8 year effect modification by age of methylphenidate on the development of the dopaminergic system in the brain

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To report on the long-term effect modification by age of MPH treatment on brain structure and function, and clinical outcome, as measured by MRI scans, neuropsychological assessment, actigraphy and questionnaires, and to compare these results with...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Structural brain disorders
Study type	Observational non invasive

Summary

ID

NL-OMON49555

Source
ToetsingOnline

Brief title
ePOD-MPH 3.0

Condition

- Structural brain disorders
- Cognitive and attention disorders and disturbances

Synonym
attention deficit hyperactivity disorder (ADHD); attention disorder

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: KiddyGoodPills

Intervention

Keyword: dopamine, methylphenidate, neurodevelopment, neuroimaging

Outcome measures

Primary outcome

- phMRI: % change in ASL signal from baseline in response to acute oral MPH challenge.

- Medication history (obtained from pharmacies of participants with ADHD that provided written consent).

- Clinical outcome: change in ADHD symptom severity and global clinical impression.

Secondary outcome

- Structural MRI: % change for several grey and white matter variables, including cortical thickness, and white matter microstructure (DTI).

- Functional MRI: % change in task-related and resting-state BOLD signal.

- Neuropsychological functioning: change in outcome of several well-validated neuropsychological (computer) tasks addressing attention, memory, simple reaction time and executive function.

- Clinical outcome parameters: emotional dysregulation, anxiety and depressive symptomatology

- Sleep log and actigraphy: % change from baseline.

Study description

Background summary

Methylphenidate (MPH) is primarily used as treatment for attention deficit hyperactivity disorder (ADHD), effectively reducing symptoms of inattention, hyperactivity, and impulsivity in up to 70% of children. MPH blocks the dopamine (DA) and norepinephrine (NE) transporters (DAT/NET), thus increasing extracellular DA and NE in the brain. Its efficacy and safety have been documented in many studies. However, there is still a gap of knowledge concerning the influence of 4-month MPH treatment on brain development and its effect on brain structure and function. Indeed, evidence is accumulating that the long term effects of psychotropic drugs are age-dependent and differ markedly between young and adult animals, due to neurochemical imprinting effects in the developing brain. To investigate the effects of MPH on the developing human brain and dopamine system, we initiated a unique randomized controlled trial (RCT) with MPH (ePOD; NTR3103) in 2011. We found at short-term (trial end), among other things, that in children, but not adults nor placebo condition, MPH increased DA-reactivity, cortical thickness and white matter integrity, as well as sleep efficiency. The aim of the proposed study is to investigate the longitudinal changes in brain structure and function in ADHD patients compared to controls, in order to assess long-term brain development and the influence of medication on the course of this development.

Study objective

To report on the long-term effect modification by age of MPH treatment on brain structure and function, and clinical outcome, as measured by MRI scans, neuropsychological assessment, actigraphy and questionnaires, and to compare these results with healthy controls in light of potential normalization of brain development.

Study design

Naturalistic 8-9 year follow-up study of the ePOD-MPH RCT (NL34509.000.10).

Study burden and risks

Subjects will spend 6 hours during the study visit, during which MRI scans will be obtained and a neuropsychological assessment will be conducted. Moreover, participants will be asked to wear and actiwatch and fill in a sleep log for five days prior to the study visit.
On the day before the study visit all participants will have to adhere to some simple restrictions regarding medication, alcohol and drug intake, as this may affect the outcome parameters. On the day of the study visit participants will have to refrain from smoking and stimulant containing drinks. ADHD patients currently using medication will have to stop for at least 1 week, in order to prevent confounding with our study parameters. There are no risks associated with a medication free period 1 week before the assessment for the ADHD patients.

In the week before the MRI scan, subjects will be asked to wear an actigraph for five days and fill in a sleep-diary. During the study visit, subjects will undergo neuropsychological assessment and will be asked to fill in questionnaires addressing sleep, substance (ab)use including smoking and drinking coffee and other possible confounding parameters. Subsequently, they will undergo the first MRI scan of a maximum of 50 minutes and then will receive an oral challenge with MPH, which is needed for the phMRI and resting-state fMRI measurements. Ninety minutes after receiving the oral challenge, subjects undergo a second MRI scan lasting a maximum of 50 minutes. MRI is a safe method with no long-term side effects. The dose of the MPH challenge may cause an increase in heart rate and systolic blood pressure, but has no significant side effects.

Though the participants of this study will have no direct benefits from participating, the results contribute to the understanding of the long-term safety of MPH in young children and adolescents, as more information about the effects of MPH on the maturing brain will be available. The overall nature and extent of the added risk associated with participation in the current study is to be classified as negligible and the burden can be considered minimal.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

ADHD patients:
- patients who participated in the ePOD-MPH RCT 8-9 years prior (NL34509.000.10), OR
- Male outpatients diagnosed with ADHD (all subtypes) as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV, American Psychiatric Association 1994) and as determined by a structured interview.

Control subjects:
- aged 19-20 years or 30-50 years
- male

Exclusion criteria

All participants:
-Contra-indications to MRI (metal implants, pacemakers, claustrophobia, etc.).
-Contraindications to MPH challenge: cardiovascular diseases such as hypertension, arrhythmia, hyperthyroidism, glaucoma, suicidality, psychosis, Tourette disorder.

Newly included ADHD participants and control subjects:
-IQ < 80 National Adult Reading Test (NART; Nelson 1991, Dutch translation Schmand et al. 1991)
-(History of) major neurological or medical illness (including epilepsy, traumatic brain injury and chronic severe tics or Tourette syndrome).
-(History of) treatment with medications that influence the DA system (for ADHD participants: not including psychostimulants for ADHD treatment) such as: neuroleptics, antipsychotics, D2/D3 agonists (pramipexole and ropinirole)
-(History of) neuropsychiatric disorder other than ADHD (including ADHD for controls) requiring pharmacological treatment
-(History of) dependency of alcohol or drugs that influence the DA such as: MDMA, amphetamine, methamphetamine, cocaine, heroin and LSD
-First-degree relative with (history of) schizophrenia or major depression
-Prenatal use of MPH by mother of the patients.

Control subjects only:
-A score >4 on the ADHD Rating Scale (ADHD-RS)(Kooij et al. 2008).
-Prior treatment with MPH or other stimulants for ADHD

Study design

Design

Study type: Observational non invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-05-2021
Enrollment:	149
Type:	Actual

Ethics review

Approved WMO

Date:	19-03-2021
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
CCMO	NL76068.018.20