MEG in Alzheimer's Disease: unravelling the underlying network to explain the stereotypical spread of Tau protein

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Encephalopathies
Study type	Observational non invasive

Summary

ID

NL-OMON48723

Source
ToetsingOnline

Brief title
MANTA

Condition

- Encephalopathies
- Dementia and amnestic conditions

Synonym
cognitive impairment, Dementia

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Het ZonMW Memorabel-programma;welke

een subsidie heeft gegeven voor het MANTA-project aan het Alzheimercentrum;Neurologie;van het VUmc

Intervention

Keyword: Brain Networks, Dementia, Functional connectivity, Tau protein

Outcome measures

Primary outcome

MEG endpoints

1) Primary MEG endpoints are:

- relative theta power (4-8- Hz) of the target regions

- normalized directed connectivity of the target regions (lower alpha band, 8 *

10 Hz)

- betweenness centrality of the target regions (lower alpha band, 8 * 10 Hz)

- path length between source and target region (lower alpha band, 8 * 10 Hz)

18F-AV1451 PET scan endpoints

1) the amount of specific 18F-AV1451 binding in each of the 90 regions of the

AAL-atlas

Secondary outcome

MEG endpoints

2) Secondary MEG endpoints are:

2.1) all other frequency specific MEG endpoints

2.2) modularity analyses

2.3) multiplex network analyses

Study description

Background summary

Alzheimer*s Disease (AD) is pathologically characterized by the accumulation of amyloid- ß and hyperphosphorylated tau in the brain. Most of the AD research has focused on amyloid- ß as the major cause of AD, because a widely accepted view is that amyloid- ß, which is deposited many decades before the first symptoms occur, induces abnormal tau formation, neuronal death and clinical dementia. However, the field has been disappointed by numerous negative study results. Most strikingly, none of the numerous amyloid-targeting drug trials has as yet yielded convincing positive effects on cognitive functioning. Additionally, several studies have suggested that tau - and not amyloid-ß- is the first neuropathological sign of AD. Interest has therefore not only shifted towards earlier pre-dementia stages of the disease, but also towards alternative disease mechanisms.
Recent in vitro and in vivo studies have presented an increasing amount of clues that tau protein spreads through the brain via anatomical connections of the brain network, leading to disrupted network activity, synaptic insufficiency and eventual cognitive decline. However, which factors and network characteristics promote the spread of tau remains as of yet unknown.
In AD, functional brain networks, based on magnetoencephalography (MEG), electroencephalography (EEG) or functional MRI, seem to display mostly hypoconnectivity and disrupted network topology. This seems to affect the most strongly connected and active network hubs in particular, suggesting a mechanism of 'activity dependent degeneration'. Additionally, in vitro and in vivo enhancement of neuronal activity has been shown to accelerate tau deposition in the brain.
Because of the recent discovery of specific tracers for PET imaging of tau-deposition enabling the visualisation of tau in living patients, we can now investigate the relationship between functional network characteristics (such as hyperactivity and topology), and the spread of tau in AD. We will also simulate several hypothesized damage mechanisms using a computational model, as an attempt to identify vulnerability factors for the progression of AD. This could not only lead to deeper knowledge about the etiology and risk factors associated with AD, but also to novel targets for future interventions.

Study objective

The primary objective of the MANTA-study is to investigate MEG-based network topology and 'activity dependent degeneration' as mechanisms in the stereotypical spread of tau pathology (18F-AV1451 retention) in preclinical and

clinical stages of AD.

Specific research questions that will be addressed include:

1. to compare MEG-based oscillatory activity, functional / directed connectivity and network topology measures across preclinical and clinical stages of AD in order to find evidence for the *activity dependent degeneration*- hypothesis

2. to investigate which changes in functional network characteristics and oscillatoryactivity mirror regional 18F-AV1451 retention in each disease stage

3a. to assess which characteristics of a healthy network predict the spread of 18F-AV1451 retention in each stage of AD
3b. to assess whether MEG-predictors of the previous disease stage improves the prediction of the spread of 18F-AV1451 retention in the subsequent disease stage (e.g. for tau-spread in AD, MEG-measures of MCI patients are used as predictors) compared to MEG-predictors of the healthy network, in order to evaluate whether tau-deposition reciprocally damages the network

4. to investigate damage and spread mechanisms in a dynamic neural network to predict pathological effects on large-scale network and compare the modeled outcome to the observed tau and hyperactivity patterns in patient data.

Study design

MANTA is a cross-sectional observational cohort study. It includes Alzheimer's Disease patients in different stages of the disease (SCD, MCI and dementia with abnormal amyloid biomarkers). It also includes a group of young healthy controls and elderly controls (patients with SCD with normal Alzheimer-specific biomarkers).

After completing a written informed consent, all patients fulfilling the inclusion criteria as described in the next chapter will undergo an MEG measurement at the MEG centre of the VU medical centre in Amsterdam. The young controls will also undergo an MRI scan in order to determine the placements of the MEG electrodes during co-registration (patients and elderly controls will have previously been submitted to an MRI scan in preparation for the PET scan for the TITAN, TRT AV-1451 and LUNAR study). Patients will be requested to complete questionnaires about physical and mental health, quality of life and use of care.

Previously acquired data from the TITAN, TRT AV-1451 and LUNAR studies will be used in this project.

Study burden and risks

Participation consists of one 1.5-2 hour (2-2.5 for controls) visit to the VUmc MEG centre, during which patients will undergo an MEG measurement and fill in a questionnaire. Controls will additionally undergo an MRI scan.

There is no direct therapeutic effect or other benefit of this study; clinical decision making will not be based on the results. The test is non-invasive, short of duration, and pain free. Risks associated with participation are negligible, and the burden is minimal. Unexpected findings which could lead to medical treatment will always be discussed with patients.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Patients:

- Fulfilling the diagnostic criteria for subjective cognitive decline (SCD), mild cognitive impairment (MCI) due to AD or probable Alzheimer's disease (AD)
- At least 50 years of age
- Received an or a planned 18F-AV1451 PET in the context of the LUNAR, TRT AV-1451 or TITAN projects
- Known amyloid status, Controls: age 20-30 years

Exclusion criteria

Patients:
- Cardiac pacemakers, ICD's and other introcorporeal devices interfering with MEG-signals
- Severe claustrophobia
- Specific exclusion criteria for 18F-AV1451 PET scanning or MRI scanning excluding patients from participation in the TITAN, LUNAR and TRT AV-1451 studies automatically disqualifies patients from participation in MANTA. ,
Controls:
- Current cognitive, neurological or psychiatric disorders
- Use of psychoactive medication
- Contra-indications for MRI scanning
- (Dental) implants, braces, cardiac pacemakers and ICD's interfering with MEG-signals
- Severe claustrophobia
- Current or planned pregnancy (both oral (telephone interview) and written (informed consent form) confirmation from participant).

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	18-07-2018
Enrollment:	180
Type:	Actual

Ethics review

Approved WMO Date:	23-05-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-11-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-09-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-11-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	NL64638.029.18