Blood-Brain Barrier function: The key to successful cognitive aging?

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cognitive and attention disorders and disturbances
Study type	Observational invasive

Summary

ID

NL-OMON47086

Source
ToetsingOnline

Brief title
Blood-Brain Barrier function and cognitive aging.

Condition

- Cognitive and attention disorders and disturbances
- Age related factors
- Vascular injuries

Synonym
age-related decline in mental ability., Blood-Brain Barrier leakage; Cognitive aging, Blood-Brain Barrier permeability

Research involving
Human

Sponsors and support

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

organisatie voor Wetenschappelijk Onderzoek;Maatschappij- en GedragsWetenschappen;Research Talent grant.

Intervention

Keyword: BBB, Cognitive aging, Human, MRI

Outcome measures

Primary outcome

- Episodic memory: Verbal Learning Test, delayed recall

- Hippocampal volume

- Blood-Brain Barrier leakage

Secondary outcome

Other measures of cognitive performance (for post-hoc analyses):

- Learning: Verbal Learning Test, immediate recall

- Basic processing speed: Letter-Digit Substitution Test

- Complex information processing: Stroop Color-Word Test

- Global cognition: Mini-Mental State Examination

Other measures of radiologically visible brain tissue abnormalities (for

post-hoc analyses):

- Cortical atrophy

- White Matter Hyperintensities

- Small cortical infarcts

- Lacunes

- Microbleeds

- Enlarged perivascular spaces

- White matter integrity

Study description

Background summary

The brain is vulnerable to age-related pathologies, which can result in cognitive decline. Nevertheless, some people age successfully, while others suffer substantially from this cognitive decline. To date, the exact mechanism of cognitive aging remains unclear.
A potential initiating mechanism is Blood-Brain Barrier breakdown. Blood-Brain Barrier breakdown can cause a suboptimal environment for neuronal cells and results in several brain pathologies, which may eventually lead to neuronal damage and cognitive decline. Most techniques to detect Blood-Brain Barrier breakdown are not sensitive enough to detect the subtle leakage that characterises normal aging, so that previous Blood-Brain Barrier studies did not focus on normal cognitive aging.
A promising method to detect subtle Blood-Brain Barrier leakage in vivo in humans is Dynamic Contrast-Enhanced Magnetic Resonance Imaging. Recently, we developed a new Dynamic Contrast-Enhanced Magnetic Resonance Imaging scan sequence, making our Dynamic Contrast-Enhanced Magnetic Resonance Imaging scan sensitive enough to detect subtle globally distributed leakage spots.

Study objective

The present study will investigate the association between Blood-Brain Barrier leakage and cognitive aging.
Primary research question:
1. a. Is stronger BBB leakage associated with greater decline in episodic memory?
b. Post-hoc explorative analyses investigating the connection between learning/processing speed/complex information processing/compound score/global cognition and Blood-Brain Barrier leakage
Secondary research question:
2. a. Is stronger BBB leakage associated with smaller hippocampal volume?
b. Post-hoc explorative analyses investigating the association of Blood-Brain Barrier leakage with cortical thickness/ WMHs/ markers of SVD/ white matter integrity

Study design

The present study is an observational Magnetic Resonance Imaging study. Participants will be subjected to blood sampling, neuropsychological assessment (approximately 60 minutes with 5 cognitive tests) and Magnetic Resonance Imaging scanning (approximately 60 minutes in total, first without, then with the gadolinium-containing contrast agent).
For the first hypothesis, information on cognitive decline over the past 23

years, obtained from the MAastricht Aging Study and our own baseline measurements, will be used to investigate the association between Blood-Brain Barrier leakage and cognitive aging. The hypothesis will be investigated using our follow-up measurements of radiologically visible brain tissue abnormalities. Potential participants will be selected from the MAastricht Aging Study database, based upon whether they have completed all testing sessions of the MAastricht Aging Study and are not deceased or have obtained a psychiatric or neurological diagnosis in the mean time. For those who meet these criteria according to the MAastricht Aging Study database, the Registration Network of Family Practices database will be checked right before the inclusion to see whether they are not deceased or have obtained any diagnosis in the meantime. The Registration Network of Family Practices works by a strictly anonymous procedure and will only convey the registration numbers of the participants we can approach. All MAastricht Aging Study participants have formally agreed that they may be approached for future studies. Potential participants will receive a short letter announcing a new part of the MAastricht Aging Study with a brief description. A week after receiving this letter, they will be contacted by phone by the principal investigator and asked if they would be interested. Those who are interested will then receive more elaborate information on the present study by mail (including the informed consent form). A week after receiving this information, they will be contacted by phone by the principal investigator again. Over the phone, the principal investigator will record medical history and fill out a questionnaire to check the inclusion and exclusion criteria. The principal investigator will then make an individual appointment for the first testing session with each suitable candidate. At the beginning of the first testing session, participant and principal investigator will sign the informed consent form. Participants will be reminded that they can ask questions the whole time before, during and after the present study. Participants will be invited to come to the Maastricht University Medical Center for blood sampling to measure their blood Haematocrit and creatinine level and determine their cardiovascular risk profile. The blood Haematocrit level will be used to calculate the red blood cell volume, which may influence the amount of leakage from the blood to the brain. The blood creatinine level will be used to calculate the estimated Glomerular Filtration Rate, which indicates renal function or the rate at which the kidneys filtrate blood. Through this filtrate mechanism, substances such as our contrast agent leave the body through the urine. Estimated Glomerular Filtration Rate thus influences how long the gadolinium-containing contrast agent is present in the bloodstream and may therefore influence the amount of leakage. Moreover, very few cases of Nephrogenic Systemic Fibrosis, a serious syndrome characterized by an excess of connective tissue on the skin and internal organs, have been related to the use of the gadolinium-containing contrast agent. Nephrogenic Systemic Fibrosis only occurs in patients with severe acute or chronic renal insufficiency (estimated Glomerular Filtration Rate < 30 mL/min), so that scanning will take place only in case estimated Glomerular Filtration Rate > 30 mL/min. Afterwards, neuropsychological assessment will be performed. If estimated Glomerular Filtration Rate and Mini-Mental State Examination and

Disability Assessment for Dementia scores are sufficient, participants will be invited to return the next week for Magnetic Resonance Imaging scanning.

Study burden and risks

Participants will be subjected to blood sampling, neuropsychological assessment (approximately 60 minutes with 5 cognitive tests) and Magnetic Resonance Imaging scanning (approximately 60 minutes in total, first without, then with the gadolinium-containing contrast agent).
The gadolinium-containing contrast agent is used by the department Radiology on a daily basis in a broad patient population. Moreover, the administration protocol is well established and the laboratory technicians well experienced in administration and handling of possible side effects. All necessary administration equipment, and medication and equipment in the rare case a severe side effect occurs that requires treatment, are standard available on every clinical Magnetic Resonance Imaging scanner.
Participants will be subjected to the risk of positioning an infusion line (bruise; bleeding; infection) and side effects of the gadolinium-containing contrast agent, of which the most severe may be an allergic reaction. The latter is very rare (from >= 1/1000 to < 1/100 cases) and all necessary precautions are taken at the Magnetic Resonance Imaging scanner that such a condition can be identified and treated properly. The gadolinium-containing contrast agent can incidentally cause mild to moderate side effects, although not in all individuals who receive this contrast agent. The most frequent observed side effects are headache, nausea, injection site reactions, disturbed sense of taste and feeling hot (from >= 1/1000 to < 1/100 cases).
Participants will be informed about unexpected medical findings. In case participants do not wish to be informed, they are not allowed to participate in the present study.
Very few cases of Nephrogenic Systemic Fibrosis, a serious syndrome characterized by an excess of connective tissue on the skin and internal organs, have been related to the use of the gadolinium-containing contrast agent. Nephrogenic Systemic Fibrosis only occurs in patients with severe acute or chronic renal insufficiency (estimated Glomerular Filtration Rate < 30 mL/min), so that all participants will be tested on renal function by a blood creatinine test. Scanning will take place only in case estimated Glomerular Filtration Rate > 30 mL/min.

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

- Informed consent before participation
- Participation in 12-year follow-up of the MAastricht Aging Study
- Mini-Mental State Examination score >= 25
- Disability Assessment for Dementia score > 90%

Exclusion criteria

- Contraindications for scanning (e.g. brain surgery, cardiac pacemaker, metal implants, claustrophobia, large body tattoos)
- Contraindications for the gadolinium-containing contrast agent (renal failure) as determined by the estimated Glomerular Filtration Rate < 30 mL/min
- Diagnosis of dementia, prodromal dementia or Mild Cognitive Impairment and in case of doubt prof. dr. Frans R.J. Verhey will decide if the participant may be included
- Diagnosis of other psychiatric or neurological disorders (major depression (< 12 months); history of schizophrenia; bipolar disorder; psychotic disorder NOS or treatment for a psychotic disorder (< 12 months); cognitive impairment due to alcohol abuse; epilepsy; Parkinson's Disease; Multiple Sclerosis; brain surgery; brain trauma; electroshock therapy; kidney dialysis; Menière's Disease; brain infections)

- Structural brain abnormalities
- Cognitive impairment due to alcohol/drug abuse or abuse of other substances

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-05-2017
Enrollment:	61
Type:	Actual

Ethics review

Approved WMO

Date:	01-03-2017
Application type:	First submission
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

ID: 24107
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
CCMO	NL54944.068.16
OMON	NL-OMON24107