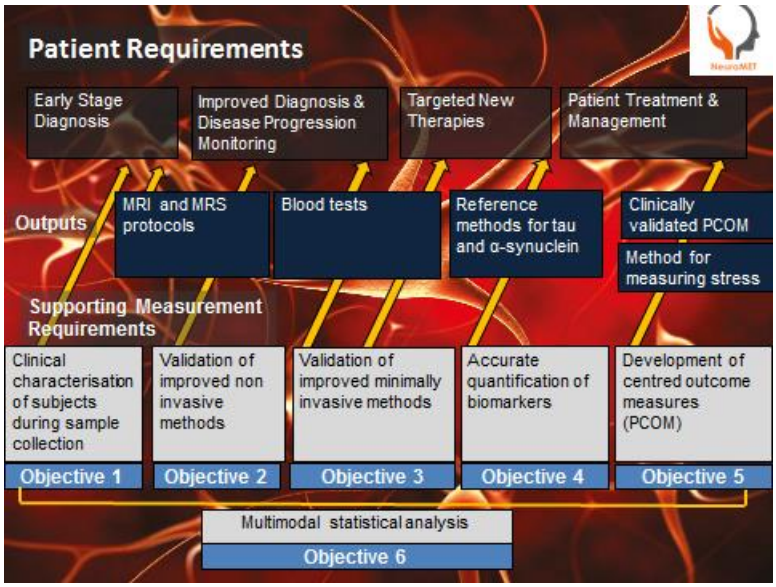
Publishable Summary for 15HLT04 NeuroMET
Innovative measurements for improved diagnosis and management of neurodegenerative diseases

Overview

Neurodegeneration is an incurable, debilitating process which presents a growing global challenge due to the increasingly ageing population. Alzheimer's disease (AD) and Parkinson's disease (PD) are the two most common neurodegenerative diseases (NDD). Both involve the build up of specific proteins in the brain and subsequent neurodegeneration leading to physical and mental impairment including dementia. Currently, there are no clinically validated, minimally invasive diagnostic tools which allow the early diagnosis and/or monitoring of disease progression in AD and PD patients and available therapeutics only offer transient symptomatic relief. This project aimed to develop reference measurement systems to support the major NDD patient needs including less invasive, more accurate diagnostic measurement, and improved treatment and anxiety monitoring. Measurement comparability, underpinned by SI traceability and uncertainty analysis, is an unmet requirement for regulatory approval of NDD biomarkers, patient centred outcome measures (PCOM), clinical thresholds and new therapeutic drugs. Therefore, the reference methods developed within the NeuroMET project, to support the production of calibrators and improve measurement comparability of established biomarkers in the NDD area will contribute significantly to advancement in the field. Furthermore the uptake of the developed PCOM will have a significant positive impact on both NDD patient and clinical trial assessments.

Need

The "Implementation report on the Commission Communication on a European initiative on Alzheimer's disease and other dementias" (2014) highlighted the importance of early diagnosis in NDD. Established biomarkers of AD from cerebrospinal fluid (CSF) have been used to differentiate between subjects with mild cognitive impairment (MCI) who have progressed to AD and those MCI patients who have not. However, the lumbar puncture procedure for CSF sample collection is time consuming, invasive and therefore limited in terms of the possibility of widespread application for early AD diagnosis. Furthermore, although AD biomarker detection from less invasive diagnostic procedures such as blood samples and neuroimaging (i.e. Magnetic Resonance Imaging (MRI)) has significant advantages, the limits in measurement sensitivity and high measurement variability of recognised and novel biomarkers for AD and PD have constrained the development of clinical thresholds for NDD early diagnosis. Major impacts of NDD, particularly the decline in cognitive function, as well as increase in psychological symptoms (agitation, anxiety, etc.), can be captured in PCOMs. These PCOMs need to be correlated with the various biomarkers and objectively monitored and managed. The NeuroMET project addressed these needs for measurement improvement and standardisation of NDD non- and minimally invasive biomarker measurements to develop PCOMs, which



were then validated by laboratory data, as well as by establishing reference measurement procedures to underpin measurement comparability. These are fundamental requirements both for the reliable development of minimally invasive early diagnostic and patient management procedures and also to support therapeutic discovery.

Objectives

This project combined the expertise of metrology laboratories together with clinicians and academics, in order to (i) overcome measurement issues currently constraining clinical innovation and uptake in NDD diagnosis and treatment, and to (ii) provide routes to directly translate research outputs into the clinic. Unusually for a metrology project, patients played a central role in the NeuroMET project, thus ensuring that metrology was correlated to patients' clinical status and is relevant to patient and clinical measurement requirements. The specific objectives of the project were :

1. **To establish patient cohorts** representative of AD (including MCI due to AD and dementia due to AD), PD neurodegeneration and a matched group of healthy control subjects.
2. **To develop and validate non-invasive magnetic resonance imaging (MRI) approaches** for *in vivo* characterisation of AD and MCI patients and healthy matched controls.
3. **To develop minimally invasive methods for early diagnosis and drug therapeutic monitoring**. This will be achieved by developing and applying conventional and innovative methods for the quantification of recognised and emerging biomarkers present in of the AD and PD patient cohorts.
4. **To improve NDD biomarker measurement comparability through the establishment of traceability chains**. This will be achieved through the development of reference methods and reference materials for measurements, in CSF, of the established AD marker, tau protein (tau), and the most promising PD marker, α-synuclein.
5. **To determine and characterise patient-centred outcome measures (PCOM) for NDD**. This will be achieved by developing improved clinical assessment questionnaires focused on the decline in motor and cognitive functions and increases in behavioural, communicative and psychological symptoms (e.g. agitation) in AD patients. For PD patients, this will be also supported by the validation of a novel immunoassay for the measurement of the stress biomarker cortisol, with the ultimate aim beyond this project of using this immunoassay to improve the assessment of the efficacy of therapeutic interventions administered to reduce anxiety.
6. **To develop, validate and verify multimodal statistical analyses** used to correlate NDD patient health status with AD biomarker and MRI data. These novel analyses will identify the most promising tools for NDD early diagnosis and disease progression monitoring, aiming for better resolution in detecting the early signs of disease and reducing the number of biomarker studies required (e.g. in cases where biomarker studies are especially challenging).
7. **To form a NeuroMet Stakeholder Network** in Europe for neurodegenerative disease diagnosis and disease progression monitoring. The NeuroMet Stakeholder Network will include the consortium (and NMI partners) and at least 10 relevant NDD stakeholders including clinicians, instrument manufacturers and national and international organisations to facilitate the uptake of the technologies and measurement infrastructure developed by the project and to ensure that patient and measurement needs are met.

Progress beyond the state of the art

The performance of a number of minimally/non-invasive approaches has been investigated and used with the NeuroMET project patient cohorts to enable disease state related differentiation for comparative experiments through validated statistical analysis:

Proton MR spectroscopy (7 T) and imaging was used to provide both metabolic and anatomical information with the final aim to improve sensitivity, resolution and delineation for volume quantification and to define transferrable protocols to 3 T scanners.

Open platform immunodetection array technologies were optimised for the quantification of recognised AD and PD protein biomarkers in blood. The methods developed were applied to clinical samples to improve sensitivity

and reduce measurement uncertainty with the final goal to identify stress and diagnostic biomarker trends in the patient cohort samples.

Digital polymerase chain reaction (dPCR), was evaluated as a putative method for accurate quantification of candidate AD microRNA (miRNA) biomarkers in blood samples and applied to clinical samples.

Liquid chromatography–mass spectrometry (LC-MS) methods were developed for monitoring the PD pathological protein α-synuclein in CSF to address challenges associated with immunoassay measurements of this recognised target for pharmaceuticals. Furthermore a method for quantification of α-synuclein in saliva was developed to exploit the potential use of this non-invasive marker for early diagnosis of PD and AD.

Significant progress has been made towards establishing SI traceability of NDD biomarker measurements. Reference methods for tau (AD biomarker) and α-synuclein are being validated and calibration approaches are being implemented for tau to facilitate immunoassay measurement comparability.

The application of novel statistical and metrological approaches to the integration of data from the NeuroMET biomarker approaches into a PCOM of NDD has been a key innovation for the project testing the concept of 3rd generation standards (beyond traditional products or management standards) by associating the results from the analysis of clinical biomarkers with the results of clinical assessments.

Overall the innovative multidisciplinary approach, developed within the NeuroMET project, has improved the state of the art for NDD by increasing accuracy in diagnosis, facilitating the development of new therapeutics and enabling more effective treatment.

Results

1. *To establish patient cohorts representative of AD (including MCI due to AD and dementia due to AD), PD neurodegeneration and a matched group of healthy control subjects.*

Two patient cohorts were established: cohort 1 (Healthy matched Controls (HC), Mild Cognitive Impairment (MCI), and AD) was used to develop validated PCOMs for AD and MCI patients through MRI and magnetic resonance spectroscopy (MRS), protein, microRNA and statistical analysis; cohort 2 (HC, AD and PD) was used to assess cortisol as a potential marker for stress in PD and AD patients.

MRI and MRS on a 7 T scanner were carried out on all patients from cohort 1, and CSF and blood samples were distributed to the project partners for immunoassay and dPCR analysis of biomarkers. The cognitive assessment data from cohort 1, the MRI, MRS (objective 2) and fluid biomarker data (objective 3) were also collated for statistical analysis and the development of Construct Specification Equations (CSE) in objective 6. In addition, blood samples from patients from cohort 2 were analysed by immunoassay for free and total cortisol as markers of stress (objective 5). The data from objective 1 on cognitive assessments were then used in objectives 5 and 6 to input into the development of a Memory Metric (objective 5) and in the mathematical model (objective 6)

2. *To develop and validate non-invasive MRI approaches for in vivo characterisation of AD and MCI patients and healthy matched controls.*

MRI and MRS scan parameters were optimised on a 7 T MR system and protocols were established to be applied *in-vivo* on the patients from cohort 1. Each *in vivo* MR measurement consisted of three major sections: 1) structural or “morphometric” measurements, in order to assess structural information on each individual participant’s brain structure and anatomy; 2) MRS measurements, to measure concentrations of neurometabolites within the brain tissue of participants; and 3) resting-state functional MRI, to extract information on functional connectivity within the participant’s brains.

The most promising MR-derived biomarkers for AD identified within this project underpin the findings from earlier studies on AD. These include the GM volume adjusted for the total intracranial volume, the average cortical thickness of the brain, the volumes of the left and right hippocampus, and the left and right posterior cingulate gyrus. Furthermore, the volumes of the left and right putamen appear to differentiate between HC and MCI subjects with increased accuracy compared to other volumes of subcortical structures.

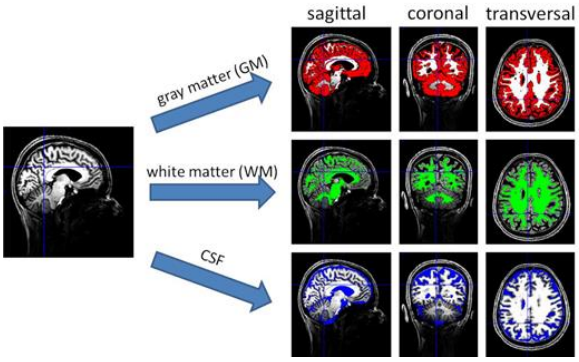


Figure 1 Anatomical Images are being automatically segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF), and the respective volumes are calculated.

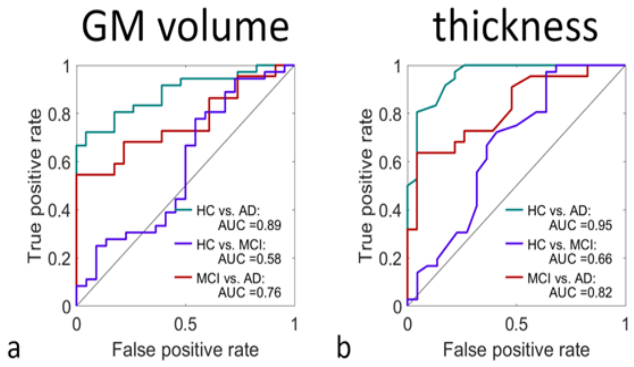


Figure 2 Receiver Operating Characteristics (ROCs) for the gray matter volume (GM volume) and the cortical thickness as differentiator between HC and AD patients in green, HC and MCI in red and MCI and AD in blue

Although the project's findings supported some of those from earlier studies, the results from earlier MRS studies, claiming an alteration of myo-inositol over the course of the progression of AD could not be confirmed within the NeuroMET project. However, alterations were observed in the concentrations of N- acetyl-aspartate, (as per other studies), and in concentrations of γ-amino butyric acid and glutamate. Further work on these findings will be carried out through longitudinal studies in the follow-on project 18HLT09 NeuroMET2.

3. *To develop minimally invasive methods for early diagnosis and drug therapeutic monitoring. This will be achieved by developing and applying conventional and innovative methods for the quantification of recognised and emerging biomarkers present in samples of the AD and PD patient cohorts.*

Nine proteins and miRNA biomarkers were selected by the consortium and in consultation with stakeholders as the most promising NDD biomarkers in plasma. They were Aβ40, Aβ42, t-tau, neurofilament light chain (NFL), α- synuclein, cortisol, Let-7g-5p, hsa-miR-15a-5p, hsa-miR-34a.

Aβ40, Aβ42, t-tau, NFL, cortisol and α-synuclein were measured in both CSF and plasma samples from cohort 1 and the data was used for the validation of cognitive assessments. In addition, a novel generic standard additions approach to overcome matrix effects associated with immunoassay measurements was developed and used for the detection of Aβ40 and Aβ42 peptides[1]. This method was used to measure the Aβ peptides within the plasma samples from cohort 1, alongside commercially available methods for quantifying the selected protein biomarkers in plasma and CSF samples. The data generated was used in objectives 6 to develop and validate multimodal mathematical model for correlation of health status, cognitive assessments and AD biomarkers.

A method for miRNA extraction and dPCR quantification was also developed by the NeuroMET project and used on the samples from cohort 1. Preliminary results obtained with synthetic miRNAs were promising, showing good linearity and limit of detection (less than 5 ng DNA). Results with the clinical blood samples from cohort 1 also showed a very good reproducibility and uncertainties of 15 %. But despite the promise shown with the method no clear correlation between patients' diagnoses was observed with the miRNA biomarkers investigated.

4. *To improve NDD biomarker measurement comparability through the establishment of traceability chains. This will be achieved through the development of reference methods and reference materials for measurements, in CSF, of the established AD marker, tau protein (tau), and the most promising PD marker, α-synuclein.*

Significant progress was made by the NeuroMET project towards the development of a total-tau (t-tau) and a α-synuclein reference measurement procedure (RMP) with traceability to the SI. However, validation of these RMPs could not be completed within the timeframe of this project and so will be continued in the follow-on project 18HLT09 NeuroMET2.

Recombinant t-tau 441 and the synthetic peptide GAAPPGQK, were SI traceably quantified using amino acid analysis, and their suitability as primary calibrators was evaluated for the quantification of t-tau in CSF. Increased variability was observed when using the synthetic peptide as an internal standard and therefore only recombinant t-tau 441 was selected for futher method development. A LC-MS method based on parallel reaction monitoring experiments was developed for the analysis of the peptides obtained after protein precipitation, solid phase extraction and tryptic digestion.

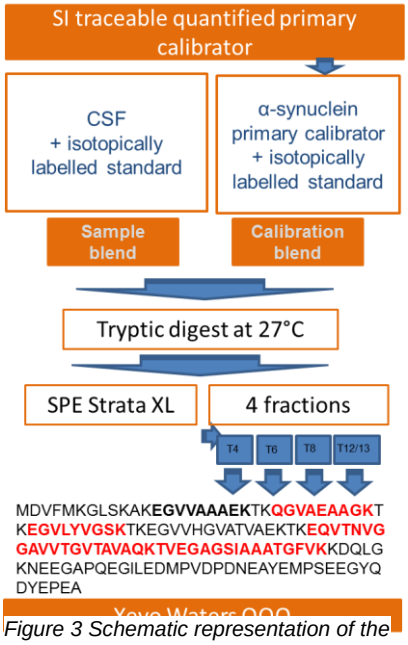


Figure 3 Schematic representation of the LC-MS method and potential reference measurement procedure for quantification of alpha-synuclein

To evaluate the potential of the LC-MS method to be used as a RMP for standardisation of t-tau measurements as well as the commutability of potential tau certified reference materials with values assigned by using the RMP; three CSF pools with low, medium and high values of t- tau 441 were prepared and SI traceably quantified by using the NeuroMET RMP. The preliminary results are promising and the analysis of 40 additional samples will be carried out in the follow on project 18HLT09 NeuroMET2.

An SI traceable LC-MS reference method was also developed for quantification of α- synuclein in CSF. Recombinant α-synuclein was prepared, purified, and SI traceably quantified by using three signature peptides and amino acid analysis. The primary calibrator was aliquoted and preliminary homogeneity studies were carried out. Results showed homogeneity (within 5 %) of the SI traceable quantified aliquots and when those aliquots were used for further fresh dilutions. A method for quantification of α- synuclein based on tryptic digestion, solid phase fractionation, and capillary-LC-MS experiments was also developed and validated. The limit of detection for this method was 0.5 ng/ml and the uncertainty was 12 %.

5. *To determine and characterise PCOM for NDD. This will be achieved by developing improved clinical assessment questionnaires focused on the decline in motor and cognitive functions and increases in behavioural, communicative and psychological symptoms in AD patients. For PD patients, this will be also supported by the validation of a novel immunoassay for the measurement of the stress biomarker cortisol.*

Currently, there exist many PCOMs of cognitive performance (e.g. memory tests), which are commonly used both in clinical practice and clinical research. But these can neither claim accuracy and sensitivity to distinguish between patients (especially in early stage disease) nor are they metrologically proven. In this project, several studies were carried out on (i) the extensive battery of legacy cognitive performance PCOMs applied to the participants in cohort 1, (ii) published data, and (iii) data obtained from the Gothenburg MCI study. The process of quality assured measurement of cognitive performance was performed through: (i) applying the Rasch Model Theory on collective prospective patient PCOM data; (ii) development of a prototype NeuroMET Memory Metric based on legacy cognitive PCOMs; (iii) formulation of construct specification equations (CSEs) to link cognitive assessment outcomes to metrological concepts.

Studies were performed on the correlation of the NeuroMET data from cohort 1 with cognitive task difficulty and instrument parameters (e.g. sequence entropy) and it was shown that the mathematical models developed in ths project and based on the Rasch Model Theory can be used to predict for example task difficulty. Figures 4a and 4b show an example where task difficulty (zR) for a sequence of increasing difficulty in the Knox cube test is explained as a sum of three terms: entropy; number of reversals and the average distance covered in each sequence. The specification equation (below) can be used to predict the difficulty of sequence *i*.

$$zR_i = \text{Intercept} + 1(1) \cdot \text{Entropy}_i + 0.6(1.3) \cdot \text{Reversals}_i + 0.4(9)\ \text{Distance}_i$$

In brackets are the measurement uncertainties with a coverage factor of 2.

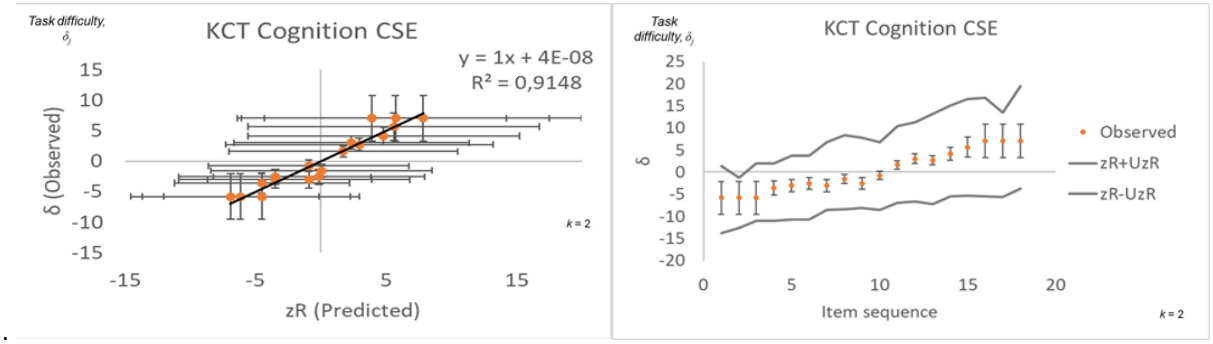
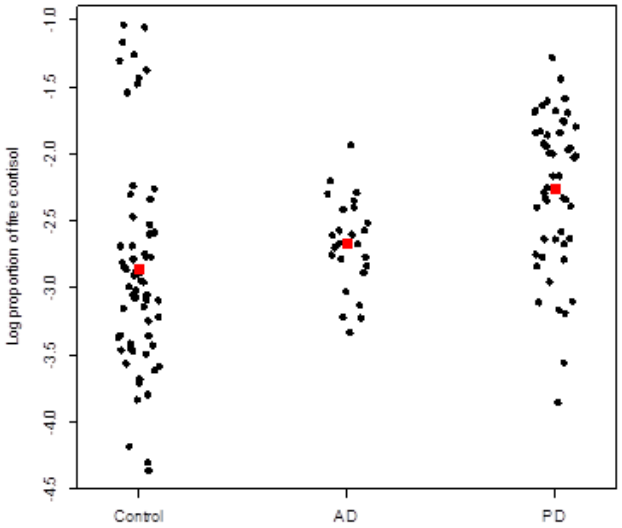


Figure 4 a. Linear regression of the measured task difficulty, δ, against the CSE estimates zR based on the three explanatory variables; X = {Entropy, Reversals, Average Distance} for the series of KCT sequences

Figure 4 b Predicted values of task difficulty, δ, for series of KCT sequences of increasing difficulty from a CSE, zR, based predominantly on entropy (with minor additional contributions from the number of reversals and average distance of each sequence), compared with corresponding measurement values (red dots with uncertainty intervals). The model uncertainties is shown as zR + UzR, uncertainty coverage factor k = 2.

Free and total cortisol as a stress marker were also measured in serum samples from cohort 2. The results were promising and it was possible to discriminate between PD and non-PD (i.e. AD and HC patients combined). However, limited overall conclusions could be drawn due to the small size of the patient cohort

Figure 5. Log free cortisol proportion (which is equivalent to assessing the percentage of free cortisol) is shown by donor type. The red squares denote the group, and the data points represent individual measurements.



6. *To develop, validate and verify multimodal statistical analyses used to correlate NDD patient health status with AD biomarker and MRI data. These novel analyses will identify the most promising tools for NDD early diagnosis and disease progression monitoring, aiming for better resolution in detecting the early signs of disease and reducing the number of biomarker studies required.*

The project developed for the first time a set of CSE in the field of cognitive assessment and NDD where person cognitive (memory) ability is described as a function of several explanatory variables such as biomarkers. The CSE enable improved understanding and prediction of both cognitive task difficultiy and person ability. Furthermore their potential to be used as reference in the field will for the first time introduce metrological and tracebility concepts into PCOM evaluation. The longitudinal studies in the follow on project 18HLT09 NeuroMET2 will further consolidate the applicability of CSE for standardisation of PCOM.

Multivariate principal component regression was also applied to the NeuroMET data from cohort 1 for all the biomarkers from objective 3 in plasma, CSF and saliva (Aβ40, Aβ42, t-tau, NFL, α-synuclein and cortisol) together with the MRI/MRS data from objective 2. Formulation of causal Rasch models as prototype metrological references for cognition was initially guided by data from other studies relating to disease state indices, while using the NeuroMET developed cognitive assessment instruments (specially for memory).

The results of this have shown the potential of the procedure to define a metrological uncertainty for the diagnosis of NDD patients.

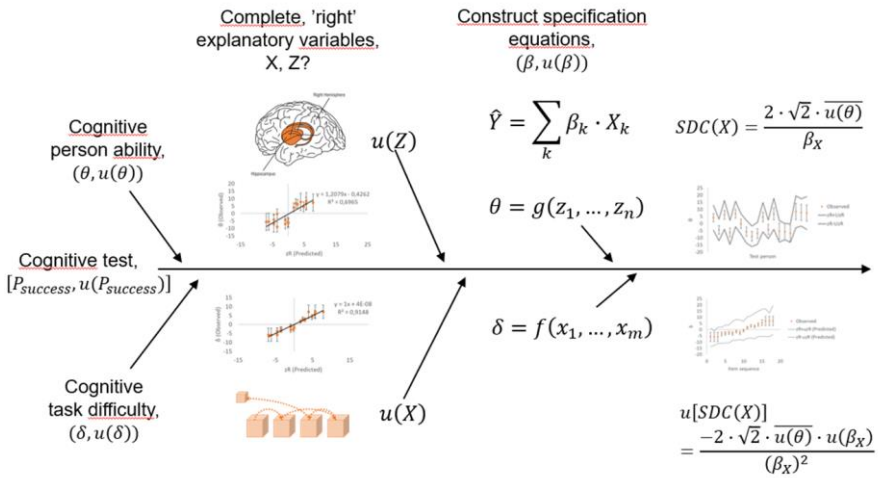


Figure 1 Propagation of measurement uncertainties, portrayed as an Ishikawa diagram, from the initial psychometric cognitive test, through Rasch analysis; formulation of CSE for both cognitive person ability (upper half) and task difficulty (lower half); and fin finally estimation of smallest detectable change (SDC) for each explanatory variable and Rasch attribute.

Impact

In this project a multidisciplinary metrological infrastructure was for the first time developed to provide RMP to improve accuracy in diagnosis of NDD and particularly AD by addressing the key steps involved in AD disgnosis including cognitive assessment, MR and fluid biomarkers. Thus providing a pool of data that together with clinicial expertise will help to define patient diagnosis and outcomes.

The NeuroMET partners attended a large number of technical and NDD diagnostic conferences over the course of the project and contributed with posters and oral presentations. A summary of the final results from the project were presented at key conferences e.g. the Alzheimer Association International Conference (2019), the IFCC EUROMEDLAB Conference (2019), and IMEKO (2019) targeting the clinical, standardisation and metrological communities. See the project website for more details https://www.lgcgroup.com/our-programmes/empir-neuromet/

The consortium also organised three stakeholder meetings in Sweden, Germany and France that were attended by academic and clinical stakeholders and targeted all aspects of the project. All stakeholder meetings we formed by three sections on cognitive assessment, MR and fluid biomarkers and were followed by a discussion with stakeholders.

In addition, project partners attended and organised a number of workshops and training course addressing quality assurance in person centred healthcare and cognitive assessments for industry and broader scientific community, PCOM (objective 5), Rasch analysis for clinicians (objective 6) and MRS data analysis also for clinicians (objective 2).

Activities from objective 2 (7T MRI and MRS) and objective 4 (t-tau) have also been positively integrated with NDD standardisation activities e.g. EUFIND (European Ultrahigh-Field Imaging Network for Neurodegenerative Diseases) and The International Federation of Clinical Chemistry and Laboratory Medicine Working Group on CSF-proteins (IFCC WG CSF) Standardisation.

Impact on industrial and other user communities

Metrological quality assurance of PCOMs is essential to underpin reliable clinical decisions for AD diagnosis and recruitment in clinical trials. Within NeuroMET an increased precision when measuring patient memory ability was demonstrated when processing data by applying the Rasch Model (from objective 6) in comparison with traditional methods. Two training courses were organise at partner Charité in Berlin and at Kristianstad University (PMHealth). The first training course was to initiate the familiarisation of clinicians with the project's Rasch Model Theory and the second training course addressed the broader scientific community. The methodologies used to develop improved cognitive assessment protocols (objective 5) were also presented to clinical end users via seminars, conferences and a number of peer review publications.

In addition, a patient group meeting targeting cohort 2 was organised with the aim of informing patients of the results of the project and the progress made in the field. The meeting attended by the lay advisory panel for cohort 2 included AD and PD patients. The participants expressed much interest in the results from the project and potential participation in follow-on studies.

The improved cognitive clinical tests and rating scales (objective 5) developed within the NeuroMET project will provide guidance and tools to clinicians for improved diagnosis and better prediction of future NDD patient decline. The prototype Memory Metric (objective 5) will be validated in the follow-on project 18HLT09 NeuroMET2 through longitudinal studies. Three training courses were organised addressing predominantly industry stakeholders. They were on (1) Assuring quality in person-centred healthcare; (2) How to calibrate a questionnaire: quality assuring categorical data with psychometric measurement theory and (3) Quality assured categorical data.

The *in-vitro* diagnostic (IVD) industry will also benefit from the results of this project by gaining additional information on instrument performance (objective 3) and by the availability of the developed reference measurement procedures (objective 4), which will facilitate regulatory approaval of new instruments and compliance with the IVD Directive 98/79/EC. Transfer into a clinical laboratory of the SI traceable LC-MS reference method for quantification of α-synuclein (objective 4) is currently on-going.

Impact on the metrological and scientific communities

The NeuroMET project has for the first time established important links between the metrological community and the NDD community through engagement in international NDD standardisation initiatives:

- round robin studies were organised with the IFCC WG CSF to underpin standardisation of t-tau with the first comparison starting in September 2019. In the comparison the NeuroMET primary calibrator for t-tau (from objective 4) will be shared between all participants to supportstandardisation of the results.
- within the EUFIND consortium NeuroMET partners were involved in the harmonisation of MRS protocols for application in NDD research cohorts and investigation of comparability of MRS data acquired at different 7T research sites and across different vendor platforms (using findings from objective 2).

The project's progress and approaches developed for the purity assessment of primary calibrators (objective 4) were regularly discussed within the BIPM Consultative Committee for Amount of Substance: Metrology in Chemistry and Biology (CCQM) metrological community. Indeed, the methods developed through NeuroMET to characterise the α-synuclein primary calibrator (also objective 4) have enabled the first ever Calibration Measurement Capability claim, for partner LGC, on purity determination of peptides.

Impact on relevant standards

The NeuroMET consortium partners were involved in and presented the project results to ISO technical committees such as TC 12 on Quantities and Units, TC 212 on Clinical laboratory testing and in-vitro diagnostic test systems, TC 215 on Health Informatics. A new ISO TC 276 Biotechnology WG3 Analytical Methods project aimed at identifying protein analytical standardisation requirements for advanced therapeutics and biotechnology, has also been initiated, and this will incorporate selected NeuroMET methods for peptide purity (from objective 4) and for structural analysis. The project was also presented at the JCTLM (Joint Committee for Traecability in Laboratory Medicine) workshop on Accurate Results for Patient Care.

Longer-term economic, social and environmental impacts

The NeuroMET project successfully combined the strengths of NMIs and NDD clinicians to establish a metrology infrastructure that will provide measurement guidance and reference tools to NDD clinicians, academics, and pharmaceutical companies for:

- Appropriate study design and definition of the uncertainty of NDD clinical assessment protocols to improve diagnosis and NDD progression monitoring;
- More accurate stratification of patient cohorts, with respect to NDD status, for enrolment into clinical trials and for more informed patient management;
- Improved measurement comparability for NDD biomarkers through optimised measurement procedures and development of SI traceable reference methods for key biomarkers.

Going forward, the follow-on project 18HLT09 NeuroMET2 will positively contribute to the uptake and validation of this project's outputs through longitudinal studies, as well as further engagment with instrument manufactures and international activities such as through the JCTLM, IFCC and EUFIND.

List of publications

[1]. S. Pang and S. Cowen, 2018, Scientific Reports, https://doi.org/10.1038/s41598-017-17823-y

[2]. G. Franceschi, 2017, JBC http://www.jbc.org/content/292/17/6927.full.pdf

[3]. Cano S, Pendrill L, Barbic S, Fisher WP, 2017, Journal of Physics, Conference Series, https://doi.org/10.1088/1742-6596/1044/1/012057

[4]. Cano S, Pendrill L, Barbic S, Fisher WP, 2017, Journal of Physics, Conference Series, https://doi.org/10.1088/1742-6596/1065/7/072033

Project start date and duration:	July 2016, 36 months	
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