Effects of methylphenidate on resting state connectivity in healthy controls and in adults with Attention Deficit Hyperactivity Disorder.

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Primary Objective:The primary objective in the current trial is to use graph theory to examine how the organization of the functional brain network may be altered by the administration of methylphenidate. The main question we intend to answer in…

Ethical review	Not approved
Status	Will not start
Health condition type	Cognitive and attention disorders and disturbances
Study type	Interventional

Summary

ID

NL-OMON39764

Source
ToetsingOnline

Brief title
Effects of methylphenidate on connectivity

Condition

- Cognitive and attention disorders and disturbances

Synonym
ADHD, Attention Deficit Hyperactivity Disorder

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht

Source(s) of monetary or material Support: Hersenstichting Nederland

Intervention

Keyword: - adults, - cognitive functioning, - functional connectivity, - methylphenidate

Outcome measures

Primary outcome

The main study endpoint is the difference in functional connectivity between participants who ingested methylphenidate and those who ingested placebo.

Secondary outcome

A secondary study endpoint is the difference in functional connectivity between participants with ADHD and healthy controls. In addition, the correlation of functional network organization with both task performance (as a measure of cognitive performance) and blood levels of methylphenidate. Lastly, the correlation of whole brain cortical thickness and white matter volume with the main study parameters and task performance (as a measure of cognitive performance).

Study description

Background summary

One of the most controversial recent developments in psychiatry is the increase in the number ADHD diagnoses (Frances 2010). The driving force behind this is the possibility to improve cognitive performance in children with ADHD with pharmacological interventions (Zhang et al. 2011). The effects of pharmacotherapy in adults with ADHD are less well documented, although most studies show a similar trend (Advokat 2010; Faraone and Glatt 2010). Psychostimulants are the most effective pharmacological treatment for ADHD and, among these, methylphenidate is the most commonly applied substance (Faraone and Buitelaar 2010).
The broad use of psychostimulants, especially in subjects with sub-threshold

symptoms and in cases of uncertain diagnosis, is controversial (Mayes et al. 2008; Thakur et al. 2010). Concerns have been raised about the yet unknown effects of long term stimulant use on the developing brain (Greely et al. 2008). Furthermore, psychostimulants may, to some extent, enhance general performance by increasing sustained attention and postponing fatigue. This may be in a way that is not disease-specific. The effects of psychostimulants on performance in healthy adults are equivocal. It is still unclear if cognitive improvement only occurs when there is a baseline deficit, or if it reflects the general effect of psychostimulants (Advokat 2010). It is of pivotal importance to provide a better understanding of how psychostimulants, such as methylphenidate, act on the neuronal mechanisms of the brain, potentially enhancing cognitive performance. In addition, it is important to know if similar effects can be found in both persons with and without ADHD. This information would illuminate if the common use of methylphenidate for patients with a borderline diagnosis of ADHD should be encouraged or rather discouraged. In the past years, neuroscientists have started to study the brain as a system of interacting brain regions. These network studies have started to explore the neuronal interactions between brain regions by combining functional MRI and structural Diffusion Imaging with network theory. This novel approach of applying graph analysis to MRI revealed that brain-wide functional communication is not random, but organized according to a highly efficient small-world organization. This is a network topology characterized by a high level of local neighbourhood clustering, leading to efficient local information processing, and several long distance connections that ensure a high level of global communication efficiency across the network and integration of information between the different regions of the brain (Bullmore and Sporns 2009; Latora and Marchiori 2001; Stam and Reijneveld 2007; Watts and Strogatz 1998). This kind of topology appears crucial for healthy cognitive functioning, as more efficiently functionally connected brains are associated with a higher level of intellectual performance (Li et al. 2009; van den Heuvel et al. 2009). Graph analysis could thus be used to measure the effects of methylphenidate on resting state functional connectivity and relating that to cognitive performance. We propose to explore functional brain communication as a new platform to test the neuropharmacological mechanism of action of methylphenidate in the healthy and diseased brain. To our knowledge, three other studies investigated the effect of methylphenidate with functional MRI. A pilot study by Sheridan et al. (2010) found that stimulants altered lateral prefrontal cortex functional connectivity. However, this study had a sample of only 5 participants with ADHD. Another study investigated the effect of methylphenidate on functional connectivity in 13 children with ADHD during a vigilant attention task. They found that methylphenidate increased frontoparietal, frontostriatal, and frontocerebellar connectivity, compared to placebo (Rubia et al. 2009). A more recent study investigated the effect of stimulants on regional functional connectivity during a working memory task in 18 children with ADHD, and found increased connectivity of fronto-parietal brain areas compared to placebo (Wong and Stevens 2012) The medication used in this study differed per individual, as they received their regular medication

(methylphenidate or dextroamphetamine/amphetamine) and dosage. Results may differ when every participant receives the same type of stimulant and the same dosage.
All three studies examined effects of stimulants on functional connectivity in children or adolescents. To our knowledge, no studies have investigated this effect in adults. These studies also measured functional connectivity during an attention or working memory task. However, measuring functional connectivity during resting state is optimal for finding more global organization patterns in the brain (van den Heuvel et al. 2009).
Furthermore, effects of methylphenidate on functional connectivity in healthy controls were not investigated in any of these studies. The question thus remains if this mechanism of action is specific for a diagnosis of ADHD or whether the use of these stimulants may also improve functional brain communication, and therewith brain efficiency, of healthy controls.

Study objective

Primary Objective:
The primary objective in the current trial is to use graph theory to examine how the organization of the functional brain network may be altered by the administration of methylphenidate. The main question we intend to answer in this study, is whether, and if so to what extent, methylphenidate affects the organization of brain networks.

Secondary Objectives:
- To examine how a reorganization of brain networks as described in the primary objective is related to improvements in cognitive performance.
- To examine if any of the effects on brain connectivity differ between participants with ADHD versus healthy controls.
- To examine if certain network structures of the brain, such as cortical thickness and white matter volume, are related to susceptibility to medication efficacy.
- To examine if the structural qualities are related to cognitive performance.

Study design

In the proposed study, we intend to measure the effects of methylphenidate on cognitive performance and on resting state connectivity in a double blind randomized placebo controlled design. A placebo-controlled design was chosen in order to differentiate between clinical effects of methylphenidate and effects caused by other factors associated with experimental treatment, such as induced expectations in participants.
40 healthy adult men and 40 men with a diagnosis of ADHD will be included. The two groups will be matched for age, handedness and education to minimize differences between groups that may confound study results. Subjects will participate in a cross-over design to remove between-subjects variability. For

each participant an MRI scan will take place twice, approximately two weeks apart (no more than 4 weeks apart), to assess resting state functional connectivity. For each subject this will happen once after ingestion of a placebo capsule/tablet and once after a single oral dose of an identical capsule/tablet with methylphenidate, in a randomized order. Following this, subjects will engage in cognitive tests. Cognitive assessment includes 5 tests tapping into the domains of, attention, sustained attention, working memory, distractibility and executive functioning. Different sets of stimuli in the cognitive tests of the first and the second occasion will be used, in order to avoid learning effects. Blood samples for drug level measurement will be drawn before the fMRI scan, before the cognitive testing, and after the cognitive testing. All measurements will be done at the University Medical Center in Utrecht.

Intervention

After a thorough screening before inclusion, two visits are planned. These visits are identical to each other for the major part; the participant will be administered a tablet. After an hour, a blood sample is taken to measure the blood level of methylphfenidate. Afterwards, the subject undergoes an fMRI scan that takes approximately 45 minutes. After the scan, the participant gets a short break. Following this, subjects will engage in cognitive tests. This takes approximately an hour. Finally, a last blood sample will be taken to measure the blood level of methylphenidate.
The one difference between these two visits is the contents of the tablet: in randomised order, the participant receives a methylphenidate tablet once, and once a placebo tablet with an inactive substance.

Study burden and risks

The major concern with the use of methylphenidate is occurrence of serious cardiovascular events due to possible increase of heart rate and blood pressure. However, a large study among young and middle-aged adults showed that current or new use of ADHD medication such as methylphenidate was not associated with an increased risk of serious cardiovascular events (Habel et al.). As subjects in the current study will only ingest a dose of 0,5 mg/kg methylphenidate once and are thoroughly screened before inclusion in the study, chances of any serious side effects are greatly diminished and health risk is minimal. Furthermore, blood samples will be drawn by experienced research physicians so health risk attributable to this procedure is minimal as well.
The MRI scan procedure is painless and safe, there are no known health risks.
The cognitive testing will take 30 minutes on each occasion and requires sustained attention from the participants.

There are no direct benefits for the participants of this study. However, the results of this study may be of value for society. The study could help unravel

if cognitive effects of methylphenidate should only be expected in cases of ADHD or if a positive response can also be found in persons without ADHD. Furthermore, it can help answer the question of how this drug affects the brain to improve cognition. If we can illuminate how methylphenidate affects the brain to improve cognition, we may have better arguments to emphasize or discourage the common use of methylphenidate for an extended population with borderline diagnosis of ADHD. With the results of this study, better recommendations can be made for people with ADHD related symptoms on optimal drug use.
In addition, discovering the route by which methylphenidate influences cognitive performance may help in the development of new cognitive enhancers. Such new cognitive enhancers may not only prove useful for the treatment of ADHD, but may, potentially, also lead to new possibilities of improving negative symptoms of schizophrenia that are related to a lack of concentration and lack of energy, or postpone the clinical symptoms of dementia such as executive functioning deficits. As the project involves minimal risk to participants, and as the potential benefits in terms of knowledge gained are quite large, the benefits clearly outweigh the risks.

Contacts

Public
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584 CX
NL
Scientific
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584 CX
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Male sex
- Written informed consent
- For the ADHD group only: a diagnosis of ADHD.
- Physically healthy (according to physical screening)

Exclusion criteria

- Age under 18 or over 40
- Previous or current medical, psychiatric, or neurological problems (with exception of ADHD for the ADHD group)
- Use of psychotropic medication
- Use of recreational drugs in the two weeks before start of the study
- Consuming an equivalent of >5 cups of coffee per day
- Consuming three or more alcohol units per day
- The presence of one or more of the contraindications or warnings
against the study drug as listed in the SPC
- Presence of any contraindication to MRI scanning (e.g. implanted metallic object or electronic device)

Study design

Design

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	80
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Ritalin
Generic name:	Methylphenidate
Registration:	Yes - NL outside intended use

Ethics review

Not approved

Date:	05-03-2013
Application type:	First submission
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	EUCTR2012-005339-95-NL
ClinicalTrials.gov	NCT01764672

Register	ID
CCMO	NL42603.041.12