EMRP Call 2011 - Health, SI Broader Scope & New Technologies

Selected Research Topic number: **SRT-h05**
Version: 1.0

Title: Metrology for neurodegenerative disorders

Abstract

The prevalence of neurodegenerative disorders, such as Alzheimer's disease, is increasing rapidly. The disorders cause an impaired quality of life for suffers and profound social and economic burdens. Whilst there is an arsenal of neuropsychological tests and measures that indicate neurodegenerative disorders once their symptoms are manifest, accurate and reliable measurement parameters for early stage diagnoses and therapeutic monitoring of neurodegenerative disorders are lacking.

A metrological infrastructure enabling high-precision measurements and correlations of the key parameters reflecting neurodegenerative disorders is urgently needed. Many neurodegenerative disorders result from progressive neurodegenerative processes that appear to be related at the sub-cellular level. Therefore, the identification of similarities in parameters such as morphometry, amyloid-β peptide, and other specific biomarkers could be essential for achieving robust, early stage diagnosis.

Conformity with the Work Programme

This Call for JRPs conforms to the EMRP Outline 2008, section on "Grand Challenges" related to Health on pages 7 and 8 and in the sections on pages 13, 22, 40 and 41.

Keywords

neurodegeneration, Alzheimer's disease, dementia, morphometry, MR spectroscopy, amyloid-β peptide, P-tau, MRI

Background to the Metrological Challenges

The ever-extending life span of modern societies has resulted in a tremendous increase in the incidence of diseases caused by degenerative alterations of the brain. Neurodegenerative disorders are currently the fourth most significant healthcare issue facing the world, but by 2040, the World Health Organistaion predicts that neurodegenerative disorders will have overtaken cancer to become the second leading cause of death and with it a significant associated socio-economic cost burden.

Several European Directives also highlight the need to address neurodegenerative disorders:

- Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the regions. 'Action plan on information and communication technologies and ageing'. Brussels, 14 June 2007, COM (2007) 332 final [1]
- Council of the European Union. 'Conclusions on public health strategies to combat neuro-degenerative diseases associated with ageing, especially Alzheimer's disease'. 2916th Employment, Social policy, Health and Consumer affairs Council meeting, Brussels, 16 December 2008 [2]
- Communication from the Commission to the European Parliament and the Council. 'A European initiative on Alzheimer's disease and other dementias'. Brussels, 22 July 2009, COM (2009) 308 final [3]
- Proposal for a Council Recommendation on joint programming of research activities. 'Measures to combat neurodegenerative diseases, especially Alzheimer's disease'. Brussels, 22 July 2009, COM (2009) 379 final [4]

Aside from neuropsychological and cognitive testing, structural brain imaging together with cerebrospinal fluid protein analysis (i.e. amyloid-β peptide (Aβ) and tau protein assays) currently represents the gold standard in early dementia diagnosis, however specificity remains below 80 %. Disease specific effects have

also been detected using electro- and magnetoencephalography. Sadly, though the most reliable diagnosis of the neurodegenerative disorder, Alzheimer's disease, is still post-mortem analysis of *ex-vivo* specimens.

Alzheimer's Disease is characterised by the appearance of senile plaques (i.e. amyloid fibrils) in the brain. The plaques usually consist of 39-42 peptide fragments known collectively as amyloid-β peptide (Aβ). Most contemporary evidence states that Alzheimer's disease is caused by diffusible misfolded proteins (i.e. Aβ-derived diffusible ligands) perturbing normal synaptic function and thereby causing memory deficits. Although much research has been conducted to confirm that these biomarkers can be detected in biological fluids, results are not consistent between different studies and cannot support clinical trials. With magnetic resonance techniques (MRI and MRS), animal studies at 7 T and above have detected amyloid plaques both with (gadolinium and 19F-labeled contrast agents) and without contrast agents, however *in vivo* MRI studies in human brain have not been successful. This is due to insufficient sensitivity of the magnetic fields ≤ 3 T and the fact that contrast agent spatial resolution is presently c.0.5 mm whilst typical plaque dimensions are 2-200 μm.

While morphological assessment by MRI can provide measurements of brain atrophy, atrophy is likely to reflect the later stages of neurodegenerative disorders, therefore for curative treatment, therapies need to target processes earlier in the disease stages. Newer MRI methods available, include T1, T2-, T2*-, diffusion-, magnetization transfer and susceptibility-weighted MRI. These quantitative MRI techniques are sensitive to changes in local biophysical properties of tissue and could be used to detect early pathological changes. For example, T2, T2* and susceptibility-weighted MRI is particularly sensitive to the presence of iron, and could aid in the determination of the role of iron in neurodegeneration. *In vivo* MRS could also be used as a non-invasive biochemical tool to determine changes in neurochemistry, including that due to mitochondrial dysfunction in neurodegenerative disorders. Indeed, it may be that a range of MRI and MRS techniques needs to be employed to assess different aspects of early stage disease pathology.

Further to this, over the past decade new and novel imaging techniques have appeared, such as Driven Equilibrium Single Pulse Observation of T1 and T2 (DESPOT 1 and DESPOT 2). These techniques do not suffer from time and resolution constraints of conventional imaging methods and permit the acquisition of whole-brain maps in under 40 mins on a clinical 3T MRI scanner. This represents an increase in spatial resolution of a factor of more than 125 and could provide the improved sensitivity and specificity required for the early detection of neurodegenerative disorder related tissue changes.

Scientific and Technological Objectives

Proposers should address the objectives stated below, which are based on the PRT submissions. Proposers may identify amendments to the objectives or choose to address a subset of them in order to maximise the overall impact, or address budgetary or scientific / technical constraints, but the reasons for this should be clearly stated in the JRP-Protocol.

The overall objective of the SRT is to provide a comprehensive set of measurements for the diagnosis of Alzheimer's disease and other neurodegenerative disorders at various disease stages.

Techniques such as magnetic resonance imaging (MRI) and spectroscopy (MRS), immunoassays, mass spectrometry and neutron activation analysis (NAA) should be systematically applied to pre-clinical models, brain bank samples and patients. As appropriate, methods such as PET and CT may also be considered. When combined, such methods could be powerful tools for early diagnosis, monitoring disease progression, risk assessment and therapy follow-up of dementia and related disorders.

The specific objectives shall include:

1. To develop metrology for morphometrics as well as quantitative concentration ranges for selected metabolites in the brain structures involved in dementias using high and ultrahigh field MRI and MRS. Morphometric resolution should be in the submillimeter range and the uncertainty for in vivo metabolite concentrations reduced to <10 %.
2. To establish quantitative methods down to nanomolar levels for the detection and aggregation monitoring of Aβ-derived diffusible ligands and P-tau protein.
3. To develop methodologies for in vitro metabolomics, metallomics, proteomic analyses and quantification of trace element levels in brain tissue by using mass spectrometry, x-ray fluorescence (XRF) or NAA methods.

The analytes under consideration should be carefully selected and prioritised according to clinical relevance and the recommendations of relevant stakeholders.

These objectives will require large-scale approaches that are beyond the capabilities of single National Metrology Institutes and Designated Institutes, and it is expected that multidisciplinary teams will be required. To enhance the impact of the research, the involvement of the appropriate user community such as medical practitioners and industry is strongly recommended, both prior to and during methodology development.

Proposers should establish the current state of the art, and explain how their proposed project goes beyond this.

The total eligible cost of any proposal received for this SRT is expected to be around the 2.7 M€ guideline for proposals in this call.

Potential Impact

Proposals must demonstrate adequate and appropriate participation/links to the "end user" community. This may be through the inclusion of unfunded JRP partners or collaborators, or by including links to industrial/policy advisory committees, standards committees or other bodies. Evidence of support from the "end user" community (eg letters of support) is encouraged.

You should detail other impacts of your proposed JRP as detailed in the document "Guide 4: Writing a Joint Research Project"

You should detail how your JRP results are going to:

- feed into the development of urgent documentary standards through appropriate standards bodies
- transfer knowledge to the medical community.

You should also detail how your approach to realising the objectives will further the aim of the EMRP to develop a coherent approach at the European level in the field of metrology. Specifically the opportunities for:

- improvement of the efficiency of use of available resources to better meet metrological needs and to assure the traceability of national standards
- the metrology capacity of Member States and countries associated with the Seventh Framework Programme whose metrology programmes are at an early stage of development to be increased
- outside researchers & research organisations other than NMIs and DIs to be involved in the work

Time-scale

The project should be of up to 3 years duration.

Additional information

The references were provided by PRT submitters; proposers should therefore establish the relevance of any references.

[1] Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the regions. 'Action plan on information and communication technologies and ageing'. Brussels, 14 June 2007, COM (2007) 332 final

[2] Council of the European Union. 'Conclusions on public health strategies to combat neuro-degenerative diseases associated with ageing, especially Alzheimer's disease'. 2916th Employment, Social policy, Health and Consumer affairs Council meeting, Brussels, 16 December 2008

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