Proactive versus reactive inhibition in ADHD: Genetics, Neurobiology and pharmacology

Published: 08-06-2012
Last updated: 26-04-2024

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

Summary

ID

NL-OMON41454

Source
ToetsingOnline

Brief title
Proactive versus reactive inhibition in ADHD

Condition

- Cognitive and attention disorders and disturbances

Synonym
aandachtstekortstoornis, ADHD

Research involving
Human

Sponsors and support

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

Intervention

Keyword: ADHD, inhibition, neurobiology, pharmacology

Outcome measures

Primary outcome

The primary outcomes of this study are

(1) Stop-associated ERP measures at baseline (N1 and P3) (objective 1.1)

(2) Stop-associated fMRI measures at baseline (activitity in IFG an SFG)

(objective 1.2)

(3) DAT1 and COMT genotype (objective 1.3)

Secondary outcome

The secondary outcomes of this study are

(1) Coherence of brain activity from EEG (objective 2.1)

(2) Connectivity between IFG and SFG from RS-MRI (objective 2.2)

Study description

Background summary

An estimated 3-5% of all children that attend school suffers of from Attention-Deficit Hyperactivity Disorder (ADHD). In the majority of the cases treatment consist of medication, with the psychostimant methylphenidate (MPH). Seventy to 80% of these children benifit from this treatment, however 20-30% does not. At the moment there are no objective methods to predict whether or not a patient will benefit from treatment. The possibility to be able to predict this response would be of great clinical value.
The current proposal stems from a new framework from ADHD, in which proactive and reactive regulation 'inhibition' are central concepts, and sets the stage for a decisive differentiation of these two components in terms of genetics, neurobiological mechanisms, and pharmacology, with considerable implications for future treatment possibilities.
Different brain changes associated with ADHD form viable endophenotypes for ADHD-research (Durston et al., 2006; Durston et al., 2004; Mulder et al.,

2008). Our recent work shows that these endophenotypes can be used to separate different brain systems involved in ADHD (e.g. (Durston et al., 2007)). Neurobiological systems involved in cognitive control, the ability to inhibit ongoing behaviour in favour of other behaviours, are one of three brain systems important for ADHD. Both proactive and reactive inhibition are key aspects of this ability. Results from neuroimaging studies suggest that the dopamine transporter gene (DAT1) is a key player in mediating the effects of genes on brain structure and function (Durston et al., 2005; Durston et al., 2008) Another line in our research on inhibitory control has focussed on inhibitory control and its disturbances in adult ADHD as measured using the stop task. The stop task is a continuous performance task that includes occasional signals to interrupt an ongoing response. Studies using EEG to measure event-related potentials (ERPs) have shown two electrocortical mechanisms associated with stopping: The stop N1 and the stop P3 (Bekker et al., 2005a; De Jong et al., 1990). Stop N1 is associated with an inhibitory connection between the sensory cortex receiving the stop signal, and the motor system. The efficacy of this connection is most likely controlled by the right inferior frontal gyrus (Aron et al., 2003), in a proactive way (that is, IFG exerts this control in anticipation of a possible stop signal). This control function depends on interactions between IFG and basal ganglia (Aron et al., 2007; Aron and Poldrack, 2006) and is dependent on adequate dopamine transporter (DAT) functioning; consistently, the stop N1 is absent in adult ADHD (Bekker et al., 2005), but restored by methylphenidate that increases synaptic dopamine levels by blocking the dopamine transporter (Overtoom et al., 2009). The stop P3 is reduced although not absent, in both adult and child ADHD (Overtoom et al., 2002). The stop P3 is not remedied by MPH. It is most likely associated with a more last-minute reactive mechanism activated by the stop signal, and based in the superior frontal gyrus (SFG; Bekker et al., 2005a; (Chambers et al., 2009; Floden and Stuss, 2006). These results point to frontal dopamine mechanisms that do not depend on DAT function to the same degree, but rather on other dopamine-modulating mechanisms such as Catechol-O-methyl transferase (COMT). The main hypothesis we aim to address is that there are two mechanisms involved in behavioural control in ADHD, one proactive mechanism, regulated by DAT function in fronto-striatal networks, and one reactive mechanism regulated by COMT function in prefrontal cortex (SFG).

Study objective

The aim of this research is, following the aforementioned theoretical framework, to investigate whether the two candidate genes in combination with EEG and fMRI markers differentiate between children that do and do not show a clinical response to Methylphenidate.

Study design

Eighty ADHD children will perform the stop task both in the fMRI scanner and

during EEG recording, before receiving (their first dose of) MPH. After a single dose of MPH they will again perform the stop task to assess improvements in performance on the cognitive task. Within a month, it will be clear whether they can be considered clinical responders or not. We predict that (1) both cognitive and clinical positive response will be associated with at-risk DAT1-genotype/ reduced IFG activity on fMRI/ reduced N1 ERP at baseline, but (2) not with variation in COMT-genotype/ SFG-activity on fMRI/ stop P3 ERP; and (3) that poor responders will have higher IFG activity on fMRI/ stop N1 ERP at baseline.

Study burden and risks

There are no known risks associated with EEG or MRI acquisition. Both techniques are non-invasive, and do not require administration of any contrast agent or ionizing radiation. For the EEG, an electrode net will be fitted on the child*s head. Although this may take up to 10 minutes, it is not unpleasant for the subject. The MRI procedure is painless and not uncomfortable, although it does require the subject to lie still with the head and part of the body in a tunnel-like device. Children do not find the experience particularly problematic. Many of our child participants have asked to be considered for follow-up studies, and send unsolicited letters to express their enjoyment of the experience.
There is no added risk associated with MPH administration, as subjects will only be included if they are (1) already on MPH or (2) about to be started on MPH for clinical reasons. Any risks associated with taking MPH on the test day therefore, are no greater than the clinical risks associated with MPH use.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

Children diagnosed with ADHD according to DSM IV criteria
Age between 8-16
Willing to discontinue methylphenidate 48 hours before testing
IQ above 75

Exclusion criteria

History of or present neurological disorder
One or more of the following comorbid disorders are diagnosed: generalized anxiety disorder, depression, tics, psychosis or autism
IQ below 75

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):	10-04-2013
Enrollment:	80
Type:	Actual

Ethics review

Approved WMO Date:	08-06-2012
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	22-04-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	24-12-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	28-01-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	25-02-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	01-09-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	26-09-2014

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	12-11-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	18-11-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	EUCTR2012-000992-18-NL
CCMO	NL39158.041.12