Assessment of clinical neurophysiological biomarkers for the differentiation of neurodegenerative disease versus non-neurological disorder in patients with mild cognitive impairment.

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Primary objectives:- To assess the differences in resting state EEG frequency spectrum analysis between patients with neurodegenerative and patients with non-neurological causes of MCI.* Power in microvolts squared of resting stage EEG for different...

Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Observational non invasive

Summary

ID

NL-OMON56487

Source
ToetsingOnline

Brief title
Clinical neurophysiological biomarkers in mild cognitive impairment.

Condition

- Other condition

Synonym
intellectual disability, mild cognitive impairment

Health condition

cognitive disorders

Research involving
Human

Sponsors and support

Primary sponsor: Centre for Human Drug Research
Source(s) of monetary or material Support: Centre for Human Drug Research

Intervention

Keyword: biomarker, cognitive impairment, neurodegenerative disease, non-neurological disorder

Outcome measures

Primary outcome

The main endpoint is to compare the resting state EEG in patients with a

non-neurological and neurodegenerative etiology of their cognitive complaints.

Secondary outcome

Secondary endpoints include the assessing diagnostic accuracy of:

- composite of parameters registered by Trial@Home wearables as a proxy for

daily activity, and

- peak latency and amplitude of event related potentials

in patients with a non-neurodegenerative and neurodegenerative aetiology of

their cognitive complaints

Study description

Background summary

Cognitive impairment is an increasing problem in modern society. In 2018, an estimated total of 270.000 people were suffering from some form of dementia in The Netherlands. Due to increasing life expectancy, this number will likely

have doubled before 20401. Alzheimer*s disease is the most prevalent neurodegenerative cause of dementia, comprising around two-thirds of all patients with diagnosed dementia. Dementia is a diagnosis based on clinical symptoms, of which memory deficit, language disorders and disorientation are the most frequently seen. When at least 2 of 5 cognitive domains are affected and interference with activities of daily living (ADL) is present, a diagnosis of dementia can be made.2

However, since symptoms progress gradually over time, in the early stages of disease patients often do not fulfil the criteria for dementia, instead qualifying as *mild cognitive impairment* (MCI). It is in these instances that additional testing can be required, searching for a biomarker to either confirm or reject the suspicion of an underlying neurodegenerative condition. This is especially helpful when the differential diagnosis includes non-neurodegenerative causes such as mood disorders, which can be a major mimic in the early stage of Alzheimer*s disease. Alongside imaging studies and protein biomarkers (mainly amyloid-beta and tau protein), electrophysiological tests such as electro-encephalography (EEG) and event-related potentials (ERP) can be used to quantify deterioration of cerebral function.

EEG abnormalities can be disease specific in rare cases, but usually comprise general slowing and reduced reactivity to stimuli.3 Previous studies have assessed the value of EEG comparing patients with different types of dementia, and probable Alzheimer*s disease with healthy controls, with moderate diagnostic accuracy4-5. However, its value in distinguishing between neurodegenerative disease and mood disorders in patients with MCI has not yet been studied.

The Trial@Home platform developed by Centre for Human Drug Research (CHDR) allows, through various devices, the collection of continuous data from patients. A commonly used device is the Withings Steel HR smartwatch, which monitors physical activity by measuring heart rate, step count, sleep duration and sleep states. Another device which is helpful in collecting continuous data is the Withings Sleep that further analyses the sleep pattern and REM state. In addition, the platform allows remote monitoring via an Android application, the MORE app, to unobtrusively collect data from smartphone sensors. The app enables data collection from multiple phone sensors (e.g., location data) as well as phone usage logs (e.g., app usage and phone call logs). The Trial@Home platform also includes an electronic patient-reported outcome (ePRO) module, the ePRO app, which captures data directly into the source database. Data is stored on a secure server in a structured data scheme ensuring clear data management processes, forming a prerequisite for comprehensive data analysis.

Study objective

Primary objectives:
- To assess the differences in resting state EEG frequency spectrum analysis

between patients with neurodegenerative and patients with non-neurological causes of MCI.
* Power in microvolts squared of resting stage EEG for different frequencies:
* Delta (1.5 - 6.04 Hz)
* Theta (6.0 - 8.5 Hz)
* Alpha (8.5 - 12.5 Hz)
* Beta (12.5 - 30.0 Hz)
* Gamma (30.0 - 40.0 Hz)
* High-Gamma (30.0 - 90.0 Hz)

Secondary objectives:
- To assess the differences in event-related potentials between patients with neurodegenerative patients with non-neurological causes of MCI.
* Passive Auditory Oddball:
o MMN amplitudes [µV] and latencies [ms] for each deviant
* Active Auditory Oddball:
o Reaction time [ms] and P300 amplitude [µV] and latency [ms] at Pz
* Auditory Steady State Response:
o Inter-trial phase coherence [a.u.] and evoked power [µV2] between 35 - 45 Hz and 200 and 500ms.
* Auditory Sensory Gating:
o Amplitudes and latencies of P50, N100, and P200 peaks for both tones.
o Difference amplitudes of both tones of the P50, N100, and P200

Exploratory objectives:
- Differences in a composite of parameters registered by Trial@Home wearables between patients with neurodegenerative and patients with non-neurological causes of MCI
- Usability of Trial@Home wearable device for patients with MCI

• Vital signs (heart rate)
• Activity (step count, sleep duration)
• Geolocation (GPS)
• Voice recording (CHDR MORE App)
• Phone usage
• Sleep mat:
o Sleep duration
o Sleep onset
o Time to wake
o Sleep cycles (deep, light, REM phases
o Snoring duration (minutes)
• Dedicated usability questionnaire

Study design

This is a single center cross-sectional biomarker study to investigate the differences of clinical neurophysiological tests (EEG and ERP) between

neurodegenerative and non-neurological causes in patients with MCI.
The total duration of the study for each subject will be up to 50 days divided as follows:
* Screening: Up to 21 days before visit day 1;
* Study assessments: day 1 to 28
* Follow-up visit: day 29.

Subjects will visit the study unit at screening, on day 1 and on the follow-up visit at approximately day 29

Study burden and risks

This is a non-interventional biomarker study. No investigational drug will be administered. There is minimal risk when executing EEG. An electrode cap is attached to the head of the subject with a special gel. When attaching the cap, the scalp is rubbed a bit, which may irritate the skin and cause redness or itchiness.

Considering the nature of the methods of data collection via smartphone employed in this study, privacy issues are a potential concern. To prevent unacceptable privacy incursions, we have developed the study assessments to be as little invasive as possible. All subjects will be informed thoroughly regarding the following:

• Data collected via the Withings study devices will be stored pseudonymized and Withings and CHDR will be co-controllers of the data. Besides data collected via the Withings study devices, only height, weight, age and a coded subject number will be stored on the Withings servers. The key for this coded subject number will be stored at CHDR only. The Withings® servers are stationed in Ireland and are secure and General Data Protection Regulation (GDPR) compliant. Respective responsibilities of CHDR and Withings regarding data protection have been established in a data sharing agreement.

• Data collected via the CHDR MORE app will be stored on the CHDR Microsoft Azure Cloud. No personal identifiable information is stored on the CHDR MORE app or the CHDR MORE Cloud. CHDR is the controller of the data. The CHDR MORE Cloud has been developed with a Privacy by Design approach and has been qualified using the standard validation procedures of CHDR. Finally, access rights to the data are handled by CHDR*s Standard Operating Procedures (SOP). During the final study visit, patients will be instructed to delete all study related applications from the smartphone, after which, further data collection will not be possible.

All devices are CE marked for their intended purpose and instructions for good care of the device will be given to the subjects to minimize any risks. There is a possibility that subjects will experience discomfort while continuously wearing the smartwatch. While we do not expect discomfort of a serious nature,

subjects will be informed of several possibilities to limit discomfort while continuing their study participation (e.g., to take the watch off for 30 minutes twice per day during meals/showers or alternating arms).

Contacts

Public
Centre for Human Drug Research

Zernikedreef 8
Leiden 2333CL
NL
Scientific
Centre for Human Drug Research

Zernikedreef 8
Leiden 2333CL
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Male or female subject of >= 45 years of age at screening.
2. Cognitive disorders defined as mild cognitive impairment diagnosed by a neurologist, suspected due to neurodegenerative disease or non-neurological disorder (e.g. psychiatric disorders).
3. Willing and able to voluntary sign the informed consent form (ICF).
4. Willing and able to communicate with the investigator and site staff and to

comply with the study requirements and visits.

Exclusion criteria

1. Clinically significant findings as determined by medical history taking, physical examination, ECG and vital signs, which, in the opinion of the Investigator, does not allow study participation.
2. Any previously diagnosed dementia or other neurodegenerative disease at or prior to screening
3. Any current, clinically significant, known neurological cause of cognitive disorders at or prior to screening.
4. Inability to willfully sign the informed consent document, supported by an MMSE < 24 at screening. Exceptionally, patients with an MMSE < 24 can be included only if the rationale is clearly documented by the investigator (i.e., clear reasoning why/how the patient can willfully sign the ICF, despite the MMSE score < 24), and there is an explicit non-objection to trial participation from the treating neurologist (which should be documented).
5. Recent infection with hospital admission < 2 months prior to screening.
6. A positive urine drug test (morphine, benzodiazepines, cocaine, amphetamine, THC, methamphetamine, MDMA) or positive alcohol breath test at screening.
7. Consume, on average, more than 8 units/day of (methyl)xanthines (e.g. coffee, tea, cola, chocolate) and unable to abstain from (methyl)xanthines from 24h before Day 1 and Day 28 up until completion of the in-clinic measurements on Day 1 and on Day 28.
8. History of clinical evidence of alcohol- or drug abuse.
9. Concerning concomitant medication:
a) First use of any concomitant medication within 28 days prior to Day 1, with the exception of incidental use of paracetamol and/or NSAIDs.
b) Dose change of pre-existing concomitant medication within 28 days prior to Day 1, with the exception of stopping medication more than 7 days or 5 times the half-life before Day 1 (whichever is longer).
10. Participation in an investigational drug or device study (last dosing of previous study was within 90 days prior to first dosing of this study)
11. Loss of blood >= 500 mL within 3 months before screening.
12. Does not own a smartphone on which the MORE application can be installed (Android 7.0 or above)
13. If a woman: pregnant, or breast-feeding, or planning to become pregnant during this study.

Study design

Design

Study type: Observational non invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-02-2024
Enrollment:	30
Type:	Anticipated

Ethics review

Approved WMO Date:	02-01-2024
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	29-01-2024
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL85451.056.23