Pharmacological and genetic imaging of executive function deficits

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Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON31059

Source
ToetsingOnline

Brief title
Pharmacological and genetic imaging of executive function deficits

Condition

- Other condition
- Chromosomal abnormalities, gene alterations and gene variants
- Schizophrenia and other psychotic disorders

Synonym
attention, executive function deficits

Health condition

psychische stoornissen: ontwikkelingsstoornissen (Autisme Spectrum Stoornissen)

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: dopamine, executive function deficits, fMRI, Metyrosine

Outcome measures

Primary outcome

Blood Oxygen Level Dependant (BOLD) contrast measured during executive

functioning tests within the MRI scanner

Secondary outcome

plasma levels of:

* (HVA),

* 3-methoxy-4 hydroxyphenethyleneglycol (MHPG),

* VMA

Urine levels of:

* HVA

* MHPG

* VMA

* dopamine

* norepinephrine

Study description

Background summary

Executive-function-deficits (EFD) are cognitive abnormalities of planning, problem-solving, response-inhibition, and goal-directed behaviour. They result in perseveration, obsessionality and repetitive-stereotypes, which are prominent clinical characteristics in several neuropsychiatric disorders. EFD are cognitive predictors for bad clinical outcome, but their aetiology and neurobiology is unclear.
Neuroanatomically, EFD are monitored by the frontal lobes. Neurofunctionally, frontal lobe EFD lead to *negative* symptoms and social-communicative impairments, which are core clinical features of autism, schizophrenia, and 22q11 deletion syndrome (22q11DS). Neurochemically, EFD are thought to be increased with reduced frontal lobe related dopaminergic neurotransmission. Frontal lobe dopaminergic degradation is modulated by catechol-O-methyltransferase (COMT), an enzyme located on chromosome 22q11. People with 22q11DS, who are haploinsufficient for COMT, have a 50% chance of having autism, and a 30% chance of developing schizophrenia-like-psychosis. EFD are common to all three disorders, causing serious cognitive impairments that result in functional disabilities for which no treatment is available.
The aim of this study is to reveal the underlying neurobiological substrates and genetic markers of EFD.
We will investigate the influence of dopaminergic depletion and genetic variation in COMT on EFD in 20 adults with autism, 20 with schizophrenia, 20 with 22q11DS and healthy controls, measuring frontal lobe executive and resting-state brain function (RSB) (using functional magnetic-resonance-imaging (fMRI)), before and during a pharmacological challenge (administering alpha-methyl-p-tyrosine, AMPT). The underlying neuroanatomy of EFD and the influence of COMT polymorphisms on brain metabolite concentrations, white-matter-connectivity and morphometry will be assessed using Magnetic-Resonance-Spectroscopy, Diffusion-Tensor and high-resolution-structural imaging.
We hypothesize that (i) EFD are increased by dopaminergic depletion, showing a common clinical aetiology across autistic spectrum disorders, schizophrenia and 22q11DS; and (ii) COMT polymorphisms have an influence on EFD, RSB (their brain activation pattern during dopaminergic depletion), and the neuroanatomy of the frontal lobes; revealing a neurogenetic profile of cognitive impairment.

Study objective

With this study we want to identify the common aetiology and neurobiology of EFD, by employing pharmacological and genetic imaging in three neuropsychiatric disorders. We want to identify an underlying functional and structural model for EFD, including possible dopaminergic genetic markers.
We will employ event related fMRI during executive function tasks designed to measure motor- and interference-inhibition, and set-shifting. Event related fMRI will be acquired, both, with- and without dopaminergic depletion. Furthermore, frontal lobe metabolite concentration, white-matter connectivity and morphometry will be measured to obtain neuroanatomical correlates of EFD. Also, the relationship between dopaminergic markers and frontal lobe function,

metabolite concentration, connectivity and structure will be assessed using information on Val/Met COMT polymorphism.

Study design

EFD and frontal lobe brain activity is assessed during three different tasks of the MARS battery using event related fMRI. MARS is a fMRI adapted neuropsychological battery designed to, amongst others, measure: (1) motor-inhibition (GO/NO-GO-task); 2) cognitive interference-inhibition (spatial STROOP-task); and 3) set-shifting (SWITCH-task). All tasks are presented with standardized instructions and in random order to account for systematic errors and fatigue. All three EF-tasks will be assessed twice: with-and without introducing dopaminergic depletion. All subjects will undergo two MRI measurements (part 1 and part 2) and one dopaminergic challenge (subjects will be randomly selected for a cross-over design).
At their first appointment (part 1) at 9:00h (four hours before the first MRI measurement) subjects will receive an oral administration of
a) reversible tyrosine hydroxylase inhibitor (AMPT) or
b) placebo tablets (cellulose, corn starch).
Thereafter, AMPT or placebo will be administered at 11:00h and 13:00h.
One hour after the last dose (at 14:00h) MRI scanning will start.

Blood will be taken at three time points (8:30h: baseline; 12:30h: during the challenge, and 15:00h: after the MRI-measurement) for the assessment of prolactine, and catecholaminergic metabolites (dopaminergic neurotransmission) and AMPT levels. Blood taken at baseline will furthermore be used for the assessment of dopaminergic genetic markers including COMT.
At part 2 of the cross-over design (implemented to assess the effect of AMPT on EFD),
group a) will receive placebo and
b) AMPT.

Intervention

temporary, acute dopamine depletion by giving alpha-metyrosine (AMPT)

Study burden and risks

Possible side effects are stifness (extrapyramidal symptoms), dysphoria, transitory anxiety, tiredness, sedation and sleeping problems. In a previous study of our research group with 24 comparable individuals, in reaction to the proposed dose of AMPT only sleepiness was reported. There have not been any reports of longer lasting side effects, which would also not be expected farmacologically, because of the half life of 3.4- 3.7 hours. In addition, there is a burden in time of 12 hours.

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

20 individuals with 22q11 deletion syndrome (DS) aged 18 till 40 years, 20 individuals with schizophrenia aged 18 till 40 years, 20 individuals with pervasive developmental disorder aged 18 till 40 years and 20 healthy volunteers, matched for age and gender, with no psychiatric history and no use of psychiatric medication.

Exclusion criteria

Pregnancy and presence of metals that are not allowed in MRI-investigation

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-10-2007
Enrollment:	80
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Demser
Generic name:	metyrosin

Ethics review

Approved WMO

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
EudraCT	EUCTR2007-004552-36-NL
CCMO	NL19245.018.07