Cognitive impairment and functional reorganization in multiple sclerosis: The role of GABA and glutamate

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

Summary

ID

NL-OMON44348

Source
ToetsingOnline

Brief title
GABA and glutamate in cognitive impairment in MS

Condition

- Demyelinating disorders

Synonym
attention and concentration, Cognitive deficits; Problems with memory

Research involving
Human

Sponsors and support

Primary sponsor: Anatomie en Neurowetenschappen
Source(s) of monetary or material Support: VUmc fonds en MoveS (www.moves.ms)

Intervention

Keyword: Cognitive impairment, GABA, Glutamate, Multiple sclerosis

Outcome measures

Primary outcome

The primary outcome parameters are the concentrations of GABA (expressed as GABA to creatine ratio) and glutamate (in mM) in the right hippocampus and thalamus and whole- brain as well as regional GABAA receptor density (in pmol/ml) in MS patients and controls.

Secondary outcome

Secondary outcome parameters are structural and functional MRI measures.

Study description

Background summary

Cognitive impairment occurs in up to 70% of persons with multiple sclerosis (MS) and is a highly disabling symptom, making studies into its underlying mechanisms necessary. Functional Magnetic Resonance Imaging (fMRI) has shown that MS patients with preserved cognition show increased functional activation during cognitive tasks, while in patients with impaired cognition decreased activation was noted. This phenomenon has been described as a process of *functional reorganization* in response to neurological damage, but how it is generated is currently unknown. Findings from neuroimaging research, as well as from post-mortem and animal studies suggest that cognitive deficits in MS and the changes in cognition-related activation levels may be explained by changes in the levels of GABA and glutamate, their receptors and the relation between these systems. However, to date no investigations in MS patients have been performed that examine both GABAergic and glutamatergic systems in relation to functional reorganization in vivo.

Study objective

The main objective of this study is to investigate if the occurrence of cognitive impairment and functional reorganization *defined as increased functional activation in cognitively preserved patients- in MS can be explained

by changes in GABA and glutamate concentration and GABAA receptor binding. The levels of GABA and glutamate will be measured with Magnetic Resonance Spectroscopy and the binding of GABAA receptors will be assessed with Positron Emission Tomography.

Study design

The proposed study is a single-center, cross-sectional patient-control study investigating the differences in glutamatergic and GABAergic systems between groups of MS patients, that show differences in cognition and task-related functional activation levels, and healthy controls.

Intervention

All participants (75) will undergo neuropsychological evaluation and MRI scanning. Based on their cognitive profile and memory-related functional activation levels, a subset of participants (39 MS patients and 13 HCs) will undergo a PET scan with the tracer [11C]flumazenil. This will allow quantification of GABAA receptor binding in the cerebral grey matter. Arterial blood will be continuously sampled during the scans. The radioactivity dose will not exceed 370 MBq

Study burden and risks

All participants will visit the VUmc at least once, for the MRI and neuropsychological examination, and twice if they are also included in the PET investigation. During the first visit one blood sample per participant is taken and the participants undergo neuropsychological testing and MRI scanning, with a total duration of ± 3.5 hours. For all the procedures during the first visit, the burden is low and the associated risks are negligible for both healthy controls and MS patients. The PET scan, during the second visit, is associated with limited risk, but with a moderate radiation burden. However, the radiation dose is subject to strict limits and will not exceed 3mSv. During the PET scan arterial blood samples will be taken (224 ml). Based on the hemoglobin values obtained during the first visit, eligibility for the PET study is determined and hence the arterial sampling is not expected to be a significant burden. This visit takes ± 3 hours. No immediate benefits are to be expected from participation in this study for the participants.

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

To participate in the MRI part of the study:
- Clinically definite Relapsing Remitting or Secondary Progressive Multiple sclerosis
- Sufficient visual acuity and motor performance to perform the MRI task
- Between 18 and 60 years of age;To participate in the PET-part of the study:
- Minimum hemoglobin values of 8 g/dl for men and 7 g/dl for women

Exclusion criteria

For the MRI-part of the study:
- MR contraindications
- Neurological and/or psychiatric disorders (other than MS; e.g. depression, schizophrenia, alcohol or drug abuse)
- For MS patients: the use of corticosteroids in the 4 weeks prior to inclusion. ;For the PET-part of the study:
- benzodiazepine use or other drug use that affects the benzodiazepine site on the GABA receptor system (e.g. imidazopyridines, pyrazolopryimidines en cyclopyrrolones) 6 weeks or less before the start of the study.

- The use of GHB (gamma-hydroxybutyrate)
- In the case of pregnancy or breastfeeding
- Insufficient haemoglobin value values as discussed in the inclusion criteria.
- (a history of) significant cardiac disease
- exposure to previous radiation leading to an annual cumulative dose of more than 10mSv

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-03-2018
Enrollment:	75
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	n.v.t.
Generic name:	Flumazenil

Ethics review

Approved WMO Date:	09-08-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-10-2017

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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
EudraCT	EUCTR2017-002636-16-NL
CCMO	NL62393.029.17