



NEUROCURE
Clinical Research Center (NCRC)

CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN



NeuroMET

NeuroMET Research Project

»Final project update NeuroMET2
December 2022«

Alzheimer's disease diagnostics

A variety of measurements can be used to diagnose people with neurodegenerative diseases, such as Alzheimer's disease, and to monitor disease progression over time and evaluate drug effects. These measurement methods for Alzheimer's disease differ across countries, clinics and laboratories. The NeuroMET consortium was the first to carry out a metrology research project to develop references and improve the accuracy of available diagnostic methods, involving the use of sophisticated mathematical models.



Metrology

Accuracy of diagnoses is important to allow health care professionals to choose the appropriate treatment for patients with neurodegenerative diseases such as Alzheimer's disease. Metrologists study how the quality of measurements can be improved. They explore how to generate **accurate** (close to the true value) and **comparable** (the same results are obtained at different visits of individual patients, by different clinics and laboratories across the world) measurements. They also define how **confident** we can be with the obtained measurements (how variable are the data).



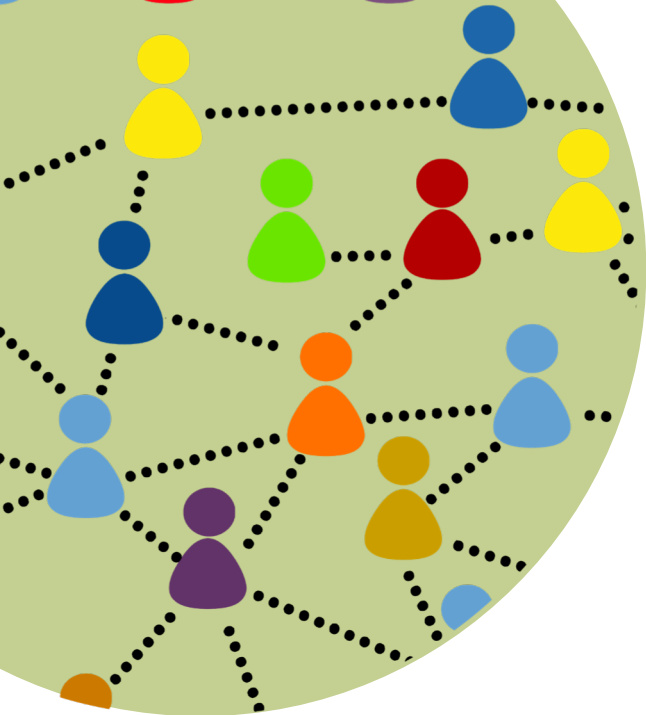


The research projects NeuroMET & NeuroMET2

Between 2016 and 2022, the NeuroMET research projects united a powerful consortium consisting of metrologists, psychologists, neuroscientists, software and biomedical engineers, and clinicians. Collectively, we aimed to improve diagnostic measurement methods for neurodegenerative diseases, especially Alzheimer's disease. Therefore, we've been focusing on the following goals:



- set up a cohort which allows us to better understand which are the best methods for early Alzheimer's disease diagnosis
- improve magnetic resonance approaches for people who have early symptoms of Alzheimer's disease
- develop more accurate, lab-based measures of cerebrospinal fluid and blood tests to detect Alzheimer's disease early
- understand and improve how neuropsychological tests measure memory
- provide health professionals with a digital tool that delivers accurate and comparable measurements of memory ability



Amount

Mean age [years]

Female

Mean Education [years]

Who was included in the NeuroMET cohort?

In 2016, we began inviting patients and caregivers to the university hospital Charité, Berlin. Our group consists of a total of 127 elderly people, split up as follows: cognitively healthy controls (HC), participants with subjective cognitive decline (SCD), patients with mild cognitive impairment (MCI) or Alzheimer's Disease (AD). Two more participants completed their baseline visits but were not stratified in one of the study groups.

HC	SCD	MCI	AD
35	35	30	27
71	69	71	75
51%	63%	27%	56%
15	16	15	14

Findings

Magnetic resonance spectroscopy (MRS)

Using MRS, we can measure concentrations of brain metabolites which contain information on biochemical processes in the brain. These concentrations change when disease is present, such as in Alzheimer's disease. Up to now, MRS is not being used in clinical routines although it is a comparably cheap and non-invasive method. This is because the metabolite concentrations and their changes over time are so small that it has been a challenge to define if the changes indicate a pathological alteration or only statistical fluctuations. To disentangle this, we introduced a statistical analysis framework that allows us to analyze measurement uncertainties of repeated measurements over time [Riemann et al, 2022].

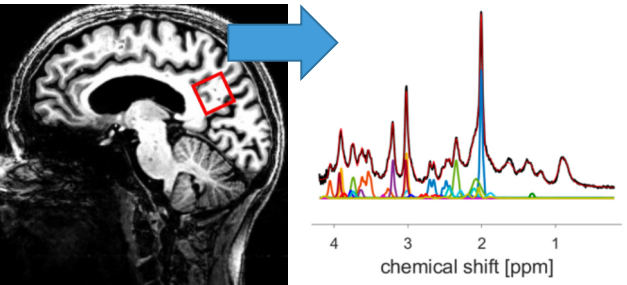


Figure 1: With magnetic resonance spectroscopy (MRS), we acquire spectra that contain information on the concentrations of metabolites in a defined voxel (red cube).

Assessment of memory ability

We selected memory tasks from commonly used cognitive tests to provide a superior, metrologically valid scale for memory - the NeuroMET memory Metric. The selection of these tasks was based on novel principles, including the use of modern measurement theory and entropy-based construct specification equations. The NeuroMET memory metric provides improved **accuracy** in terms of significantly reduced measurement uncertainties, **comparability** via an item-bank, and increased **confidence** in the measure of memory, thanks to the unique combination and justification of the chosen memory tasks [Melin et al 2021].

To make the NeuroMET memory metric accessible to health professionals and researchers, we developed an app using the THREAD research platform that delivers the required cognitive tests.

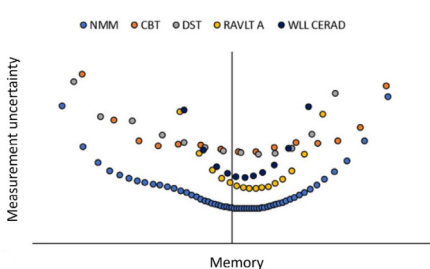


Figure 2: The NeuroMET memory metric (NMM) shows lower uncertainties in the measurement of memory than other tests that are commonly used as individual cognitive measures such as the Corsi block tapping test (CBT), digit span test (DST), Rey auditory verbal learning test (RAVLT) or the word learning list of the CERAD test battery (WLL CERAD).



Biofluid biomarkers

We developed methods for an improved **accuracy** and **confidence** in the quantification of α -synuclein, neurofilament light (NFL) and phosphorylated Tau (p-Tau) in plasma and cerebrospinal fluid. These are proteins that are related to neurodegenerative diseases, especially Alzheimer's disease. These methods will be used to improve **comparability** of the diagnostic tests that are currently used in clinical practice, leading to better patients stratification.

Combining information

We confirmed that changes in common biomarkers for Alzheimer's disease caused changes in individual memory ability. Strikingly, the improved accuracy of the new NeuroMET metric provided the best degree of correlation with biomarkers seen so far. The most promising markers for an advanced understanding of variation in memory functions have been identified by combining measurements from MRI, MRS and blood-based biomarkers with our novel NeuroMET memory metric. In turn, this can be used by clinicians to make well-informed decisions about diagnoses, disease progression and drug effects.

Patient Engagement

During the entire project, the well-being and satisfaction of our participants has been a priority to us. We invited our participants twice to gain general and NeuroMET-related knowledge about Alzheimer's disease. In this context, our participants expressed their special interest in potential future projects such as:

- exploring the main reasons for caregivers not to make use of support from Berlin based organizations
- defining the safety of stents and other implants as well as their approval for 7T MRI scanners

Open Data

The NeuroMET consortium intends to improve sustainability in research which is why the generated data will be published online so that other researchers can make further use of them. Needless to say, sensitive or personally identifiable data will not be accessible.

If you would like to learn more about the NeuroMET consortium, please visit our website <https://www.lgcgroup.com/our-programmes/empir-neu>

References

Melin, J., Cano, S., Flöel, A., Göschel, L., Pendrill, L., & EMPIR NeuroMET and NeuroMET2 consortiums. (2021). More than a memory test: A new metric linking blocks, numbers, and words. *Alzheimer's & Dementia*, 17(S6), e050291. <https://doi.org/10.1002/alz.050291>

Riemann LT, Aigner CS, Ellison SLR, Brühl R, Mekle R, Schmitter S, Speck O, Rose G, Ittermann B, Fillmer A. Assessment of measurement precision in single-voxel spectroscopy at 7 T: Toward minimal detectable changes of metabolite concentrations in the human brain in vivo. *Magn Reson Med*. 2022 Mar;87(3):1119-1135. doi: 10.1002/mrm.29034. Epub 2021 Nov 16. PMID: 34783376.

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EMPIR



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