MRI determinants of long-term trajectories of ADHD

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To identify brain determinants (moderators) and mechanisms (mediators) of ADHD persistence into adulthood by studying fine-grained neuroanatomy and connectivity in a longitudinal study of genetically stratified patients across the full spectrum of...

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

Summary

ID

NL-OMON44241

Source
ToetsingOnline

Brief title
DELTA

Condition

- Cognitive and attention disorders and disturbances

Synonym
ADD, attention disorder with or without hyperactivity

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Attention-deficit / Hyperactivity disorder, longitudinal, magnetic resonance imaging, myelin

Outcome measures

Primary outcome

The main study parameters are:

- Ratings of clinical symptoms of ADHD and their alterations over time

- MRI-based markers of cortical microstructure, deep white matter

microstructure, and functional connectivity in the brain (see Table 3).

Secondary outcome

The following secondary measurements are taken as part of DELTA either as

exploratory investigations of novel promising directions of study, or as

potential confounders to be taken into account during the statistical analysis:

- Personal history of medication use and therapy

- Wechsler abbreviated scale of intelligence: block design and vocabulary

subtests

- Family interview for genetic studies

- Response inhibition task (Stop-signal task)

- Substance use and dependence questionnaire

- Academic achievement questionnaire

- Mental Health Continuum questionnaire (about positive mental health and level

of functioning)

- Imaginal processes inventory (about mind wandering)

- NEO-five factor invetory of personality

Study description

Background summary

ADHD is a neurodevelopmental disorder that is burdensome for patients, their family and the general society. ADHD has a biological and heritable basis, but its causes have not been identified, and treatments are not universally effective. A subset of patients with childhood ADHD recovers by early adulthood, and most patients experience significant symptom improvement in this developmental period. But, the degree of symptom improvement varies from worsening to complete recovery, and the biological determinants behind this process are completely unknown. A better insight into the biology underlying course of illness in ADHD is necessary to improve and tailor treatments, and will facilitate the designs of future studies focused on interfering with the processes that can facilitate a beneficial long-term course of ADHD for all young patients. In the proposed study entitled *Determinants of Long-term Trajectories of ADHD* (DELTA), we will perform state-of-the-art neuroimaging analysis in one of the largest and best characterized longitudinal neuroimaging studies in ADHD worldwide.
Two leading neurobiological theories, supported by an array of inter-disciplinary evidence, posit that the prefrontal cortex plays a protective and compensatory role in long-term trajectories of ADHD (Halperin & Schulz, 2006; Johnson, 2012). However, due to a lack of repeated MRI measurements in previous studies, the neural moderators and mediators, which give mechanistic insights into this process, have not been distinguished. We hypothesize that DELTA will confirm the central role of the prefrontal cortex and its functional and anatomical connections win course of illness in ADHD. Moreover, the long-term longitudinal design of DELTA will enable us to more specifically characterize the mediating or moderating role of the prefrontal cortex in more detail.
Critical to DELTA are the longitudinal design and the new measurements of intracortical myelin using MRI at 7 Tesla. The longitudinal design is necessary because we need to test mediating and moderating effects of course of illness, which requires the assessments of changes in symptom severity and brain features over time. The scan at 7 Tesla is necessary to test a new hypothesis about fine-grained intracortical organization that is known to undergo drastic neurodevelopmental changes during the typical period of symptom remission in ADHD.

Study objective

To identify brain determinants (moderators) and mechanisms (mediators) of ADHD persistence into adulthood by studying fine-grained neuroanatomy and connectivity in a longitudinal study of genetically stratified patients across the full spectrum of symptom remission and persistence. The objective is to

assess the roles of following neural characteristics on the basis of in vivo MRI:
a. White matter microstructure in large association fiber tracts connecting the prefrontal cortex to the rest of the brain
b. Intracortical myelin across the depth of the prefrontal cortex
c. Functional connectivity of the prefrontal cortex, using a method optimized for our longitudinal design

Study design

This study is observational. DELTA involves new measurements, including new MRI scans, of participants who previously particpated in the IMAGE/NeuroIMAGE studies at our centre, and who at the time gave permission to be contacted again.,

Study burden and risks

The risk of participating in this study is negligible.

The burden of participation is mostly due to the time spent on the study. For some participants also the MRI scan may be somewhat uncomfortable because one is asked to lie still for a long time, and/or because of the noise of some of the scanner sequences. This scanner-related discomfort has been described as "mild" is the past.
It is also possible that the participants are uncomfortable with discussin their past or current psychiatric symptoms and mental health.
Both types of burden are known to the participants because they have previously participated in IMAGE/NeuroIMAGE and because the have been explicitly informed about it before the start of the study. Of course, they are also informed that they can withdraw from participation at any time, without having to provide any reason for their discontinuation.

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

For the NeuroIMAGE study, which forms the basic population within we recruit participants for DELTA, the following inclusion criteria applied: (1) a proband diagnosed with ADHD prior to the IMAGE study by a paediatrician or child psychiatrist, (2) availability of one or more siblings of each proband, (3) age of proband and sibling(s) between 6 and 18 at the time of assessment, (4) availability of proband plus sibling and at least one of their biological parents for DNA collection, and (5) To ensure the genetic homogeneity of the sample, only white Caucasians of European ancestry were included based on information on ethnicity going back to grandparents of the proband/sibling pairs. ;In order to be eligible to participate in the present study, a subject must in addition meet all of the following additional criteria:
- Have been diagnosed with ADHD in childhood, as assessed originally before the IMAGE study, or at any previous phase of IMAGE/NeuroIMAGE, and according to DSM-5 criteria of ADHD. Of note, we will adhere to the requirement of these criteria that symptoms of ADHD must have appeared before the age of 12.
- Have participated in at least one previous phase of IMAGE/NeuroIMAGE, and have thereby provided an anatomical, resting-state and diffusion MRI scan (that passed previous standard quality control criteria) as a result of this.
- Be older than 18 years. This makes it less likely that significant symptom remission typically associated with early adulthood will occur after the current assessment.

Exclusion criteria

(1) IQ<70
(2) a diagnosis of schizophrenia or autism that might confound the diagnosis of ADHD;
(3) neurological disorders such as epilepsy and brain injury, as well as any genetic or medical

disorder associated with externalising behaviors that might mimic ADHD
(4) Contra-indications for MRI, including any metal or ferromagnetic materials inside the body (e.g. dental implants, surgical implants, metal fragments as a result of accidents, pacemakers), pregnancy or suspected pregnancy, claustrophobia.

Study design

Design

Study type: Observational non invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	28-03-2018
Enrollment:	60
Type:	Actual

Ethics review

Approved WMO Date:	16-10-2017
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-03-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-05-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	NL61971.091.17