Neurochemical determinants of fast EEG oscillations

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RationaleSince gamma band activity is thought to be an important mechanism in perceptual binding and cognitive function, interest in changes in gamma band activity in neuropsychiatric disorders has grown rapidly. Changes in gamma band oscillations...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Dementia and amnestic conditions
Study type	Interventional

Summary

ID

NL-OMON33528

Source
ToetsingOnline

Brief title
Drugs and fast EEG oscillations

Condition

- Dementia and amnestic conditions

Synonym
Alzheimer's Disease, Dementia

Research involving
Human

Sponsors and support

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

Intervention

Keyword: EEG, GABA, gamma band, Glutamate

Outcome measures

Primary outcome

EEG paradigms

- 40 Hz steady state response

- music listening

- movie watching

- story listening

- resting state

- P300 paradigm

- CNV

Cognitive testing

- Verbal learning task

Immediate recall

Delayed recall after 45 minutes

- Simple Reaction time task

- Choice reaction time task

For more detailed information see chapter 4 of the study protocol.

Secondary outcome

Mood Rating

- Subjective attention scale

- Profile of Mood Scale

Blood sampling

A blood sample of 5 ml is taken via vena puncture. This sample will be centrifuged at 4°C 4000 rpm for 10 minutes. The blood plasma will used to examine the pharmacodynamic properties of the medications used. The blood samples will be stored at freezing temperature at -80 °C until analysis.

Study description

Background summary

A basic question in functional brain research is how the manifold of serial and parallel neuronal activations needed to process basic stimuli are integrated and bound together. The precise timing and integration of neural activation is crucial for successful information processing in the brain. This is known as the
binding problem. Several studies have suggested an important role for high frequency or Gamma Band activity (30 - 100 Hz) in the binding and integration process of neuronal networks in the brain. Gamma band activity can be measured in different paradigms. One is during ongoing cognitive activity. It has been shown that gamma band activity can be measured in relatively simple tasks; movie watching, music listening, story listening.
Patients with Alzheimer*s disease (AD) show impaired performance in tasks that require transfer of information from different locations in the brain. A
review by suggested that the neuropsychological impairment in AD is consistent with a syndrome of disconnection. Several studies have reported decreased gamma

band
synchonisation in AD. The decrease of gamma band synchronization in AD has been considered as a measure of functional disconnection. In a previous study we demonstrated increased gamma band power during music listening, story listening and movie watching, in AD when compared to Mild Cognitive Impairment (MCI) patients and healthy controls. In this study we analysed induced gamma band power, which is considered to reflect perceptual processing of the stimuli.
We furthermore demonstrated that induced gamma band power has a high test-retest reliability in patient groups and that the gamma band power correlated to cognitive performance. An explanation for our findings increased gamma band power in AD reflects compensation for synaptic disconnection in AD. Another explanation is that there is a change in function of the neurotransmitters that normally generate and regulate the gamma band. Acetylcholine, glutamate and GABA are know regulators of the gamma and are changes in function in AD. To evaluate the role of glutamate and GABA in induced gamma band activity, we will repeat our earlier experiment in healthy subjects.
In this study memantine and lorazepam will be used to alter GABA and glutamate function. Memantine is a NMDA receptor antagonist, which is used to reduce neurotoxic glutamatergic activity in AD. Memantine earlier showed to reduce memory performance in healthy subjects.
Lorazepam is a GABA agonist which is common used as an anxiolytic drug.
Hypothesis
Blockade of Glutamatergic neurotransmission by the administration of Memantine will results in decreased gamma band power and synchronization.
Stimulation of GABA-ergic neurotransmission will have no effect on synchronization but will decrease gamma band power. On behavioral tasks it is to be expected that both memantine and lorazepam produce cognitive impairment.

Study objective

Rationale
Since gamma band activity is thought to be an important mechanism in perceptual binding and cognitive function, interest in changes in gamma band activity in neuropsychiatric disorders has grown rapidly. Changes in gamma band oscillations have been shown in a variety of cognitive disorders (Herrmann & Demiralp, 2005). Knowledge on the pharmacological constituents of the gamma band is necessary to be able to use gamma band oscillations as a biomarker in clinical studies or as an endpoint in therapeutical trails. There is evidence that there is an important role for GABA and glutamate in the generation and regulation of the gamma band. Most evidence comes from animal studies and there is little knowledge on how the induced gamma band is regulated in humans. Memantine and lorazepam will be used to alter the GABA-ergic and glutamergic neurotransmission, to evaluate their role in the generation and modulation of the gamma band.

Objectives
• To determine whether induced gamma band power decreases after Memantine compared to Lorazepam and placebo condition.
• To determine whether induced gamma band power increases after Lorazepam
• To determine whether 40 Hz SSR decreases after Memantine, compared to Lorazepam and placebo condition.
• To determine whether 40 Hz SSR increases after Lorazepam, compared to Memantine and placebo condition.
• To determine the effects of Lorazepam and Memantine on synchronization of the 40 Hz SSR.
• To determine the effects of Lorazepam and Memantine on synchronization of induced gamma band.

Study design

The study will be conducted according to a double blind, 3-way crossover design. Treatments will be single oral doses of memantine 30 mg, lorazepam 1 mg and placebo. Balancing of treatments will be accomplished by block-randomization using six treatment orders residing in two 3x3 Latin squares. The minimum washout period between treatments will be 7 days.

Intervention

Memantine a NMDA recptor antagonst and Lorazepam, a GABA agonsist and a placebo will be adminsitered to the participants on tree seperape occasions.

Study burden and risks

The burden for the subjects will be the three testing days, which take 7 hours and might be experienced long and intensive. The EEG paradigms have been used earlier in a study with Alzheimer patients. These Alzheimer patients were able to perform these test without much burden. It is therefore to be expected that these patients are able to perform these test without trouble. The medication used might evoke adverse effects. Earlier publications reported mild adverse effects of memantine and lorazepam. The risks in participating in this study are very low.
The aim of this study is to provide more knowledge on the involvement GABA and glutamate in the regulation gamma band oscillations. These findings are relevant for the evaluation of gamma band changes as a marker of cognitive function.

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

• Is aged >= 21 to <= 35 years
• Is right handed.
• Has the ability to comply with requirements of cognitive and other testing.
• Has provided full written informed consent prior to the performance of any protocol-specified procedure
• Needs to be able to abstain from tobacco use on the day of testing.

Exclusion criteria

• Known, or pre-existing, seizure disorder;
• Previously confirmed EEG abnormality;
• Space-occupying lesion, on history or confirmed by imaging modalities;
• Substance abuse or substance dependence.
• Pregnancy
• Use of medication/s known to cause EEG alterations.

• Systolic blood pressure >165 mmHg or diastolic blood pressure >95 mmHg whilst receiving optimal antihypertensive therapy according to local practice.
• Any clinically relevant abnormality, medical or psychiatric condition, which, in the opinion of the investigator, makes the subject unsuitable for inclusion in the study.
• Use of any investigational agent within 30 days or 5 half-lives (whichever is longer) prior to the screening visit.
• History of alcohol abuse or of drug abuse within the past 6 months.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-09-2008
Enrollment:	31
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ebixa
Generic name:	Memantine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Lorazepam
Generic name:	Lorazepam
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	17-07-2007
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	19-09-2007
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	02-11-2009
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	11-11-2009
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
EudraCT	EUCTR2007-003789-17-NL
CCMO	NL18040.068.07