Attention Defficity Hyperactivity Disorder and fMRI neurofeedback: A randomized controlled trial on the effects of self-modulating anterior cingulate cortex activation levels.

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The principal objective of this study will be to critically evaluate if the fMRI-neurofeedback training is successful in reducing ADHD symptoms and improving cognitive functioning. Thus, the first goal is to show that ADHD patients are able to...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Cognitive and attention disorders and disturbances
Study type	Interventional

Summary

ID

NL-OMON37512

Source
ToetsingOnline

Brief title
ADHD and fMRI-neurofeedback

Condition

- Cognitive and attention disorders and disturbances

Synonym
Attention Deficit Hyperactivity Disorder

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: The project is part of BrainGAIN;funded by NWO

Intervention

Keyword: ADHD, anterior cingulate cortex, fMRI, neurofeedback

Outcome measures

Primary outcome

Primary outcome messure

• ADHD symptom score according to the ADHD DSM-IV rating scale

Statistical Analysis (primary and secondary study parameters)

Related to primary objective (1): Investigate whether fMRI-neurofeedback

training reduces ADHD symptoms:

For the ADHD symptom score, the sustained attention measures, the working

memory measures, and the fMRI resting state anterior cingulate cortex

connectivity several independent 2 x 2- way ANCOVAs (one per outcome measure)

will be conducted (two-tailed, significance level is set at 5%) with session

(pre-vs. post-treatment) as within-subjects factor, group (fMRI-neurofeedback

vs. control neurofeedback) as between-subjects factor, and age, sex and IQ as

covariates.

For the cognitive interference measures, and the fMRI anterior cingulate cortex activation level/ connectivity during MSIT several independent 6 x 2- way ANCOVA (one per outcome measure) will be conducted (two-tailed, significance level is set at 5%) with session (number of training session) as within-subjects factor, group (fMRI-neurofeedback vs. control neurofeedback) as between-subjects factor, and age, sex and IQ as covariates.

The influence of current state of motivation on training success will be calculated by computing non-parametric Spearman*s rank correlations within each individual patient.

The mental strategies used will be scored and their influence on training success will be evaluated by computing non-parametric Spearman*s rank correlations within each individual patient.

Related to primary objective (2): Investigate if the abnormal activation levels in ADHD patients play a causal role in ADHD pathophysiology:

To estimate the influence of the neurofeedback training on the symptoms a measure of change in activation level during the neurofeedback training/ the transfer blocks at the end of the training will be developed. This measure (sessions x subjects) will be correlated with the performance on the MSIT task

in the subsequent session within and across the two groups (fMRI-neurofeedback and control neurofeedback).

Secondary outcome

Attention & Hyperactivity (before and after training)

• Sustained attention score according to SA-DOTS and SART

• Working memory score according to Digit Span and Nback-task

• Anterior cingulate cortex activation connectivity during resting-state fMRI

fMRI Neurofeedback Training (during each training session)

• Current Motivation according to QCM

• Cognitive interference score according to MSIT

• Anterior cingulate cortex activation level during MSIT/ neurofeedback training

• Mental strategies used during neurofeedback task

Study description

Background summary

ADHD

Attention-deficit/hyperactivity disorder (ADHD) is the most commonly diagnosed childhood-onset neuropsychiatric disorder. It is characterized by inattention, hyperactivity, and impulsivity, either alone or in combination (American Psychiatric Association, 2000). While 5 to 10% of all school-aged children in European countries are affected, the disorder may persist into adulthood in one third of the cases or more (Spencer, Biederman, & Mick, 2007). Individual and societal costs include impaired academic, occupational, and social functioning, increased rates of substance abuse, traffic accidents, and persistent

neuropsychological impairments (Biederman, 2004; Secnik, Swensen, & Lage, 2005). Because of the severity and enduring nature of the functional impairments associated with ADHD, a substantial amount of scientific effort has been directed on understanding the pathophysiology of ADHD and identifying effective treatments of ADHD. Both topics will be addressed by this study.

Current treatment of ADHD

While first-line treatment for children with ADHD is the prescription of psychostimulants (i.e., methylphenidate or dextro-amphetamine), there is no approved first-line treatment for treating adults with ADHD in the Netherlands. In general drug treatment in adults has proven to be less effective than drug treatment in children. A review on the efficacy of medications in ADHD adults concluded that the response rates to medication were only 50 % when stimulants were prescribed and as low as 20 % when nonstimulants were taken (Faraone & Glatt, 2010). Common adverse effects of stimulants include vertigo, decreased appetite, weight loss, mood lability, tension, and depression (Santosh, Sattar, & Canagaratnam, 2011). Adverse effects are especially problematic because treatment is generally long term, as symptoms of ADHD reappear after discontinuing drug treatment. Also, while medication does improve attention, it is still unclear if it has a positive effect on academic, occupational and social functioning in adults with ADHD (Santosh, Sattar, & Canagaratnam, 2011). Data on the efficacy of alternative treatments as for example cognitive behavioral treatment in ADHD in adults is still preliminary (Antshel et al., 2011).

One proposed alternative treatment without adverse side effects is EEG-neurofeedback. Neurofeedback in general is defined as a procedure during which a participant learns self-control over some aspect of neuronal functioning of his brain through getting feedback on it. The aim in general is to normalize a deviant neuronal pattern, which should also lead to a reduction of the symptoms of the patient. The goal in ADHD patients is to teach participants how to control certain EEG signals that are an indicator of alertness (Sterman, 1996). Recent reviews on EEG-neurofeedback have concluded that preliminary results are very promising regarding the reduction of ADHD symptoms and improvement of cognitive deficits (Fox, Tharp, & Fox, 2005; Heinrich, Gevensleben, & Strehl, 2007; Hirshberg, 2007; Loo & Barkley, 2005; Rossiter, 2004).
These results have spurred interest into the development of other neurofeedback methods as well, as for example neurofeedback based on functional magnetic resonance imaging (fMRI). The advantage of fMRI-neurofeedback over EEG-neurofeedback may be the higher spatial resolution and full brain coverage achieved with fMRI, and therefore also a faster treatment response. Functional magnetic resonance imaging (fMRI) was the first non-invasive imaging method to provide us with high spatial resolution measurements of blood oxygenation as an indirect measure of neuronal activity (Bandettini, Birn, & Donahue, 2000), and has thus advanced our understanding of the human brain considerably over the

last 20 years.

fMRI-neurofeedback

fMRI is a method with a high degree of patient safety, there is no evidence for hazards associated with increasing exposure (Hawkinson et al., 2011; Schenck, 2000). Since the mid-1990s several research groups have been working on the development of fMRI real-time techniques, techniques which allow for immediate data processing and data analysis during fMRI scanning. Current real-time fMRI procedures include most state-of-the-art data preprocessing and analysis steps of its classical offline counterpart (Weiskopf, in press; Weiskopf et al., 2007). Importantly, it has been show that real-time fMRI setups have a safety level similar to a normal fMRI setup (Hawkinson et al., 2011).
Next many studies have focused on the general feasibility of fMRI-neurofeedback. As in EEG-neurofeedback the goal is to learn how to voluntarily modulate some aspect of neuronal activity. Numerous studies have shown that participants are indeed able to control their brain activation patterns in very specific ways, and that participants profit from using fMRI-neurofeedback when learning how to do this (Weiskopf, in press). Importantly, specific behavioral effects are correlated with specific changes in brain activation patterns (Weiskopf, in press). Also, first studies with patients indicate that patients with disorders as diverse as chronic pain, tinnitus, schizophrenia, psychopathy, parkinson and stroke may experience some relief from their symptoms after a fMRI-neurofeedback training (deCharms et al., 2005; Haller, Birbaumer, & Veit, 2010; Ruiz et al., 2011; Sitaram et al., 2011; Subramanian et al., 2011; Veit, 2009).

fMRI research on ADHD

As the general goal in patient studies is the normalization of the brain activation patterns which are linked to the behavioral symptoms of this disorder, one of the most important considerations for setting up an fMRI-neurofeedback training is which aspect of the brain activation patterns are most closely linked to the behavioral symptoms. By convergent data from a variety of sources, including neuroimaging, neuropsychological, neurochemical and genetic studies, the core symptoms of ADHD have been linked to abnormalities in the functioning of frontal, cingulated and parietal cortical brain regions (Bush, 2011). The brain region that has been most consistently linked to ADHD pathology across all these studies is the dorsal anterior cingulate cortex (Bush, 2011). Long term structural changes have been shown in this region (Amico, Stauber, Koutsouleris, & Frodl, 2011; Konrad et al., 2010; Makris et al., 2007; Seidman et al., 2011; Seidman et al., 2006), and fMRI research has consistently found a characteristic pattern of hypoactivation when subjects are performing tasks which are typically challenging to them, e.g. interference task, continuous performance test, switch task, response inhibition task (Bush, 2011; Bush et al., 1999; Bush et al., 2008; Cubillo et al., 2010; Dickstein, Bannon, Castellanos, & Milham, 2006; Schneider et al.,

2010). It has also been shown that this hypoactivation normalizes after successful treatment with ADHD medication (Bush et al., 2008). Normalization of this pattern of hypoactivation thus seems to be a crucial aspect in treatment success.

In the proposed study we want to train ADHD patients how to voluntarily upregulate the activation level of the dorsal anterior cingulated cortex. Several previous studies with healthy participants as well as with pain patients has already shown that in general it is possible to upregulate the activation level of the anterior cingulate cortex (deCharms et al., 2005; Hamilton, Glover, Hsu, Johnson, & Gotlib, 2011; Weiskopf et al., 2003).

Study objective

The principal objective of this study will be to critically evaluate if the fMRI-neurofeedback training is successful in reducing ADHD symptoms and improving cognitive functioning. Thus, the first goal is to show that ADHD patients are able to voluntarily modulate their individual anterior cingulate cortex activation level. Secondly, it has to be demonstrated that this modulation has a specific influence on ADHD symptoms and the performance during cognitive tasks. Finally, it has to be critically evaluated which outcome measures are positively modulated, and which are the moderating factors for treatment success. All the cognitive tasks that have been included in the design are also possible moderating factors.

The second objective of this study is further enhancing the understanding of the pathophysiology of ADHD. Neurofeedback studies in general are seen as an excellent tool for investigating the causal influence of abnormal brain activation levels. As the regional brain activation level is manipulated in a neurofeedback experiment, the ADHD symptoms and cognitive functioning become the outcome measure. If one would succeed in influencing behavior through manipulating brain activation patterns, this would be strong evidence for a causal role of the abnormal activation levels of the anterior cingulate cortex in the pathophysiology of ADHD.

Summary objectives

(1) To investigate whether fMRI-neurofeedback training of ACC activation level reduces ADHD symptoms and improves cognitive functioning.

(2) To investigate if abnormal activation levels of ACC in ADHD patients play a causal role in ADHD pathophysiology.

Study design

This study is a randomized controlled trial (RTC) with blinding of the participants and blinding of all raters. ADHD adults will be randomly and blind allocated to one of the following 2 groups:

1. fMRI-neurofeedback training, feedback from dorsal anterior cingulate cortex (n=10)
2. fMRI-neurofeedback training, feedback from control brain region (n=10)

Each group will receive the same screening, pre- and post-assessment and 6 fMRI-neurofeedback training sessions. The duration of each fMRI-neurofeedback training session will be approximately 75 minutes. The frequency will be weekly sessions. The duration of the experiment for each participant from the selection until the last session will be approximately 8 weeks.
The control group will receive exactly the same as the fMRI-neurofeedback group, except for the feedback. The control group will receive feedback from a control brain region, which will be selected such that it is activated by different tasks than the dorsal anterior cingulate cortex. This selection will be made based on literature research, previous data, and data from an ongoing pilot experiment.

In the following part, we will describe detailed the whole procedure from beginning till end, including the rationale for the proposed measurements.

Location

Selection of subjects, screening for eligibility and assessments, and the fMRI-neurofeedback training will be performed at the FCDC. All fMRI assessments will be performed on a Siemens T3 Magnetom MRI scanner.

During the screening session (~ 75 minutes) the inclusion/ exclusion criteria will be assessed (DSM IV interview, fMRI screening interview, age, IQ Test, use of medication, significant medical conditions, participation in therapy, and participation in other clinical trials). Also the following two baseline measurements will be made:

• A first assessment of the severity of ADHD symptoms the ADHD DSM-IV rating scale, which is a widely used instrument for determine the severity of ADHD, fully based on the DSM-IV (American Psychiatric Association, 2000; Kooij et al., 2005).

• To estimate the intelligence, a shortened version of the WAIS-III-NL (Uterwijk, 2005) will be administered; the Vocabulary test (~10 minutes) and the Block Design test (~10 minutes). Validity coefficients for the Vocabulary and Block Design scores relative to the full form are .88 for Verbal IQ and .83 for Performance IQ (Antshel et al., 2007).

After the screening session randomization will be performed. Randomization will

be used to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown factors (expectations of the therapy, motivation etc.) are evenly balanced across treatment groups and to enhance the validity of statistical comparisons across treatment groups. Randomization will be stratified according to ADHD symptom score and IQ score.

An elaborate assessment of the ADHD symptoms will take place during the pre-training session (~75 minutes). During this session a neuropsychological assessment and a resting-state fMRI measurement will be completed. The following neuropsychological tests will be used:

Meta-analytic studies of neuropsychological function in ADHD report moderate to large effect sizes a sustained attention deficit in ADHD (Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). To assess sustained attention we will use the Sustained Attention dots task (SA-DOTS) as well as the Sustained Attention to Response Task (SART). Both tasks have been shown to discriminate ADHD patients from healthy subjects (Marchetta et al., 2008; Slaats-Willemse et al., 2005; Smilek et al., 2010).

• The SA-DOTS (~15 minutes) is the so-called continuous performance task from the ANT, a computerized neuropsychological test battery (De Sonneville, 1999). During the SA-DOTS task the subject is presented random spatial dot patterns with 3-5 dots. The subject needs to press yes for a 4 dot pattern and no for a 3, or 5 dot pattern. Premature responses, false alarms, misses, the reaction time and the standard deviation of the reaction time are indicators of the ability to maintain attention over time. The test-retest reliability of the SA-DOTS is excellent (0.93 - 0.97, personal correspondence with Leo de Sonneville), which makes the test suited for measuring differences in the ability to sustain attention before and after the fMRI-neurofeedback training.
• During the SART (~10 minutes) single digits are presented at a rate of just over one per second. Participants are told to press a button to every number, except if that number is 3. As the task is repetitive and apparently easy, it requires participants to maintain attention.

Another neuropsychological function that has been implicated in the ADHD is working memory. Differences to healthy participants have been found for verbal as well a spatial working memory, meta-analytic findings show an effect size of 0.41 to 0.51 for ADHD versus non-ADHD (Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). Additionally, working memory capacity has been linked to successful learning during neurofeedback trainings (Hammer et al., 2012). We will thus assess verbal working memory with the Digit Span subtest of the WAIS-III-NL and visuo-spatial working memory using a visuo-spatial Nback task.

• During the Digit Span (~10 minutes) test a sequence of digits is presented orally. The digit span is then measured by forward- and reverse-order (backward) recall of the digit sequences. Backward recall is interpreted as a measure of working memory. In the standard digit span test, the sequences are

presented with increasing length and testing ceases as soon as the participant makes two consecutive errors. We will use a slightly different procedure, which was developed recently: all possible trials are presented and a mean score across all trials is calculated (Woods et al., 2011). Test-retest reliability for this procedure has been shown to be very good (0.83 for backward span)(Woods et al., 2011).
• To assess visuo-spatial working memory > NBack task in IMpACT
Finally will assess cognitive interference, as subjects with ADHD usually underperform on tasks that require cognitive interference (Bush, 2011; Bush et al., 1999; Bush et al., 2008; Cubillo et al., 2010; Dickstein, Bannon, Castellanos, & Milham, 2006; Schneider et al., 2010). We will use the Multi-Source Interference Task (MSIT), a task that has been especially developed such that it reliably and robustly causes very strong interference effects (Bush & Shin, 2006). It has also been shown that the MSIT discriminate ADHD patients from healthy subjects (Bush et al., 2008).

• During the MSIT (~10 minutes) subjects are presented with a visual display of a set of three numbers (0, 1, 2 or 3). They are asked to report, via button press, the identity of the number that differs from the other two numbers. Interference is caused between the value of the target number, the value of the accompanying numbers, the value of the location of the target number, and the location of the hand used to answer.

After the neuropsychological testing the pre-training session continues with a short fMRI scanning session (~20 minutes total), which includes an anatomical scan (~10 minutes) and a resting-state fMRI scan (~8 minutes). This resting-state fMRI scan will serve as a baseline measure to estimate the severity of the ADHD brain pathophysiology. Previous studies have shown that adults with ADHD show decreased coupling of the anterior cingulate cortex with other brain regions in comparison with healthy subjects (Castellanos et al., 2008). Additionally, this fMRI session will have the function of a practice session, during which subjects can get acquainted with the scanner environment, and the researchers who will be present during the later fMRI-neurofeedback training. If subjects are not comfortable in the scanner environment during the practise session they will be excluded from the study at this point.

• The fMRI session will proceed as follows. Subjects will be carefully instructed to remove all metal objects before entering the MRI scanner. To restrict head movements and to limit motion artefacts, the participant*s head will be fixed by foam cushions and ear clamps positioned behind the neck and around the head. Participants will also be reminded to keep their head as still as possible. Headphones customized for MRI experiments will be inserted into the head coil and will provide isolation from scanner noise. These headphones will also be used to present instructions to the participants. To accustom subjects to the scanner noise the anatomical scan will be performed first.
• A high-resolution anatomical MRI scan will be acquired that is optimized for volumetric measurement of individual brain areas and of gray and white matter

volumes and that can serve as anatomical reference for the functional scans. Subjects are told to relax and lie still during the anatomical scan.
• Second the resting-state scan will be performed. Resting-state fMRI measures fluctuations in the Blood-Oxygen-Level-Dependent (BOLD) signal in gray matter brain areas while the subject is at rest (not performing a task). Participants will be instructed to relax and remain still with eyes open for 8 minutes in the fMRI scanner.

During the second week the first fMRI-neurofeedback training session (~75 minutes) will take place. At the beginning of the session subjects are asked to fill in a short questionnaire on their current state of motivation regarding the training. Previous neurofeedback studies have shown that state of motivation is an important predictor of training success (Hammer et al., 2012; Nijboer, Birbaumer, & Kubler, 2010). Current state of motivation will be measured using an adapted version of Questionnaire for Current Motivation (QCM) (Nijboer, Birbaumer, & Kubler, 2010; Rheinberg, Vollmeyer, & Burns, 2001).

• The QCM (~10 minutes) consists of 18 short statements which have to be rated to which extend they apply on a 7-point Likert-type scale. Four factors of motivation (mastery confidence, incompetence fear, interest, and challenge) can be extracted from these 18 items.

After this the fMRI training session (~50 minutes total) will start. Each training session consists of three parts: a) localizer task (~10 minutes), b) anatomical scan (~8 minutes), and c) neurofeedback training (~30 minutes). Only during the sixth and last training session there will be an additional resting-state fMRI scan (~8 minutes) at the end of the session (see above).

In this study the designated feedback region will be defined individually at the beginning of each training. At the beginning of the session subjects will thus be asked to perform the Multi-Source Interference Task (MSIT) as the localizer task. The individual fMRI data collected during performance of localizer task will be analyzed immediately using fMRI online analysis software (TurboBrainVoyager 3.0, http://www.brainvoyager.com/products/turbobrainvoyager.html). The general procedure and safety precautions are the same as during the resting-state fMRI (see above). Visual stimuli will be presented on a screen that the participant will be able to see by means of a mirror attached to the head coil of the MR scanner.

The MSIT is chosen as the localizer task because subjects will already be acquainted with the task, as they have performed it during neuropsychological testing (see description above). It is also known that this task robustly and reliably activates the dorsal anterior cingulate cortex, also across sessions (Bush & Shin, 2006; Bush et al., 2008). Finally, this task has been successfully used in an ADHD patient group to localize dorsal anterior cingulate cortex (Bush et al., 2008).

After localizer task and the anatomical scan the fMRI-neurofeedback training will start (see description in section 5. treatment). The fMRI setup during the training will be the same as during the localizer task.

After each training subjects will be asked to fill in a short questionnaire (~10 minutes) on the strategies that they used during this training (Sorger, 2010). Participants will also be encouraged to practise and think about the mental strategies at home in-between the training sessions. Training sessions will take place once a week.

One week after the last training session the post-training session (~75 minutes) will take place. All the neuropsychological tests from the pre-training session will be repeated (SA-DOTS, SART, Digit Span, Nback-task, MSIT-task, see above), as well as the assessment of ADHD symptoms performed during the screening (see above).

Intervention

The fMRI-neurofeedback training will proceed as follows. Before the training the subjects will be suggested a set of mental strategies that they may use during the neurofeedback training (same set of strategies in both groups). It will be stressed that they are always free to choose any strategy that seems to work, and that they should be guided by the feedback in the selection of their mental strategy. During the training they will receive visual feedback about the current activation level (% signal change) of their dorsal anterior cingulate cortex (experimental group), or the control region (control group). This feedback will be presented using a visual thermometer display, which will be continuously updated (every 1.5 second) (Sorger, 2010). The thermometer will be individually scaled according to the activation level measured during the previous localizer task (Sorger, 2010). Participants will be instructed to increase and maintain activation levels to a 50% or to a 100% level, depending on the cue at the beginning of a 30 second *block*. A similar instruction has been successfully used in previous studies with healthy participants (Sorger, 2010). Each block of 30 seconds with neurofeedback will be followed by a resting period of 20 seconds. Subjects will perform 3x8 feedback blocks, with self-paced breaks after each *run* of 8 blocks. Then, an additional 8 blocks will follow, during which subjects will be asked to apply whatever strategy they have learned previously, but now without neurofeedback. They will thus be asked to transfer what they have learned during the training to a situation without neurofeedback.

Study burden and risks

Risks or side-effects are not expected. The burden for the ADHD subjects consists of an intake, pre- and post-treatment assessments (3 visits of 75 minutes), and 6 visits of approximately 75 minutes for the fMRI-neurofeedback

training. Intake, pre-assessment without fMRI, a treatment-phase and an evaluation carry the same burden as treatment as usual. The benefit involves of the a priori chance of positive effect of the fMRI-neurofeedback on ADHD symptoms.

For all ADHD subjects treatment effect is prospected. The risks of this study are estimated as very low. Potential benefit of this study is not only expected for the subjects of this study in terms of treatment response, but for all ADHD patients in terms of expanding knowledge and extending treatment opportunities.

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

1.) Diagnosis of ADHD according to the DSM-IV TR criteria
2.) fMRI screening criteria
3.) Age > 18
4.) IQ > 85
5.) Psychopharmaca-naïve or -free, or being on a fixed dose of medication for the study period

Exclusion criteria

1.) Current diagnosis of one or more Axis I diagnosis other than ADHD according to the DSM-IV TR criteria
2.) Other significant medical condition/ regular use of medication other than psychostimulants
3.) Participation in another clinical trial simultaneously

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-08-2013
Enrollment:	0
Type:	Actual

Ethics review

Approved WMO Date:	27-09-2012
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-06-2013
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	NL40273.091.12