Translating network hyperexcitability in preclinical familial Alzheimer's disease

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Neurological disorders congenital
Study type	Observational invasive

Summary

ID

NL-OMON49729

Source
ToetsingOnline

Brief title
T-REX

Condition

- Neurological disorders congenital
- Neurological disorders NEC
- Dementia and amnestic conditions

Synonym
Alzheimer's Disease, Inheritable Dementia

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: ZonMW

Intervention

Keyword: Brain Networks, Dementia, Translational research

Outcome measures

Primary outcome

Hippocampal and global brain MEG based measures of oscillatory brain activity, represented in total broadband power and E/I balance (from 1/f of the powerspectrum or new method for fE/I, based on DFA and power.

Secondary outcome

MEG-based measures of:

- oscillatory activity, represented in (average) peak frequency and relative power of the following frequency bands: theta (4-8 Hz), alpha (8*13 Hz), beta (13-30 Hz), and gamma (30-48Hz).

- functional connectivity between target regions in specific frequency bands, expressed as amplitude envelope correlation corrected (AECc) for volume conduction.

- functional network measures by the use of graph theoretical measures, including degree, modularity, path length, betweenness centrality.

Structural MRI:

- Structural connectome

- Grey & White matter volumes

- White matter integrity & microbleeds

Neuropsychological performance

- Scores from different tests will be used as indices of cognitive performance

on different domains

- Score of the working memory task during the MEG recording will be used as

indicator for working memory

Study description

Background summary

Despite decades of research, the pathophysiology of Alzheimer*s disease (AD) remains poorly understood and effective treatment is still not available. AD has a long prodromal phase and clinical signs become apparent only decades after onset of the disease. Detailed characterization of this preclinical disease stage holds the key to early diagnosis and intervention. Recent studies suggest that neuronal excitation/inhibition (E/I) imbalance in and network hyperexcitability are early signs of AD. Alterations in neuronal E/I ratios and network function can in principle be detected with non-invasive electro- or magnetoencephalography (M/EEG), but robust M/EEG markers for early AD are still not available. This study will characterize neurophysiological alterations in early brain network function of truly preclinical AD patients, in particular dominantly inherited Alzheimer's Disease (DIAD) mutation carriers, and aims to find proof-of-concept for translatability of findings in rodents to humans.

Study objective

The main objective of the study is to investigate MEG-based hippocampal and whole brain neuronal hyperactivity in preclinical DIAD mutation carriers and to find proof-of-concept for the translatability of findings from preclinical AD mouse models to findings from the clinic.

In addition, we will asses whether similar alterations in MEG-based measures of brain activity of DIAD mutation carriers can be found in the early phase of sporadic Alzheimer's disease (using available cohortdata).

Also, computer models and in vitro investigations of induced pluripotent stem cell-derived neuronal networks will help to find mechanistic explanations for changes in brain activity underlying the earliest changes in AD on a multi-level.

Study design

Proof-of-concept, cross-sectional observational study.

Study burden and risks

This study will take approximately 3.5 hours and participants will be asked to come to the AUMC, location VUmc to undergo an MEG recording as well as MRI scan. Participants will also complete a neuropsychological test and additional questionnaires regarding their mental health among other subjects of which the risk is considered neglegible. The main procedures, i.e. MEG and MRI recordings, are non-invasive and involves lying in a supine position in a shielded room. Thede procedures (45-60 minutes for MEG and 30 minutes for MRI) are not painful in any way, are not considered to be difficult or stressful (except for patients with extreme claustrophobia), and has negligible risks. MRI scanning may have a risk of chance findings. Skin biopsy is a regular medical procedure often used in the clinic and has minimal risk of bleeding, hyperreactivity to local anaesthetics or scar formation. There is no individual benefit from participation in the study.

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

Potential subjects need to have a dominantly inherited Alzheimer's Disease (DIAD) mutation and must be at least 18 years of age.

Exclusion criteria

Participants who show dementia due to (familial) AD will be excluded from the study. In addition, participants who have for example cardiac pacemakers, ICD's or other intracorporal devices which excessively interfer with MEG-signals may be excluded.
Additional contra-indications for MRI scanning (e.g. implanted metals), current or planned pregnancy and subjects with severe claustrophobia cannot participate.

Study design

Design

Study type:	Observational 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):	01-12-2020

Enrollment:	15
Type:	Actual

Ethics review

Approved WMO Date:	28-09-2020
Application type:	First submission
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	NL70688.029.20