to give a clinical priority (high, medium, low) to a list of generic EEG data acquisition methods for biomarker determination with the following paradigms: (1) resting state eyes-closed EEG (rsEEG) rhythms at standard delta, theta, alpha, beta frequency bands; (2) event-related potentials (e.g. oddball paradigm for the study of late positive components peaking at about 300 milliseconds post-stimulus, P3), and event-related EEG oscillations in the above frequency bands. A total of 82 responded. The results are shown in Table Q30. They are also summarized in the following:
    - **AD biomarkers:** ≥85% gave high/medium priority on all proposed EEG methods, with the highest priority for rsEEG rhythms (100%).
    - **PD biomarkers:** ≥ 80% gave high/medium priority to all proposed methods with rsEEG rhythms ranking first (93.75%).
    - **DLB biomarkers:** ≥80% gave high/medium priority to all proposed methods with rsEEG rhythms ranking first (94.12%).

- **FTD biomarkers**≥80% gave high/medium priority to all proposed methods with rsEEG rhythms ranking first (94.12%).
- **HD biomarkers**: ≥ 60% gave high/medium priority to all proposed methods with event-related oscillations ranking first (69.44%).
- **CJD biomarkers:** ≥ 55% gave high/medium priority to all proposed methods with rsEEG rhythms ranking first (66.67%).
- **PSP/CBS biomarkers**: ≥ 50% gave high/medium priority all proposed methods with rsEEG rhythms ranking first (64.71%).
- **ALS biomarkers:** ≥ 50% gave high/medium priority all proposed methods with event-related potentials ranking first.

These results suggest that the vast majority of the Survey participants think that EEG biomarkers are relevant to the research on brain function in patients with neurodegenerative disorders, especially AD, PD, DLB, and FTD. Among those EEG biomarkers, all think that those derived from rsEEG rhythms are particularly suitable for the clinical research. However, the vast majority of the Survey participants believe that all EEG biomarkers should be explored in clinical research on AD, PD, DLB, and FTD. The present EEG-WG agrees with this view as the potential of the mentioned EEG biomarkers is poorly known and could deserve the chance to enrich the actual neurobiological model of the neurodegenerative diseases with the essential aspect of the neurophysiological reserve. This reserve would reflect the functioning of neurophysiological mechanisms underpinning the synchronization and coupling of neural populations in brain circuits related to vigilance and cognitive functions.

- **Q31:** Survey participants were invited to suggest other EEG biomarkers relevant to ND disorders. In total, 35 people responded. In summary, the EEG methods recommended which were not related to those already discussed in Q30 were (1) those already mentioned in the clinical diagnostic guidelines of DLB and sporadic CJD such as the detection of abnormal EEG slow-frequency waveforms in DLB (McKeith et al., 2005) or triphasic EEG waveforms in a sporadic variant of CJD (Zerr et al., 2009); (2) other paradigms of cognitive event-related potentials probing the N400 and P600 components related to language and episodic memory; (3) those analyzing the sleep EEG stages; and (4) the procedures testing nonlinear dynamics and complexity of the EEG brain functional connectivity.

Table Q30: Clinical priority (high, medium, low) for potential EEG biomarkers for the relevant neurodegenerative diseases (82 people responded). AD: Alzheimer's disease. PD/PDD: Parkinson's disease/Parkinson's disease dementia. FTD: Fronto-temporal Dementia. HD: Huntington's disease. CJD: Creutzfeldt-Jakob disease. PSP/CBS: Progressive supranuclear palsy with corticobasal syndrome. ALS: Amyotrophic Lateral Sclerosis

EEG AD biomarkers	High priority (%)	Medium priority (%)	Low priority (%)	High + medium (%)	Response Count
Resting state eyes-closed EEG (rsEEG) rhythms (delta, theta, alpha, beta waveforms)	79.75	20.25	0.00	100.00	79
Event-related potentials (ERP, P3)	62.86	27.14	10.00	90.00	70
Event-related oscillations (ERO)	61.02	28.81	10.17	89.83	59

EEG PD biomarkers	High priority (%)	Medium priority (%)	Low priority (%)	High + medium (%)	Response Count
Resting state eyes-closed EEG (rsEEG) rhythms (delta, theta, alpha, beta waveforms)	56.25	37.5	6.25	93.75	64
Event-related potentials (ERP, P3)	48.15	37.04	14.81	85.19	54
Event-related oscillations (ERO)	56.52	26.09	17.39	82.61	46

EEG DLB biomarkers	High priority (%)	Medium priority (%)	Low priority (%)	High + medium (%)	Response Count
Resting state eyes-closed EEG (rsEEG) rhythms (delta, theta, alpha, beta waveforms)	68.63	25.49	5.88	94.12	51
Event-related oscillations (ERO)	58.33	25.00	16.67	83.33	36
Event-related potentials (ERP, P3)	55.00	27.50	17.50	82.50	40

EEG FTD biomarkers	High priority (%)	Medium priority (%)	Low priority (%)	High + medium (%)	Response Count
Resting state eyes-closed EEG (rsEEG) rhythms (delta, theta, alpha, beta waveforms)	74.51	19.61	5.88	94.12	51
Event-related potentials (ERP, P3)	55.00	32.50	17.50	87.50	40
Event-related oscillations (ERO)	52.78	30.56	16.67	83.33	36

EEG HD biomarkers	High priority (%)	Medium priority (%)	Low priority (%)	High + medium (%)	Response Count
Event-related oscillations (ERO)	41.67	27.78	22.22	69.44	36
Resting state eyes-closed EEG (rsEEG) rhythms (delta, theta, alpha, beta	37.25	31.37	9.80	68.63	51

waveforms)					
Event-related potentials (ERP, P3)	37.50	25.00	25.00	62.50	40

EEG CJD biomarkers	High priority (%)	Medium priority (%)	Low priority (%)	High + medium (%)	Response Count
Resting state eyes-closed EEG (rsEEG) rhythms (delta, theta, alpha, beta waveforms)	54.90	11.76	7.84	66.67	51
Event-related potentials (ERP, P3)	35.00	25.00	22.50	60.00	40
Event-related oscillations (ERO)	33.33	25.00	27.78	58.33	36

EEG PSP/CBS biomarkers	High priority (%)	Medium priority (%)	Low priority (%)	High + medium (%)	Response Count
Resting state eyes-closed EEG (rsEEG) rhythms (delta, theta, alpha, beta waveforms)	37.25	27.45	13.73	64.71	51
Event-related potentials (ERP, P3)	25.00	32.50	20.00	57.50	40
Event-related oscillations (ERO)	33.33	19.44	27.78	52.78	36

EEG ALS biomarkers	High priority (%)	Medium priority (%)	Low priority (%)	High + medium (%)	Response Count
Event-related potentials (ERP, P3)	27.50	35.00	22.50	62.50	40
Resting state eyes-closed EEG (rsEEG) rhythms (delta, theta, alpha, beta waveforms)	31.37	23.53	25.49	54.90	51
Event-related oscillations (ERO)	36.11	16.67	33.33	52.78	36

EEG Summary: Protocol Harmonization (Q47-Q49)

The goal of this section is to identify specific harmonization needs for different EEG pathology biomarkers.

- **Q47:** Survey participants were asked to list methodological barriers relevant for the harmonization of biomarkers derived from resting state EEG. 96 people responded (Table Q47). Standardization of spectral EEG analysis (76%), harmonization of high-resolution EEG recordings (60.4%), and harmonization of automated removal of ocular, muscular, and EKG artefacts (60.4%) were the highest ranked problems.

Table 47 Methodological barriers relevant for the harmonization of biomarkers derived from rsEEG. The barriers are listed in decreasing order of survey votes (96 participants).

Answer Options	Response Percent	Response Count
Standardization of spectral EEG (source) analysis	76.0%	73
Harmonization of high-resolution EEG recordings	60.4%	58
Harmonization of automated removal of ocular, muscular, and EKG artefacts	60.4%	58
Harmonization of non-linear indexes	40.6%	39
Harmonization with state-of-the art multivendor	38.5%	37
Other	11.5%	11

- **Q48:** Survey participants were asked to list additional EEG biomarkers considered important to include with barriers for their harmonization. 76 people responded (Table Q48).

Answer Options	Response Percent	Response Count
Event-related potentials	40.8%	31
Event-related oscillations	43.4%	33
Other	15.8%	12

- **Q49:** Survey participants were asked to propose facilitators for multicenter EEG harmonization. In total, 33 people responded to this open question. To summarize the suggestions we classified them in the following broad categories:
    - Produce expert consensus guidelines and White Papers on the limits and opportunity of EEG biomarkers (rsEEG, ERP, and ERO) applied on NDs;
    - Deliver standard operating procedures on EEG data recording and analysis (including statistical models) in the public domain;
    - Validate software toolboxes for biomarker extraction and statistical modeling on optimal EEG biomarkers for the whole spectrum of NDs (with an especially promising application to AD, CJD, FTD, PD, and DLB). These boxes will have to be released in the public domain;
    - Deploy WEB-based expert “hubs” with professional personnel assisting in the definition of the optimal design, data collection, EEG biomarker extraction, and statistical modeling;
    - Deploy WEB-based platforms providing central facilities for EEG data upload and storage.

4.3 Final comments

The goal of this section was to identify potentially important aspects that were not sufficiently covered in the survey.

Q50: Participants were asked to provide perspectives, needs and barriers for multimodal data integration between MRI, PET and EEG. A total of 129 people responded to this open question. The responses were evaluated from two perspectives, one related to explicit positive, negative or doubtful views on data integration and the other related to the methodological barriers for data integration.

There was a clear majority of people who expressed explicit positive views about multimodal integration (17%) relative to people who expressed negative views (3%) or doubts (5%) about multimodal neuroimaging integration. The rest of the responders raised barrier issues without being necessarily explicitly positive, negative or doubtful about data integration. People who were explicitly positive were similarly distributed relative to the particular neuroimaging combinations of interest (EEG-fMRI, PET-MRI). The negative view related to time consuming issues and patient burden. The explicit doubtful views related all to the same crucial aspect: lack of evidence for the added clinical value of the integration of simultaneously acquired multimodal neuroimaging data.

Rather than being explicitly in favor or against integration, most participants who responded focused on barriers to multimodal neuroimaging integration. The barriers included the following ones:

- There is a need for funding focused studies that demonstrate the robustness, reliability and benefits of multimodal neuroimaging integration. Only after this is successful it may make sense to consider deploying such integrations to a multicenter scale.
- There is a need of improved multimodal image co-registration methods
  - Need standardization of cross-modality co-registration protocols
  - Need to minimize sensitivity of co-registration quality to image acquisition protocols
- A key challenge in multimodal acquisitions is related to the additional patient burden (multiple visits). The ideal scenario may be a single session that acquires simultaneously EEG-PET-MRI, assuming it offers added clinical value. However, to-date there is no widespread availability of imaging centers that could accommodate this level of multimodal acquisitions.
- Another channel of multimodal studies will be the increased funding needs, not only to support neuroimaging costs but also the funds to attract human resources with the relevant expertise to follow data acquisition and analysis.
- There is a need to support the development of open-access multimodal analysis tools
- There is currently a lack of public multimodal datasets to asses analysis strategies

Q51: Participants were invited to provide additional comments concerning the questionnaire. A total of 25 participants responded to this open question commenting on topics that are considered relevant but that were not addressed by the questionnaire. Topics missing in the survey included:

- MEG (magneto encephalography) was not included as a neuroimaging method.

- Mathematical frameworks and statistical issues for the evaluation of quantitative imaging biomarkers. As an example, a pointer was offered to the important work being performed by the Quantitative Imaging Biomarkers Alliance (QIBA) under the Radiological Society of North America (RSNA): http://www.rsna.org/QIBA-Metrology-Papers/
- From the survey some people were left with the unintended impression that this project assumes that multicenter acquisitions will be always better and that the goal is to have one protocol that is optimal for all diseases rather than focused disease-specific protocols.

Q52: Participants were invited to provide final comments about the project. A total of 36 participants responded to this open question. In general there were positive comments of support for the project and expressions of interest for the publication of its findings. Most of the other comments were in line with previously stated comments.

One comment stressed the need of establishing a dedicated website/forum to facilitate contact between EEG centers worldwide. "*The purpose should not be so much the education of students and new staff but rather a professional database of highly specialized, latest and specific EEG standards and handling procedures (including, if necessary, individually for each equipment type, as well as combined equipment standards). Another, communication-oriented module on the website should ensure that suggestions, summaries, and decisions are immediately available for specialized review (only to individually approved users with min. 1 journal publication in EEG).*"

Another comment stressed the importance of motivating experts from different professional groups (e.g. radiology and nuclear medicine, image acquisition/analysis experts and clinicians) in order to have them participate and integrate in these multicenter or multimodal imaging projects.

A final comment brought up the importance of involving medical insurance in relation to costs. One of the hurdles is that research on the diagnosis performance of brain imaging depends heavily on resources. With the exception of MRI, which may be reimbursed with no difficulties even on follow up, other imaging modalities are not typically reimbursed.

5. Strategic Research Agenda: Priorities and Enabling Activities

The survey helped identify a number of barriers and potential solutions for the problem of harmonizing ND biomarkers obtained from multicenter neuroimaging studies. Some barriers were common across the neuroimaging modalities considered (i.e. MRI, PET-SPECT and EEG), and other barriers were rather specific to neuroimaging modality. In what follows, we summarize and integrate this information proposing a framework of actions aimed at addressing the collective harmonization needs identified both by the survey and the opinion leaders participating in the project. This series of actions defines the proposed strategic research agenda for the harmonization of large-scale multicenter neuroimaging biomarkers.

Furthermore, the actions proposed are consistent with current EU legislation developments aimed at allowing secondary use of health data ("Regulation on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation), L119, 4/5/2016, p. 1–88). Such legislation would also lend itself to the secondary use of multicenter neuroimaging data once these data has been obtained within a common methodological framework. This underscores that funding for the hereby proposed actions would come timely given the political agenda of health research legislation in the EU.

5.1 General recommendations to address harmonization barriers

The survey helped individuate a number of barriers that were common across the three neuroimaging modalities (i.e. MRI, PET-SPECT and EEG). We identified five actions aimed at addressing these barriers from a general perspective.

5.1.1 Develop a Web-based forum for neuroimaging harmonization knowledge sharing

Problem reported by survey: The survey shows that, independent of neuroimaging modality, the community perceives barriers to effectively participate in multicenter neuroimaging neurodegenerative studies (77 % MRI, 61% EEG, and 75% PET-SPECT groups). We found a strong agreement across the neuroimaging experts of MRI, PET-SPECT and EEG in that these barriers could be solved by the implementation of: (1) updated guidelines by expert groups; (2) open-access forums that facilitate exchange of updated and relevant harmonization guidelines & materials, (3) uniform ethical committee and data sharing guidelines, and (4) centralized data storage and analyses facilities.

Recommendation: We suggest an action funded by JPND or JPND and industry partners that (1) promotes the development of updated consensus guidelines for the harmonization of the recording, biomarker extraction, and specific use for clinical applications in neurodegenerative diseases; (2) supports the creation and maintenance of a web-based forum that serves as a centralized repository of harmonization relevant information as well as a portal where people can openly exchange information. We suggest that this becomes an open access resource.

The forum will need funding to support its development and a sustainable model that can allow for keeping it updated involving content curators with expertise. The site and forum would provide updated information such as: harmonization guidelines, pointers to facilities for data storage and analysis, and collection or pointer to relevant neuroimaging biomarker literature. The site and forum would provide a discussion portal for exchanging information about ethical committee guidelines potentially developing also a public template ethical committee document that can be used as reference for multicenter studies.

5.1.2 Develop a standardized registry for multicenter study planning

Problem reported by survey: The survey shows that, regardless of neuroimaging modality, access to and funding for expertise on multicenter implementation issues is often missing or underestimated, especially for acquisition and analysis. The survey reports as urgent the lack of standard operating procedures for acquisition and insufficient funding for administration, expertise and harmonization related costs. This suggests that projects get often funded with insufficient support costs (personnel with expertise in multisite acquisition and data analysis, harmonization costs, data storage and analysis costs). It also suggests that many times, applicants do not anticipate the problem and neither do grant reviewers. Finally, there is a lack of standardized guidelines (e.g. like ethical committees have) for planning multicenter studies. Such guidelines could be helpful to both researchers preparing grant applications and funding agencies when reviewing project proposals.

Recommendation: We suggest the funding of an action aimed at developing a standardized registry or template module, with international consensus, 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. Each item in the registry will have a description for how it will be addressed and the budget cost associated to it. Such a registry could help synchronize the planning needs of researchers and expectations from funding sources. This standardized registry should be made available in the web-based forum proposed in Section 5.1.1.

5.1.3 Harmonization of recommendations

Problem identified: Several EU multicenter harmonization projects are currently active or have recently concluded, including but not limited to: EPAD and AMYPAD (IMI-funded), APGEM (JPND funding), DDI (Norway), Rete-AD (Italy), ICINET (Sweden), CATI (France), PharmaCog (IMI funding), and EU Medical Information Framework (subgroups AD, metabolic disorders) IMI funded. The existence of these parallel efforts raises some questions. How should recommendation efforts be harmonized? How should information of key differences and commonalities between these projects be used effectively for future ones? Sometimes key participants take part in several of these projects and this may facilitate sharing information. However, a more structured integrative approach may be more effective.

Recommendations: We suggest the funding of an action that creates an EU neuroimaging harmonization working group, with representatives of ongoing and recent harmonization projects (MRI, PET-SPECT, EEG), to define criteria that promote constructive interference between projects and are useful for future multicenter studies.

The group could be formed by voluntary representation from EU harmonization projects, with of at most two members per neuroimaging modality, promoting exchange of members every 2 years considering projects that are currently active or that were completed within a time frame of 6 years prior to the membership renewal phase.

The goals of this group could include: (1) maintain an updated registry with results from clinical trials testing imaging biomarkers with a description of the study goals, markers tested, type of ND disease and application (diagnosis, progression, etc.); (2) standardize documentation of specific acquisition (with driving criteria) and analyses procedures, including QA (public analysis pipelines); (3) standardize the reporting of and create an incentive for declaring «lessons learned»; (4) create an updated registry of harmonization efforts that outlines key differences and common aspects of past/ongoing projects; (5) develop advanced statistical methods (multivariate, machine learning, etc.) for harmonizing data which was not acquired in a harmonized way; and (6) contribute to leading periodic training and formation courses/seminars/workshops topics relevant to

the harmonized use of neuroimaging biomarkers in neurodegenerative diseases. Relevant information and documentation would be shared through the web-based forum suggested in Section 5.1.1.

This group may provide support for the design, development and implementation of informatics platforms that facilitate harmonized data recording/analysis in multicenter neuroimaging studies in neurodegenerative diseases, with a perspective of facilitating big data analytic concepts.

5.1.4 Should investments go to central data acquisition facilities?

Survey findings: The survey showed that, regardless of neuroimaging modality, availability of neuroimaging facilities were rated as the least important barriers for participating in multicenter studies. This result could reflect a bias of the survey participants, indicating that most had easy access to imaging resources, despite the fact of representing a highly multidisciplinary group working on highly varied topics.

Recommendation: Based on these results we suggest that broad funding actions aimed at building central neuroimaging facilities for data-acquisition should not be a priority.

5.2 Recommendations for the harmonization of MRI biomarkers

Problems reported by the survey: The MRI acquisition protocols evaluated in the survey were found to be all relevant for early prediction/progression and with different contrast preferences across different ND diseases. However, the survey shows (Q33-Q39) that there are currently insufficient updated harmonization guidelines across these sequences. In particular, with state-of-the-art MRI technology, each one of the sequences currently has a number of cross-vendor harmonization issues. As a result there are currently no SOPs for MRI acquisition and data analysis in relation to specific biomarkers & applications.

Recommendations: We strongly recommend actions to fund the harmonization of multivendor state-of-the-art MRI acquisition & analysis for structural 3D T1, 3D SWI, 3D FLAIR, diffusion MRI, task-free short TR fMRI, 3D pCASL, and quantitative tissue mapping techniques. The action may consider:

- Current interest is in early longitudinal prediction/progression studies, so action emphasis should be on test-retest reproducibility within/across multivendor sites
- Development of standardized phantoms where appropriate
- Harmonization of quantitative automated public analysis pipelines should also include the proposal of automated QA metrics in relation to sequences and biomarkers. QA metrics should be developed that help objectively characterize both raw data quality and derived results at the level of single site as well as the degree of multicenter data harmonization.
- Development of advanced statistical methods (multivariate, machine learning, etc.) for harmonizing retrospective MRI data which was not acquired in a harmonized way.

5.3 Recommendations for the harmonization of PET-SPECT biomarkers

Problems reported by the survey: all four PET and SPECT biomarkers evaluated in the survey (FDG PET, amyloid PET, tau PET and dopaminergic PET/SPECT) were found to be relevant for

early prediction/progression across different ND diseases. However, the survey shows (Q41-44) that there are methodological barriers for their harmonization. An important methodological issue related to image reconstruction was raised: it is unclear how to harmonize iterative reconstruction approaches. This was raised for the three clinically validated and used markers, namely FDG PET, amyloid PET and dopaminergic markers. An understanding of this issue is crucial before the effects of the subsequent image analysis steps are evaluated. Specific problems were also raised with respect to specific biomarkers: among these, the highest priorities were given to the harmonized definition of analysis approaches for FDG PET and dopaminergic markers, standardization across amyloid tracers, and quantification for tau tracers which are considered in an earlier development phase.

Recommendations: We strongly recommend actions to fund the harmonization of image reconstruction parameters across PET and SPECT centers as a first necessary step. The action may consider:

- Developments based on existing standards for multicenter accreditation and harmonization initiative from the European Association of Nuclear Medicine).
- Development of centralized processing and reconstruction utilities combined with data analysis platforms.
- Create public databases with normal and neurodegenerative disease patient data that are uniform with respect to reconstruction and quantification parameters.
- Create centralized analysis platforms for widely available markers lacking standardization of analysis such as FDG and dopaminergic markers.
- Promote open-access initiatives for image reconstruction techniques which can be implemented if vendors grant access to (and specification of) projection data prior to reconstruction.

Finally, it should be noted that harmonization on MRI will be beneficial also for some of the issues raised for PET and SPECT biomarkers, namely all aspects related with definition of ROI and quantification of the impact of brain atrophy.

5.4 Recommendations for the harmonization of EEG biomarkers

Problems reported by the survey: The harmonization of EEG acquisition and calibration, biomarker extraction, and clinical application protocols evaluated in the survey was found to be relevant for early disease prediction/progression. The EEG biomarker with the prominent preference was that of rsEEG rhythms for the most prevalent neurodegenerative diseases such as AD, PD, DLB, and FDT. The results of the survey show that there are currently insufficient updated harmonization guidelines, financial, and human resources for the exploitation of the EEG biomarkers of the neurodegenerative diseases. Nowadays, several alternative procedures and heterogeneous approaches are used for the recording, biomarker extraction, and clinical applications in this field. As a result, there are currently no specific SOPs for clinical research applications.

Another important challenge emerging from the survey results is the lack of interest in the inclusion of EEG biomarkers by clinical principal investigators in the current national and international research studies in neurodegenerative diseases. This challenge is probably due to the general lack of international consensus guidelines encouraging the use of those EEG biomarkers in the clinical trials carried out in neurodegenerative diseases, despite the bulk of recent exciting EEG studies in patients with AD, PD, and DLB (Don Schomer and Lopes da Silva, 2011).

Finally, the EEG WG of this initiative stresses the importance of a methodological problem that could potentially increase the variance and limit the reliability of fMRI and FDG-PET biomarkers obtained in patients staying in resting state condition. There is consensus that during the recording of fMRI and FDG-PET scans, patients can change the state of consciousness from quiet wakefulness to the first stage of sleep through drowsiness. Experimental data are insufficient to understand the implication of this possible change in the consciousness state on the value of the resting sate fMRI and FDG-PET biomarkers of disease status and progression. Future clinical research should clarify this issue. In this sense, the multicenter harmonization of the procedures for the simultaneous recording of heart rate variability and EEG can provide very useful information on the general brain arousal and consciousness state from quiet wakefulness to sleep.

Recommendations: We strongly recommend actions to fund the harmonization of multivendor state-of-the-art EEG acquisition and calibration, biomarker extraction, and clinical use for specific neurodegenerative diseases. Furthermore, future investments should promote the research about how to harmonize the recording of EEG with fMRI and FDG-PET scans for clinical research.

The action may consider:

- Current interest is in early longitudinal prediction/progression studies, so action emphasis should be on test-retest reproducibility within/across multivendor sites;
- Development of devices for the injection of EEG waveforms of defined amplitude and frequency content to test the response of the EEG amplifiers;
- Harmonization of quantitative automated public analyses pipelines should also include the proposal of automated or semi-automated procedures for the detection of the main biological and instrumental artifacts in the EEG data (i.e. eye blinking, saccades, electrocardiographic, head movements, mouth and tongue movements). QA metrics should be developed that help objectively characterize data quality at single site levels and degree of multicenter harmonization.

5.4.1 Call to validate the specificity of EEG derived metrics as potential biomarkers in ND

Nowadays, EEG biomarkers of neurodegenerative diseases are not sufficiently mature to be used in the clinical practice except the diagnosis of DLB (“supportive features”, McKeith et al., 2005) and sporadic CJD (Zerr et al., 2009). However, the results of the survey confirmed the extreme interest of the neuroimaging community for the use of EEG biomarkers in clinical research, in particular for the study of vast populations of elderly subjects at risk of diffuse neurodegenerative disorders as AD, PD, DLB, and FTD.

The present EEG WG agrees with the survey outcome and recommends future investments of JPND for overcoming the above barriers. Keeping in mind the view of the EEG WG and the survey outcome, the investments of the JPND should prioritize both (1) the generation of guidelines about the harmonization of the procedures for recording of EEG and extraction of the EEG biomarkers in multicenter studies carried out in AD, PD, DLB, and FTD and (2) initiatives for cross-validating the specificity of EEG biomarkers, especially for tracking over time (longitudinal studies) the interaction between the pathophysiological and neuroimaging markers of those disease and the “neurophysiological reserve” of brain neural synchronization and coupling in quiet wakefulness (“resting state”) and during attentional and memory tasks in longitudinal studies.

In this line, the EEG WG recommends more research and strict cooperation among the experts of the field in the future. A promising approach may be a JPND call for the creation of a public

repository with shared software tools for the EEG frequency and topographical analyses, as well as simulated and real EEG data for the development of validation experiments and comparison of analysis tools. Ideally, the solutions of the EEG frequency and topographical analyses should be compared at the scalp, modeled dura mater, and modeled cortical sources. The interpretation of the results should critically take into account the opportunities/limitations and the different spatial scale of those analyses in the modeling of the human brain connectome and the oscillatory code of neural activity. The findings of such an initiative may represent a reference for a future public consensus on the use of the different techniques of EEG frequency and topographical analyses and their further application in Clinical Neurophysiology research in neurodegenerative disorders.

Contributors

Working group members

Name[1]	Institute	Country
Jorge Jovicich (Co-PI, MRI WG lead)	University of Trento	Italy
Frederik Barkhof (MRI WG Co-lead)	VU University Medical Center Amsterdam	The Netherlands
Karl Herholz (PET WG lead)	Wolfson Molecular Imaging Centre – University of Manchester	UK
Bart van Berckel (PET WG Co-lead)	VU University Medical Center Amsterdam,	The Netherlands
Christoph H. T. Mulert (EEG WG lead)	University Medical Center Hamburg – Eppendorf	Germany
Claudio Babiloni (EEG WG Co-lead)	University of Rome "La Sapienza"	Italy
Dag Årsland (PET WG)	Stavanger University Hospital	Norway
Rok Berlot (MRI WG)	University Medical Centre Ljubljana	Slovenia
Marie Chupin (MRI WG)	CNRS / ICM Institut du Cerveau et de la Moelle épinière	France
Wilhelmus H. Drinkenburg (EEG WG)	Janssen R&D / J&J Pharmaceutical Companies	Belgium
Alexander Drzezga (PET WG)	University Hospital of Cologne	Germany
Derya Durusu Emek-Savas (EEG WG)	Dokuz Eylul University	Turkey
Tormod Fladby (MRI WG)	Akershus University Hospital / University of Oslo	Norway
Valentina Garibotto (PET WG)	Hôpitaux Universitaires de Gèneve	Switzerland
Marie-Odile Habert (PET WG)	University Pierre & Marie Curie	France
Jakub Hort (PET WG)	Charles University	Czech Republic
Vesna Jelic (EEG WG)	Karolinska University Hospital	Sweden
Clare E. Mackay (MRI WG)	University of Oxford	UK
Jean-François Mangin (PET/MRI WG)	Neurospin	France
Micah M. Murray (EEG WG)	University of Lausanne	Switzerland
Zuzana Nedelska (MRI WG)	St. Anne's University Hospital	Czech Republic
Flavio Nobili (PET WG)	University of Genoa / IRCCS AOU San Martino-IST	Italy
Agneta Nordberg (PET/MRI WG)	Karolinska Institutet	Sweden

Pierre Payoux (PET WG)	University of Toulouse	UK
Rachael I. Scahill (MRI WG)	University College London	UK
Stefan Teipel (MRI WG)	University of Rostock / DZNE	Germany
David L. Thomas (MRI WG)	UCL Institute of Neurology	UK
Eric Westman (MRI WG)	Karolinska Institutet	Sweden
Görsev G. Yener (EEG WG)	Dokuz Eylul University	Turkey
Laura Bonanni (EEG WG)	University G. d'Annunzio di Chieti-Pescara	Italy
Irena Jatro (Project Manager)	University of Trento/IRCCS Fatebenefratelli	Italy
Rosita Haddad (Workshop Coordinator)	University of Geneva	Switzerland
Giovanni B. Frisoni (PI)	University of Geneva	Switzerland

[1] WG: Working Group

Advisory group members

Name	**Institute**	**Country**
Clifford R. Jack	Mayo Clinic, Rochester	USA
William B. Jagust	University of California Berkeley	USA
Leslie Prichep	New York School of Medicine	USA
Chris Rowe	University of Melbourne	Australia
Hiroshi Matsuda	National Center of Neurology and Psychiatry, Tokyo	Japan
Sieske Sikkes	VU University Medical Center, Amsterdam	The Netherlands
Jean François Démonet	Centre Hospitalier Universitaire Vaudois University Hospital, Lausanne	Swizterland

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Appendix 1: Glossary

AD: Alzheimer's Disease

ASL: Arterial Spin Labeling

EEG: Electroencephalography

ERP: Event-related potentials

ERO: Event-related oscillations

fMRI: Functional Magnetic Resonance Imaging

FTD: Fronto Temporal Dementia

HD: Huntington's Disease

LBD: Lewy Body Dementia

MCI: Mild Cognitive Impairment

MRI: Magnetic Resonance Imaging

ND: Neurodegenerative Diseases

PET: Positron Emission Tomography

PCASL: Pseudo Continuous Arterial Spin Labeling

PD: Parkinson's Disease

ROI: Region of interest

rsfMRI: resting-state functional MRI

rsEEG: resting-state EEG

QA/QC: Quality Assurance / Quality Control

QSWI: Quantitative Susceptibility Weighted Imaging

SOPs: Standard Operating Procedures

SPECT: Single Photon Emission Tomography

SRA: Strategic Research Agenda

SUVr: Standardized Uptake Value ratio

SWI: Susceptibility Weighted Imaging

WG: Working Group

Appendix 2: Invitations to survey

1 Alzheimer's Disease Neuroimaging Initiative (ADNI) - MRI Working group
2 Alzheimer's and Parkinson's Disease Network (AD/PD™)
3 Arterial spin labeling Initiative in Dementia (AID)
4 Asian-Oceanian Chapter of the International Federation of Clinical Neurophysiology
5 Austrian Chapter of the International Federation of Clinical Neurophysiology
6 Belgian Chapter of the International Federation of Clinical Neurophysiology
7 Brain Products
8 British Chapter of the International Federation of Clinical Neurophysiology
9 Bulgarian Chapter of the International Federation of Clinical Neurophysiology
10 Croatian Chapter of the International Federation of Clinical Neurophysiology
11 Czech Chapter of the International Federation of Clinical Neurophysiology
12 Danish Chapter of the International Federation of Clinical Neurophysiology
13 Directory Alzeheimer's Disease Centers
14 Dutch Chapter of the International Federation of Clinical Neurophysiology
15 EEG & Clinical Neuroscience Society (ECNS)
16 Egyptian Chapter of the International Federation of Clinical Neurophysiology
17 Estonian Chapter of the International Federation of Clinical Neurophysiology
18 European Association of Nulcear Medicine (EANM)
19 European Chapter of the International Federation of Clinical Neurophysiology
20 European Huntington's disease Network (EURO-HD)
21 European Society of Neuroradiology (ESNR)
22 European Society for Magnetic Resonance in Medicine and Biology (ESRMB)
23 European DLB study group
24 European Alzheimer's Disease Consortium (EADC)
25 European Academy of Neurology (EAN)
26 Finnish Chapter of the International Federation of Clinical Neurophysiology
27 French Chapter of the International Federation of Clinical Neurophysiology
28 French society of nuclear medicine
29 French federation of memory research centres
30 French Society of NeuroRadiology
31 Genetics of Endophenotypes of Neurofunction to Understand Schizophrenia
32 Hellenic Chapter of the International Federation of Clinical Neurophysiology
33 Imaging Neuroinflammation in Neurodegenerative Diseases (INMiND)
34 International Society for Neuroimaging in Psychiatry (ISNIP)
35 International Pharmaco-EEG Society (IPEG)
36 Irish Chapter of the International Federation of Clinical Neurophysiolog
37 International Federation of Clinical Neurophysiology (IFCN)

38 Italian Chapter of the International Federation of Clinical Neurophysiology
39 Italian Neurology Society- Dementia (SINdem)
40 Latin American Brain Mapping Network (LABMAN)
41 Latin American Chapter of the International Federation of Clinical Neurophysiology (LA-IFCN)
42 Luxemburg Chapter of the International Federation of Clinical Neurophysiology
43 Neuroimaging Society in ALS (NiSALS)
44 North American Chapter of the International Federation of Clinical Neurophysiology
45 Oceanian Chapter of the International Federation of Clinical Neurophysiology
46 Pharmacog Consortium
47 Polish Chapter of the International Federation of Clinical Neurophysiology
48 Portuguese Chapter of the International Federation of Clinical Neurophysiology
49 Presidents and Officers of the International Federation of Clinical Neurophysiology
50 Presidents and Officers of the Swiss Chapter of the International Federation of Clinical Neurophysiology
51 Presidents and Officers of the Turkish Chapter of the International Federation of Clinical Neurophysiology
52 President and Officers of the German Chapter of the International Federation of Clinical Neurophysiology
53 Romanian Chapter of the International Federation of Clinical Neurophysiology
54 Russian Chapter of the International Federation of Clinical Neurophysiology
55 Quantitative Imaging Biomarkers Alliance (QIBA)
56 Québec Bio-imaging Network Group (QBIN)
57 Scientific panel on ALS and frontotemporal dementia
58 Slovak Chapter of the International Federation of Clinical Neurophysiology
59 Slovenian Chapter of the International Federation of Clinical Neurophysiology
60 Spanish Chapter of the International Federation of Clinical Neurophysiology
61 Swiss society of nuclear medicine (SGNM)
62 Swiss society of neuroradiology (SGNR)
63 Swiss federation of clinical neuro societies (SFCNS)
64 Swedish Chapter of the International Federation of Clinical Neurophysiology
65 Serbian Chapter of the International Federation of Clinical Neurophysiology
66 The International Society for Brain Electromagnetic Topography (ISBET)

Appendix 3: SRA-NED Survey Questionnaire

SRA-NED Survey
Harmonization of acquisition and processing of Brain Imaging Biomarkers for Neurodegenerative Diseases: A strategic Research Agenda for best-practice guidelines

Survey: Home page

Survey goals

- This survey aims at identifying barriers for the harmonized application of neurodegenerative imaging biomarkers obtained from large-scale multicentric neuroimaging (MRI, PET/SPECT and EEG).
- The results of the survey will be used to develop a proposal of actions (e.g., funding in particular areas) to address these barriers
- This project is funded by the EU Joint Program of Neurodegenerative Diseases
- The survey should take about 10 minutes of your time

Survey outline

1. Background information
2. Barriers for the harmonization of multicentric neuroimaging pathology biomarkers relevant to neurodegenerative disorders
   - High-level barriers for effectively participating in multi/centric neuroimaging studies of neurodegenerative disorder
   - Identification of relevant neuroimaging biomarkers of neurodegenerative
   - disorders Harmonization needs/barriers
3. Final remarks

SRA-NED Survey
Harmonization of acquisition and processing of Brain Imaging Biomarkers for Neurodegenerative Diseases: A strategic Research Agenda for best-practice guidelines

Survey Page 1: Background information

* 1. How did you find out about this survey?

- ◯ Direct email invitation
- ◯ Being part of a European Neuroimaging network
- ◯ Colleagues
- ◯ Other

* 2. What is your function?

- ◯ Neurologist
- ◯ Nuclear medicine physician
- ◯ Geriatrician
- ◯ Engineer
- ◯ Psychiatrist
- ◯ Physicist
- ◯ Radiologist
- ◯ Psychologist
- ◯ Other

* 3. For what type of organization are you working? Multiple choice possible

- ☐ University
- ☐ Teaching hospital
- ☐ Research institute
- ☐ Specialized clinic
- ☐ General practice
- ☐ Industry
- ☐ General hospital
- ☐ Other

* 4. In which country are you working?

* 5. Which one imaging modality are you mostly experienced with?

○ MRI ◐ EEG ○ PET/SPECT

* 6. What type of research are you currently involved in? Multiple choice possible

- [ ] None
- [ ] Non-pharmacological interventions
- [ ] Observational
- [ ] Clinical trials
- [ ] Other

* 7. Which neurodegenerative disorders are you mostly interested in? Multiple choice possible

- [ ] Healthy aging
- [ ] Lewy Boby Disease (LBD)
- [ ] Alzheimer's disease (AD)
- [ ] Creutzfeldt-Jakob disease (CJD)
- [ ] Fronto temporal dementia (FTD)
- [ ] Progressive supranuclear palsy with corticobasal syndrome (PSP/CBS)
- [ ] Parkinson's disease (PD) /Parkinson's disease Dementia (PDD)
- [ ] Multiple System Atrophy (MSA)
- [ ] Huntington's disease (HD)
- [ ] Amyotrophic Lateral Sclerosis (ALS)
- [ ] Other

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Survey Page 2:

Survey Page 2.1 High-level barriers for multicentric MRI neurodegenerative studies

Goal of this section: In this section of the survey we aim at identifying practical high-level barriers that limit the effective participation of center/groups in large-scale multicentric neuroimaging neurodegenerative disorder studies.

You will see pages relevant to the imaging modalities you indicated expertise on in the Background page of the Survey.

* 8. Do you think there are barriers to joining multicentric **MRI** studies of neurodegenerative disease?

◯ Yes ◯ No

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Survey Page 2:

Page 2.1 High-level barriers for multicentric MRI neurodegenerative studies

9. Please score the urgency problem of the following barriers that may prevent the effective participation of a center/group in a multicentric **MRI** neurodegenerative study. Where not answered, we assume the answer is "Don't know".

	Not a problem	Non urgent problem	Urgent problem
Insufficient access to information about the possibility of participating in multicentric studies	○	○	○
Insufficient access to patient population	○	○	○
Insufficient access to clinical resources to interact with patients	○	○	○
Insufficient access to administrative resources (e.g., support for ethical committee, recruiting, etc.)	○	○	○
Insufficient access to imaging facilities	○	○	○
Insufficient access to expertise and resources for the choice of and optimization of image acquisition protocols	○	○	○
Insufficient access to expertise and resources for the optimization of image analyses protocols	○	○	○
Insufficient standard operating procedures for neuroimaging data acquisition	○	○	○
Insufficient access to expertise and resources for the optimization of a local IT and informatics infrastructure	○	○	○
Insufficient access to an IT infrastructure that facilitates the integration and management of the project (data storage, secure data transfer etc.)	○	○	○
Insufficient standard operating procedures for neuroimaging data analysis	○	○	○
Insufficient support for statistical analyses	○	○	○
Bureaucratic hurdles (data protection/privacy, anonymisation, unclear legal situation regarding data transfer with/without patient consent etc.)	○	○	○
Insufficient access to expertise and resources for the interpretation of results	○	○	○
Insufficient funding	○	○	○

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Survey Page 2:

Page 2.1 High-level barriers for multicentric MRI neurodegenerative studies

10. Please indicate additional high-level factors that might be considered as barriers for effectively participating in large-scale multicentric **MRI** neurodegenerative studies

11. Please indicate if the following recommendations could help address some of these high-level barriers. Where not answered, we assume the answer is "Don't know"

	☐	☐
	○	○
Central facilities for data-acquisition	○	○
Central facilities for data analysis	○	○
Central facilities for data upload and storage	☐	☐
Establishing common ethical guidelines on required patient consent for data sharing and rules for making use of publicly available data	○	○

12. Please suggest other recommendations that could help address some of these high level barriers

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Survey page 2:

Survey Page 2.1 High-level barriers for multicentric PET/SPECT neurodegenerative studies

Goal of this section: In this section of the survey we aim at identifying practical high-level barriers that limit the effective participation of center/groups in large-scale multicentric neuroimaging neurodegenerative disorder studies.

You will see pages relevant to the imaging modalities you indicated expertise on in the Background page of the Survey.

* 13. Do you think there are barriers to joining multicentric **PET-SPECT** studies of neurodegenerative disease?

◯ Yes ◯ No

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Survey page 2:

Page 2.1 High-level barriers for multicentric PET/SPECT neurodegenerative studies

14. Please score the urgency problem of the following barriers that may prevent the effective participation of a center/group in a multicentric **PET-SPECT** neurodegenerative study. Where not answered, we assume the answer is "Don't know"

	Not a problem	Non urgent problem	Urgent problem
Insufficient access to information about the possibility of participating in multicentric studies	○	○	○
Insufficient access to patient population	○	○	○
Insufficient access to clinical resources to interact with patients	○	○	○
Insufficient access to administrative resources (e.g., support for ethical committee, recruiting, etc.)	○	○	○
Insufficient access to imaging facilities	○	○	○
Insufficient access to expertise and resources for the choice of and optimization of image acquisition protocols	○	○	○
Insufficient access to expertise and resources for the optimization of image analyses protocols	○	○	○
Insufficient standard operating procedures for neuroimaging data acquisition	○	○	○
Insufficient access to expertise and resources for the optimization of a local IT and informatics infrastructure	○	○	○
Insufficient access to an IT infrastructure that facilitates the integration and management of the project (data storage, secure data transfer etc.)	○	○	○
Insufficient standard operating procedures for neuroimaging data analysis	○	○	○
Insufficient support for statistical analyses	○	○	○
Bureaucratic hurdles (data protection/privacy, anonymisation, unclear legal situation regarding data transfer with/without patient consent etc.)	○	○	○
Insufficient access to expertise and resources for the interpretation of results	○	○	○
Insufficient funding	○	○	○

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Survey page 2:

Page 2.1 High-level barriers for multicentric PET/SPECT neurodegenerative studies

15. Please indicate additional high-level factors that might be considered as barriers for effectively participating in large-scale multicentric **PET-SPECT** neurodegenerative studies

16. Please indicate if the following recommendations could help address some of these high-level barriers. Where not answered, we assume the answer is "Don't know"

	○	○
	○	○
	○	○
	○	○
Central facilities for data upload and storage	○	○
use of publicly available data	○	○

17. Please suggest other recommendations that could help address some of these high level barriers

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Survey page 2:

Survey Page 2.1 High-level barriers for multicentric EEG neurodegenerative studies

Goal of this section: In this section of the survey, we aim at identifying practical high-level barriers that limit the effective participation of center/groups in large-scale multicentric EEG neurodegenerative disorder studies. You will see pages relevant to the imaging modalities you indicated expertise on in the Background page of the Survey.

* 18. Do you think there are barriers to joining multicentric **EEG** studies of neurodegenerative disease?

- ◯ Yes
- ◯ No

19. Please score the urgency problem of the following barriers that may prevent the effective participation of a center/group in a multicentric **EEG** study in patients with neurodegenerative disorders. Where not answered, we assume the answer is "Don't know".

	Not a problem	Non urgent problem	Urgent problem
Insufficient access to information about the possibility of participating in multicentric studies	○	○	○
Insufficient access to patient population	○	○	○
Insufficient access to clinical resources to interact with patients	○	○	○
Insufficient access to administrative resources (e.g., support for ethical committee, recruiting, etc.)	○	○	○
Insufficient access to imaging facilities	○	○	○
Insufficient access to expertise and resources for the choice of and optimization of image acquisition protocols	○	○	○
Insufficient access to expertise and resources for the optimization of image analyses protocols	○	○	○
Insufficient standard operating procedures for neuroimaging data acquisition	○	○	○
Insufficient access to expertise and resources for the optimization of a local IT and informatics infrastructure	○	○	○
Insufficient access to an IT infrastructure that facilitates the integration and management of the project (data storage, secure data transfer etc.)	○	○	○
Insufficient standard operating procedures for neuroimaging data analysis	○	○	○
Insufficient support for statistical analyses	○	○	○
Bureaucratic hurdles (data protection/privacy, anonymisation, unclear legal situation regarding data transfer with/without patient consent etc.)	○	○	○
Insufficient access to expertise and resources for the interpretation of results	○	○	○
Insufficient funding	○	○	○

20. Please indicate additional high-level factors that might be considered as barriers for effectively participating in large-scale multicentric **EEG** neurodegenerative studies

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Survey page 2:

Page 2.1 High-level barriers for multicentric EEG neurodegenerative studies

21. Please indicate if the following recommendations could help address some of these high-level barriers. Where not answered, we assume the answer is "Don't know"

	Yes	No
Institution of a public web-based forum in which clinical and basic researchers can communicate with their peers to discuss and exchange updated information relevant to multi-centric longitudinal studies on neurodegenerative disorders.	◯	◯
Production of an open access WEB-based knowledge platform with documentation about biomarkers for specific modalities as well as other general issues that need special consideration in multi-centric longitudinal studies on neurodegenerative disorders	◯	◯
Central facilities for data-acquisition	◯	◯
Central facilities for data analysis	◯	◯
Central facilities for data upload and storage	◯	◯
Establishing common ethical guidelines on required patient consent for data sharing and rules for making use of publicly available data	◯	◯

22. Please suggest other recommendations that could help address some of these high-level barriers

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Survey Page 2.2 MRI: Prioritizing neuroimaging biomarkers to harmonize

Goal of this section: This part of the survey aims at identifying the most useful neuroimaging biomarkers to be used in future multi-centric longitudinal studies of neurodegenerative disorders such as Alzheimer's Disease (AD), Fronto temporal dementia (FTD), Parkinson's Disease (PD) /Parkinson's Disease Dementia (PDD), Huntington's Disease (HD), Lewy Boby Disease (LBD), Creutzfeldt-Jakob disease (CJD), Progressive supranuclear palsy with corticobasal syndrome (PSP/CBS), Multiple System Atrophy (MSA), Amyotrophic Lateral Sclerosis (ALS).

You will see pages relevant to the imaging modalities you indicated expertise on in the Background page of the Survey.

* 23. Do you think that there is need to prioritize which are the most relevant **MRI** markers to harmonize?

◯ Yes ◯ No

24. Indicate a clinical priority (high/medium/low) for each potential **MRI** biomarker for the relevant neurodegenerative disorder. Cells without an answer will be considered as "Don't know" (default answer on all cells).

Disease acronyms: Alzheimer's Disease (AD), Fronto temporal dementia (FTD), Parkinson's Disease (PD) /Parkinson's Disease Dementia (PDD), Huntington's Disease (HD), Lewy Boby Disease (LBD), Creutzfeldt-Jakob disease (CJD), Progressive supranuclear palsy with corticobasal syndrome (PSP/CBS), Multiple System Atrophy (MSA), Amyotrophic Lateral Sclerosis (ALS).

	AD	PD/PDD	FTD	HD	CJ	PSP/CBS	ALS
Brain atrophy from T1 MRI							
Cerebral microbleeds on T2* or SWI MRI from T2* or SWI MRI							
White matter vascular damage from FLAIR MRI							
Functional connectivity from resting state BOLD fMRI							
Microstructure and structural connectivity from diffusion MRI							
Cerebral perfusion from arterial spin labeling							

25. Please indicate other **MRI** pathology biomarkers that you would recommend, with their relevant neurodegenerative disorder and clinical value.

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Survey Page 2.2 PET/SPECT: Prioritizing neuroimaging biomarkers to harmonize

Goal of this section: This part of the survey aims at identifying the most useful neuroimaging biomarkers to be used in future multi-centric longitudinal studies of neurodegenerative disorders (such as Alzheimer's Disease, Parkinson's Disease and Parkinson's disease dementia, Frontotemporal lobar degenerative disorders, Lewy Body Disease, Huntington's Disease, PSP/CBS, ALS, and Creutzfeldt-Jakob disease). You see pages relevant to the imaging modalities you indicated expertise on in the Background page of the Survey.

* 26. Do you think that there is need to prioritize which are the most relevant **PET/SPECT** markers to harmonize?

◯ Yes ◯ No

27. Indicate a clinical priority (high/medium/low) for each potential **PET/SPECT** biomarker for the relevant neurodegenerative disorder. Cells without an answer will be considered as "Don't know" (default answer on all cells).

Disease acronyms: Alzheimer's Disease (AD), Fronto temporal dementia (FTD), Parkinson's Disease (PD) /Parkinson's Disease Dementia (PDD), Huntington's Disease (HD), Lewy Boby Disease (LBD), Creutzfeldt-Jakob disease (CJD), Progressive supranuclear palsy with corticobasal syndrome (PSP/CBS), Multiple System Atrophy (MSA), Amyotrophic Lateral Sclerosis (ALS).

	AD	PD	DLB	FTD	HD	CJ	PSP/CBS	ALS
FDG PET – glucose								
Amyloid PET								
Tau PET								
Dopaminergic PET / SPECT								

28. Please indicate other **PET/SPECT** pathology biomarkers that you would recommend, with their relevant neurodegenerative disorder and clinical value.

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Survey Page 2.2 EEG: Prioritizing neuroimaging biomarkers to harmonize

Goal of this section: This part of the survey aims at identifying the most useful neuroimaging biomarkers to be used in future multi-centric longitudinal studies of neurodegenerative disorders (such as Alzheimer's Disease, Parkinson's Disease and Parkinson's disease dementia, Frontotemporal lobar degenerative disorders, Lewy Body Disease, Huntington's Disease, PSP/CBS, ALS, and Creutzfeldt-Jakob disease). You see pages relevant to the imaging modalities you indicated expertise on in the Background page of the Survey.

* 29. Do you think that there is need to prioritize which are the most relevant **EEG** markers to harmonize?

◯ Yes ◯ No

30. Indicate a clinical priority (high/medium/low) for each potential **EEG** biomarker for the relevant neurodegenerative disorder. Cells without an answer will be considered as "Don't know" (default answer on all cells).

Disease acronyms: Alzheimer's Disease (AD), Fronto temporal dementia (FTD), Parkinson's Disease (PD) /Parkinson's Disease Dementia (PDD), Huntington's Disease (HD), Lewy Boby Disease (LBD), Creutzfeldt-Jakob disease (CJD), Progressive supranuclear palsy with corticobasal syndrome (PSP/CBS), Multiple System Atrophy (MSA), Amyotrophic Lateral Sclerosis (ALS).

	AD	PD	DLB	FTD	HD	CJD	PSP/CBS	ALS
rsEEG[1]								
ERP[2]								
ERO[3]								

1 Resting state EEG: eyes closed (delta, theta, alpha, beta waveforms

2 Event-related potentials (ERP, P3)

3 Event-related oscillations (ERO)

31. Please indicate other **EEG** pathology biomarkers that you would recommend, with their relevant neurodegenerative disorder and clinical value.

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Survey Page 2.3 MRI: Biomarker harmonization needs or barriers

This part of the survey aims at identifying specific harmonization needs for different neuroimaging pathology biomarkers of neurodegenerative disorders. You see pages relevant to the imaging modalities you indicated expertise on in the Background page of the Survey. As guideline, when suggesting harmonization needs you may consider including factors such as the following ones, which you are also welcome to further specify:

- **Subject selection criteria and preparation**
- **Imaging data acquisition**
- **Peripheral data acquisition (non-imaging);**
- **Cognitive stimulation**
- **Data quality assurance**
- **Data processing**
- **Data sharing (raw data, processed data)**
- **Data interpretation**
- **Education & training of personnel involved in data acquisition**
- **Education & training of personnel involved in result interpretation/analysisPlus other factors you may want to add.**

* 32. Which general methodological barriers do you consider relevant for the harmonization of MRI biomarkers obtained from multicentre studies?

- ☐ Unclear target measures, data analysis and acquisition
- ☐ Unclear MRI protocol based on time constraints and population
- ☐ Unclear quality control guidelines during acquisition to decide on repeated scans/exclusions
- ☐ Lack of central quality control post acquisition
- ☐ Other

33. Which specific multicentre methodological barriers are relevant for the harmonization of the biomarkers listed in the table of section 2.2 in the survey?

- Brain atrophy from T1

- [ ] Multivendor online head motion correction effects on brain morphometry
- [ ] Histology validation studies of automated and manual segmentation methods
- [ ] Multivendor multispectral MR protocols effects on brain morphometry
- [ ] Evaluating shape analysis tools based on free and paid-for software tools
- [ ] Retrospective measures of head motion and their effects on the final metrics
- [ ] Other

34. - Cerebral microbleeds on T2* or SWI MRI from T2* or SWI MRI.

35. - White matter vascular damage from FLAIR MRI.

36. - Functional connectivity from resting state BOLD fMRI.

37. - Microstructure and structural from diffusion MRI.

38. - Cerebral perfusion from arterial spin labeling MRI.

39. Please list other MRI biomarkers you think are important to include, with barriers for their harmonization in multicentric studies.

40. Which facilitators are needed for the harmonization of MRI research?

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Survey Page 2.3 PET/SPECT: Biomarker harmonization needs or barriers

This part of the survey aims at identifying specific harmonization needs for different neuroimaging pathology biomarkers of neurodegenerative disorders. You see pages relevant to the imaging modalities you indicated expertise on in the Background page of the Survey. As guideline, when suggesting harmonization needs you may consider including factors such as the following ones, which you are also welcome to further specify:

- **Subject selection criteria and preparation**
- **Imaging data acquisition**
- **Peripheral data acquisition (non-imaging);**
- **Cognitive stimulation**
- **Data quality assurance**
- **Data processing**
- **Data sharing (raw data, processed data)**
- **Data interpretation**
- **Education & training of personnel involved in data acquisition**
- **Education & training of personnel involved in result interpretation/analysisPlus other factors you may want to add.**

* 41. Which methodological barriers are relevant for the harmonization of biomarkers derived from:

- FDG-PET?

- [ ] Analyses tools
- [ ] Patient injection protocol: eyes open versus eyes closed during experiment
- [ ] Acquisition duration and time-interval between injection and acquisition
- [ ] Image co registrations between CT and PET scans
- [ ] Head movement artefacts correction
- [ ] Other
- [ ] Image reconstruction protocol: iterative/FBP
- [ ] Semi quantification tools
- [ ] Definition of normal controls
- [ ] Missing public brain bank of FDG-PET healthy controls coming from several centers
- [ ] Harmonization in the reference region selection

* 42. - Amyloid PET?

- [ ] Standardization across tracers
- [ ] Reconstruction protocol: iterative/FBP
- [ ] Harmonization of criteria used for visual readings across vendors and nuclear medicine physicians.
- [ ] ROI selection for SUVr computation (atlas, MRI-based, etc.)
- [ ] Analytical strategies proposed by the different vendors
- [ ] Acquisition time points
- [ ] Movement artifacts
- [ ] Handling of atrophy hampering interpretation of cortical tracer uptake
- [ ] Reference region
- [ ] Use of kinetic parameters (distribution volumes, binding potentials)
- [ ] Need for other metrics
- [ ] Other

* 43. - Tau PET?

- Affinity profile of different tracers for different isoforms
- Quantification
- Other
- Tracer uptake in health trols (mesial temporal)
- Unspecific tracer uptake in basal ganglia/brainstem Reference region

* 44. - Dopaminergic PET/SPECT?

- Comparability of PET and SPECT approaches
- Missing public brain bank of Dopaminergic PET/SPECT healthy controls coming from several centers
- Other
- Analysis tools: Visual vs. semi-quantitative
- Reconstruction protocol: iterative/FBP

45. Please list other PET/SPECT biomarkers you think are important to include with barriers for their harmonization.

46. Which facilitators are needed for the harmonization of PET/SPECT research?

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Survey Page 2.3 EEG: Biomarker harmonization needs or barriers

This part of the survey aims at identifying specific harmonization needs for different neuroimaging pathology biomarkers of neurodegenerative disorders. You see pages relevant to the imaging modalities you indicated expertise on in the Background page of the Survey. As guideline, when suggesting harmonization needs you may consider including factors such as the following ones, which you are also welcome to further specify:

- **Subject selection criteria and preparation**
- **Imaging data acquisition**
- **Peripheral data acquisition (non-imaging);**
- **Cognitive stimulation**
- **Data quality assurance**
- **Data processing**
- **Data sharing (raw data, processed data)**
- **Data interpretation**
- **Education & training of personnel involved in data acquisition**
- **Education & training of personnel involved in result interpretation/analysisPlus other factors you may want to add.**

* 47. Which general methodological barriers are relevant for the harmonization of biomarkers derived from: Resting state EEG

- [ ] Harmonization with state-of-the art multivendor
- [ ] Harmonization of non-linear indexes
- [ ] Harmonization of high-resolution EEG recordings
- [ ] Other
- [ ] Harmonization of automated removal of ocular, muscular, and EKG artefacts
- [ ] Standardization of spectral EEG (source) analysis

48. Please list other EEG biomarkers you think are important to include with barriers for their harmonization.

- ○
- ○
- ○

49. Which facilitators are needed for the harmonization of EEG research?

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Survey page 3: Final remarks

50. Which perspectives, needs and barriers do you see for combining methods, e.g.

integration of MRI, PET and/or EEG?

51. Any additional comments concerning this questionnaire please enter them here.

52. Any additional general comments concerning this project please enter them here.