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fMRI neurofeedback as a novel treatment for children with attention deficit hyperactivity disorder (ADHD)

Submission date
28/06/2017

Recruitment status
No longer recruiting

Registration date
30/06/2017

Overall study status
Completed

Last Edited
12/08/2022

Condition category
Mental and Behavioural Disorders

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Attention deficit hyperactivity disorder (ADHD) is one of the most prevalent childhood disorders, with symptoms of poor attention and poor self-control. The aim of this study is to test a new, non-drug, brain-based treatment for ADHD that has no known side effects and is expected to be welcomed by patients, parents and professionals. ADHD is linked to reduced activation in part of the brain called the right inferior prefrontal cortex (rIFC) and its associated networks. rIFC activity is increased by psychostimulant medication, the benchmark treatment for moderate to severe ADHD. However, stimulants are associated with side effects, are not suitable for all patients, and longer-term effects have not been demonstrated. Furthermore, patients and their families prefer non-drug alternatives to medication. However, to date these have shown modest effectiveness. A treatment that is based on the neuroscience of ADHD and targets the key brain function deficit of ADHD may be successful. Neurofeedback (NF) teaches participants to achieve self-control over the activation of specific brain areas and networks associated with the specific region, affecting the associated behaviours. Real-time functional magnetic resonance imaging neurofeedback (rtfMRI-NF) is able to target the key brain function abnormalities in ADHD. A previous small study showed that children with ADHD can learn to self-regulate the rIFC within 11 rtfMRI-NF sessions of less than 10 minutes each, with significant transfer effects (learned self-regulation without NF), and that this is associated with improved symptoms, cognitive (thinking) improvements and enhanced activation of the rIFC during a task of self-control. This larger study aims to test the effectiveness of rtfMRI-NF in children with ADHD on improving ADHD behaviour, brain function and cognition.

Who can participate?
Boys aged between 10 and 18 with ADHD

What does the study involve?
Participants are randomly allocated to receive either active neurofeedback or sham neurofeedback. Participants in the active neurofeedback group undergo rtfMRI-NF to learn to increase their own brain activation in the rIFC in 15 sessions of 7.5 minutes each. This is done over four MRI sessions of 60-70 minute duration each over 2 weeks. Within each MRI session

there will be 2-5 runs of rtfMRI-NF of 7.5 minutes each. The sham neurofeedback group receive the same number of runs of rtfMRI-NF as the active group but the feedback is from another person from the active group. Participants are tested before and after the treatment to assess ADHD severity, attention, self-control, brain activation, and side effects. ADHD symptoms and cognitive performance are also measured 6 months after the neurofeedback to test whether the benefits persist in the long term.

What are the possible benefits and risks of participating?
It is possible that the ADHD behaviour improves with the neurofeedback, in particular for patients who are in the active group. This is what was found in the previous study. However, it cannot be guaranteed that patients get better as this is a research study and there is no guarantee that every child gets better with the neurofeedback treatment. Previous studies have shown that some children improve a lot after neurofeedback and other children do not improve that much. Given that we have two types of neurofeedback training, the active group who receive the optimal neurofeedback and the other group that receive sham (i.e. dummy) neurofeedback (not real neurofeedback, but like a placebo), it is expected that patients only get better if they are in the group of children who do the active neurofeedback. If they are in the group of children who do the sham neurofeedback, only small changes are expected, which they may not notice. Participation in the study will help develop better treatment in the future for ADHD children. It is hoped that the information from this study will help treat other young people with ADHD with neurofeedback in the future. If successful, the study will provide the first evidence for a new brain-based treatment for ADHD that may potentially be longer-lasting than medication and have no side effects. No side effects have ever been reported with neurofeedback or fMRI and therefore no side effects are expected. Because patients are asked to increase brain activity they are asked to be scanned four times. In addition, they are asked to come into the clinic beforehand for a detailed assessment of their problems, and they are also tested again at the end of the neurofeedback training and after 6 months. This means they have to come into the clinic many times (seven times). Rarely some of the questions seem personal and can cause distress (if for example the patients have mental health problems or epilepsy). Questions are only asked that might be important in gaining a full understanding of the patients, their family and their school situation.

Where is the study run from?
King's College London (UK)

When is the study starting and how long is it expected to run for?
September 2017 to June 2021

Who is funding the study?
Medical Research Council (UK)

Who is the main contact?
Prof. Katya Rubia

Contact information

Type(s)
Scientific

Contact name
Prof Katya Rubia

ORCID ID
https://orcid.org/0000-0002-1410-7701

Contact details
Department of Child & Adolescent Psychiatry
Institute of Psychiatry, Psychology & Neuroscience
SGDP PO46
London
United Kingdom
SE5 8AF

Additional identifiers

Protocol serial number
-

Study information

Scientific Title
fMRI neurofeedback as a novel neurotherapy for children with attention deficit hyperactivity disorder (ADHD): a randomised controlled trial

Acronym
AFNIS

Study objectives
Updated 24/04/2020: Current study hypothesis as of 24/10/2017:
The hypothesis is that ADHD children will be able to progressively upregulate right inferior prefrontal cortex activations in 15 sessions of 7.5 minutes of fMRI-Neurofeedback and that this upregulation will be associated with an improvement in symptom severity of inattention, hyperactivity and impulsiveness as measured in ADHD behavioural rating scales. It is also hypothesised that they will improve in cognitive functions associated with ADHD and in their brain activation during a fMRI Stop task. Furthermore it is hypothesised that the clinical and cognitive benefits will still be observed 6 months after the treatment.

Previous study hypothesis:
The hypothesis is that ADHD children will be able to progressively upregulate right inferior prefrontal cortex activations in 14 sessions of 8.5 minutes of fMRI-Neurofeedback and that this upregulation will be associated with an improvement in symptom severity of inattention, hyperactivity and impulsiveness as measured in ADHD behavioural rating scales. It is also hypothesised that they will improve in cognitive functions associated with ADHD and in their brain activation during a fMRI Stop task. Furthermore it is hypothesised that the clinical and cognitive benefits will still be observed 6 months after the treatment.

Ethics approval required
Old ethics approval format

Ethics approval(s)

Approved 24/10/2017, London Bromley Research Ethical Committee Reference (Bristol HRA Centre, Level 3, Block B, Whitefriars, Lewins Mead, Bristol, BS1 2NT, UK; +44 (0)207 104 8027; nrescommittee.london-bromley@nhs.net), REC ref: 17/LO/1368

Study design
Double-blind randomised controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Attention Deficit Hyperactivity Disorder (ADHD)

Interventions
Updated 24/04/2020: Current interventions as of 24/10/2017:
Patients are randomised (1:1 block randomisation) to the active group or the control group.

Patients in the active group will undergo fMRI-Neurofeedback to learn to upregulate their own brain activation in right inferior prefrontal cortex in 15 sessions of 7.5 minutes each. This will be done over 4 MRI sessions of 60 min duration each over 2 weeks. Within each MRI session there will be 2-5 runs of fMRI-Neurofeedback of 8.5 minutes each.

A sham fMRI Neurofeedback condition will be administered to the control group with the same number of runs as the active group. Feedback for the sham Neurofeedback group will be from another person from the active group.

Patients will be tested before and after the treatment in clinical ADHD severity measures, in cognitive tests of attention and self-control, in their brain activation in response to a task of self-control, and in measures of side-effects. Clinical severity symptoms and cognitive performance will also be measured 6 months after the neurofeedback to test whether the benefits persist longer-term.

Previous interventions:
Patients are randomised (1:1 block randomisation) to the active group or the control group.

Patients in the active group will undergo fMRI-Neurofeedback to learn to upregulate their own brain activation in right inferior prefrontal cortex in 14 sessions of 8.5 minutes each. This will be done over 4 MRI sessions of 70 min duration each over 2 weeks. Within each MRI session there will be 3-4 runs of fMRI-Neurofeedback of 8.5 minutes each.

A sham fMRI Neurofeedback condition will be administered to the control group with the same number of runs as the active group. Feedback for the sham Neurofeedback group will be from another person from the active group.

Patients will be tested before and after the treatment in clinical ADHD severity measures, in cognitive tests of attention and self-control, in their brain activation in response to a task of self-control, and in measures of side-effects. Clinical severity symptoms and cognitive performance

will also be measured 6 months after the neurofeedback to test whether the benefits persist longer-term.

Intervention Type
Other

Primary outcome(s)
Current primary outcome measures as of 05/10/2020:
ADHD symptom severity, measured using the ADHD Rating Scale (ADHD-RS) at baseline, after the 2 weeks treatment and 6 months after the trial

Previous primary outcome measures:
ADHD symptom severity, measured using the ADHD Rating Scale (ADHD-RS) at baseline, after the 2 weeks treatment and 6 months after the trial

Main fMRI neurofeedback outcome measure:
Monotonic change in activation of the right inferior prefrontal cortex that is being upregulated, measured across the 4 fMRI Neurofeedback hours

Key secondary outcome(s))
Current secondary outcome measures as of 05/10/2020:
1. fMRI neurofeedback outcome measure: Monotonic change in activation of the right inferior prefrontal cortex that is being upregulated, measured across the 4 fMRI Neurofeedback hours
2. Parent-rated ADHD severity, measured using the ADHD Index of the Conners Parent Rating Scales (CPRS) at baseline, after the 2 weeks treatment and at 6 months follow-up
3. Other clinical measures:
3.1. Overall general behavioural functioning in children, measured using WREMB-R, Weekly Rating of Evening and Morning Behavior-Revised at baseline and after the 2 weeks treatment
3.2. Irritability Index measured using the Affective Reactivity index (ARI) rated by parents and children (5 min) at baseline, after the 2 weeks treatment, and at 6 months follow-up
3.3. Global measure of impairment (CIS score) measured using the Columbia Impairment Scale (CIS) at baseline and after the 2 weeks treatment
3.4. Scores of subjective experience of mind-wandering measured using the Mind excessive wandering scale (MEWS) at baseline, after 2 weeks treatment, and at 6 months follow-up
4. Motor and interference inhibition, sustained attention, vigilance, visual-spatial working memory, Wisconsin Card Sorting Switching task, measured using a cognitive task battery for ADHD at baseline, after the 2 weeks treatment and 6 months after the treatment
5. General side effects measured using side effects and adverse effects measures (5 min) at baseline and after the 2 weeks treatment. The adverse effects measure is measured after the 2 weeks treatment and is specifically measuring any adverse effects the patients may have noticed and which they think is due to the treatment specifically
6. Brain activation in response to a task of motor inhibition in the fMRI scanner, measured using fMRI activation and performance in an fMRI Stop task at baseline, before the first neurofeedback run and after the very last neurofeedback run, after the 2 weeks treatment
7. Long-term effects assessed using the primary outcome measures, some of the clinical measures (CPRS, MEWS, ARI), and the cognitive task battery 6 months after training

Updated 24/04/2020: previous secondary outcome measures as of 24/10/2017:
1. Parent-rated ADHD severity, measured using the ADHD Index of the Conners Parent Rating Scales (CPRS) at baseline, after the 2 weeks treatment and at 6 months follow-up
2. Other clinical measures:

2.1. Overall general behavioural functioning in children, measured using WREMB-R, Weekly Rating of Evening and Morning Behavior-Revised at baseline and after the 2 weeks treatment
2.2. Irritability Index measured using the Affective Reactivity index (ARI) rated by parents and children (5 min) at baseline, after the 2 weeks treatment, and at 6 months follow-up
2.3. Global measure of impairment (CIS score) measured using the Columbia Impairment Scale (CIS) at baseline and after the 2 weeks treatment
2.4. Scores of subjective experience of mind-wandering measured using the Mind excessive wandering scale (MEWS) at baseline, after 2 weeks treatment, and at 6 months follow-up
3. Motor and interference inhibition, sustained attention, vigilance, visual-spatial working memory, Wisconsin Card Sorting Switching task, measured using a cognitive task battery for ADHD at baseline, after the 2 weeks treatment and 6 months after the treatment
4. General side effects measured using side effects and adverse effects measures (5 min) at baseline and after the 2 weeks treatment. The adverse effects measure is measured after the 2 weeks treatment and is specifically measuring any adverse effects the patients may have noticed and which they think is due to the treatment specifically
5. Brain activation in response to a task of motor inhibition in the fMRI scanner, measured using fMRI activation and performance in an fMRI Stop task at baseline, before the first neurofeedback run and after the very last neurofeedback run, after the 2 weeks treatment
6. Long-term effects assessed using the primary outcome measures, some of the clinical measures (CPRS, MEWS, ARI), and the cognitive task battery 6 months after training

Original secondary outcome measures:
1. Parent-rated ADHD severity, measured using the ADHD Index of the Conners Parent Rating Scales (CPRS) at baseline and after the 2 weeks treatment
2. Other clinical measures:
2.1. Overall general behavioural functioning in children, measured using the Children Global Assessment Scale (CGAS) (Guy et al., 1976) (2 min) at baseline and after the 2 weeks treatment
2.2. General impairment or problems the child has with his behaviour at school, at home and with peers, measured using the Columbia Impairment Scale (CIS) (5 min) at baseline and after the 2 weeks treatment
2.3. General child mental health, measured using the Child Health Questionnaire at baseline and after the 2 weeks treatment
3. Motor and interference inhibition, time estimation, and sustained attention, measured using a cognitive task battery for ADHD at baseline, after the 2 weeks treatment and 6 months after the treatment
4. General side effects, measured using side effects and adverse effects measures (5 min) at baseline and after the 2 weeks treatment. The adverse effects measure is measured after the 2 weeks treatment and is specifically measuring any adverse effects the patients may have noticed and which they think is due to the treatment specifically
5. Brain activation in response to a task of motor inhibition in the fMRI scanner, measured using fMRI activation and performance in a fMRI Stop task at baseline, before the first neurofeedback run and after the very last neurofeedback run, after the 2 weeks treatment
6. Long-term effects, assessed using the primary outcome measures and the cognitive task battery 6 months after training

Completion date
01/06/2021

Eligibility

Key inclusion criteria

Updated 24/04/2020: Current inclusion criteria as of 24/10/2017:
1. Age range: 10-18 years
2. Gender: male
3. Meeting DSM-5 diagnosis of ADHD
4. Score above clinical cut-off on the Schedule for Affective Disorders and Schizophrenia, ADHD module (K-SADS)(Kaufman et al., 1996)
5. Score about clinical cut-off for ADHD on the short forms of the Conners Parent Rating Scale (CPRS) (Conners et al., 1998)
6. Patients will be either medication naïve or on their usual stable medication without change in regime throughout the study; they will be taken off their medication for the cognitive pre and post or follow-up assessments 24 hours which is optional
7. IQ > 80 as tested on the 4 subtests of the WASI (Wechsler, 1999) that assesses intellectual ability of individuals aged 6 years and over. Administration of 4 subtests takes ~ 40 minutes, and produces a full-scale IQ score
8. Score below clinical cut-off on the Social Communications Questionnaire (SCQ) (Rutter et al., 2003)

Previous inclusion criteria:
1. Age range: 10-18 years
2. Gender: male
3. Meeting DSM-5 diagnosis of ADHD
4. Score above clinical cut-off on the Schedule for Affective Disorders and Schizophrenia, ADHD module (K-SADS)(Kaufman et al., 1996)
5. Score about clinical cut-off for ADHD on the short forms of the Conners Parent and Teacher Rating Scales (CPRS/CTRS) (Conners et al., 1998)
6. Patients will be either medication naïve or on their usual stable medication without change in regime throughout the study
7. IQ > 80 as tested on the 4 subtests of the WASI (Wechsler, 1999) that assesses intellectual ability of individuals aged 6 years and over. Administration of 4 subtests takes ~ 40 minutes, and produces a full-scale IQ score

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Child

Lower age limit
10 years

Upper age limit
18 years

Sex
Male

Total final enrolment
94

Key exclusion criteria
1. IQ < 80 (Wechsler et al., 1999)
2. Comorbidity with any other major psychiatric disorder such as schizophrenia, autism, bipolar disorder, learning disability, severe depression with current suicidal behaviour (as assessed by clinician). Mood problems and anxiety will be allowed if they are not the primary diagnosis
3. Neurological problems, i.e. a history of severe neurological illness, e.g. brain tumour, epilepsy or a history of symptomatic seizures, polyneuropathy etc
4. Alcohol and substance abuse history
5. Contraindication to fMRI. i.e., previous implantation of metallic material, pacemaker, implanted medication pumps, neural stimulators, or claustrophobia
6. Unable to give informed consent of the child and parent

Date of first enrolment
01/11/2017

Date of final enrolment
30/04/2020

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
King's College London
Institute of Psychiatry, Psychology & Neuroscience
16 De Crespigny Park
London
United Kingdom
SE5 8AF

Sponsor information

Organisation
King's College London (UK)

ROR
https://ror.org/0220mzb33

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be available upon request from Prof. Katya Rubia.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Preprint results			12/08/2022	No	No
Protocol file	version 3	03/05/2018	12/08/2022	No	No