The Locus coeruleus hits the bull's eye: stress-vulnerability as a predictor for cognitive decline.

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

Summary

ID

NL-OMON54496

Source
ToetsingOnline

Brief title
Stress, pupils and memory

Condition

- Other condition

Synonym
Alzheimer's disease; dementia

Health condition

prodromale/preclinische fase van de ziekte van Alzheimer

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Memory, Noradrenalin, Pupils, Stress

Outcome measures

Primary outcome

The primary outcome measures:

- Cognition

-The Blood-Oxygen-Level-Dependent (BOLD) respons

predictors are objective (pupil) and subjective (questionnaires) stress measures

Moderating variables are sex, age, education, reported sleep quality, caffeine

use, AD related biomakers, estrogen levels and genetics.

Secondary outcome

The secondary outcome measures are:

Alpha-amylase salivary activity over time

Noradrenergic network connectivity

-Structural brain measures

-Blood markers of risk factors for Alzheimer's disease

Study description

Background summary

Stress is an intricate part of modern life, and the high demands of the current society puts people under more stress constituting a risk for cognitive decline in later years. Stress activates the brains noradrenergic system and the hypothalamic pituitary adrenal (HPA) axis. In younger adults, this noradrenergic activation predicts memory performance following an inverted U-curve. However, advanced age is associated with changes in activation of the HPA axis and the adrenergic system. Noradrenergic brain activity is commonly measured by monitoring pupil dilation during arousing conditions. The locus coeruleus, a small nucleus in the brainstem, is the main source of noradrenalin. This property puts the locus coeruleus at the forefront of the stress-cognition association. Interestingly, neuropathological studies suggest that the locus coeruleus, is affected early on in life and might be the site of the initial accumulation of Alzheimer Disease pathology. Therefore, it can be hypothesized that stress-vulnerability at a younger age may be a predictor for incipient cognitive decline and potentially development of prodromal Alzheimer*s disease.

Study objective

Objective: Main outcome measures are: brain activity, pupil dilation, noradrenergic network activity and memory performance.
We aim:
i) To investigate risk and protective factors for cognitive decline in high and low stress vulnerable persons across the adult lifespan.
ii) To investigate whether individuals with higher stress vulnerability show patterns of noradrenergic network integrity that is similar to the patterns of MCI patients as compared to individuals with lower stress vulnerability.
iii) How stress vulnerability as well as subjective stress about cognitive performance relates to cognitive decline over time.

Study design

This study entails a longitudinal study with 2 measurement days at baseline and 3 follow ups.
There is also a cross-sectional variant of the study for prospective new participants.

Study burden and risks

The expected risks and burden are expected to be minimal, since strict inclusion and exclusion criteria for participation in the MRI procedure are maintained. Participants will complete a standard medical questionnaire that screens for contraindications. When included in the longitudinal study, the burden and risks associated with this study are restricted to the testing days. At baseline, day one will consist of administration of several neuropsychological tests and questionnaires, a behavioral stress measurement

with pupil measurements. The behavioral stress measurement contributes to the burden of participating in the study. However, the stress-induction will only occur once and there have been no reports of long-term conditions attributable to exposure to the task. Day two will consist of a short scan session, and blood drawing. At follow-up sessions for healthy participants cognitive performance will be retested by administration of neuropsychological tests and questionnaires, and pupil dilations will be measured. For the cross-sectional observational study, on day one participants will undergo several neuropsychological tests and questionnaires. On the second day, patients will be scanned in the MRI scanner for 1 hour including an emotional memory task and pupil dilation measurements. MRI is a non-invasive method and the risks are negligible (temporary dizziness in some individuals).

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

For the healthy participant group:
1. No substantial memory complaints (according to the participant)
2. Age: between 30 and 95 years old
3. Right-handedness
4. Informed consent before participation in the study, For the MCI reference group (patients):
1. Diagnosis of MCI based on the latest research criteria (clinical assessment at the memory clinic (prof. Frans RJ Verhey): presence of at least a memory impairment, memory complaints expressed by the patient or informant, no problems in daily life functioning, no dementia and presence of biomarkers
2. Clinical Dementia Rating score of 0.5 (CDR distinguishes a stage of questionable dementia (CDR 0.5) from people termed healthy (CDR 0) and those with mild dementia (CDR 1)
3. Mini-Mental State Examination (MMSE) 23 and being mentally competent (in general, individuals with a MMSE 18 are considered mentally competent)
4. Age: between 60 and 85 years old
5. Right-handedness
6. Informed consent before participation in the study

Exclusion criteria

1. Reduced vision (glasses with > -6 or +6 corrected)
2. Psychoactive medication use
3. Abuse of alcohol and drugs
4. Cognitive impairment due to alcohol/drug abuse or abuse of other substances
5. Below average neuropsychological test results, in accordance with normative data, corrected for age, education and sex (Criterion for healthy participants only).
6. Past or present psychiatric or neurological disorders (major depression, schizophrenia, bipolar disorder, psychotic disorder (or treatment for it), epilepsy, stroke, Parkinson*s Disease, multiple sclerosis, brain surgery, brain trauma, electroshock therapy, kidney dialysis, Menière*s Disease, brain infections) (with exception of AD in the patient group)
7. Major vascular disorders (e.g. stroke)
8. Heart diseases or pacemakers
9. Contraindications for scanning (e.g. brain surgery, cardiac pacemaker, metal implants, claustrophobia, body tattoos)
10. Contraindications for pupil measurements (e.g. Cataracts, Glaucoma, detached retina*s, eye surgery involving the muscle, penetrating eye wounds, use of cholinesterase inhibitors, anticholinergic eye drop use, droopy eyelids preventing eye measurements)

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:	Recruiting
Start date (anticipated):	25-02-2019
Enrollment:	180
Type:	Actual

Ethics review

Approved WMO Date:	27-07-2018
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	14-11-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	20-03-2020
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	11-05-2020
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	30-09-2020
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	02-07-2021
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	29-09-2022
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	22-06-2023
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	NL64700.068.18