Note to authors – this template is a guide – all the sections below must be included however this is not exhaustive, other sections may be added. Don't forget to delete the blue "guides" from each section! Once your protocol content is complete, update the index by clicking in the left of the field and pressing F9

1. PROTOCOL FULL TITLE

Protocol Short Title/ Acronym:

Trial Identifiers

ISRCTN:	ISRCTN		
REC Number:	230303		
UKCRN Number:			
Protocol Version Number:	3	Date:	03/05/2018

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This is usually the substantive employer of the CI. If this is KCL then co-sponsorship with the participating NHS Trust may be required.

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2. Study Synopsis

TITLE OF CLINICAL TRIAL:	fMRI Neurofeedback as a novel neurotherapy for children with ADHD
Protocol Short Title/ Acronym:	AFNIS
Study Phase If Not Mentioned In Title:	Proof of concept randomised controlled trial
Sponsor Name:	King's College London, South London and Maudsley Trust
Chief Investigator:	Prof Katya Rubia
UKCRN Number:	
REC Number:	230303
Medical Condition Or Disease Under Investigation:	Attention Deficit Hyperactivity Disorder (ADHD)
Purpose Of Clinical Trial:	Powered proof of concept experimental randomized placebo-controlled double-blind trial to test the mechanism and clinical efficacy of real-time fMRI neurofeedback (fMRI-NF) of right inferior frontal cortex (rIFC) compared to sham fMRI-NF in ADHD children
Primary Objective:	To examine whether fMRI neurofeedback of right frontal cortex (rIFC) in ADHD children will 1) reduce their ADHD symptoms

	2) increase activation in rIFC over the 14 sessions
Secondary Objective(s):	To test whether the fMRI neurofeedback will : 1) improve other clinical ADHD severity measures 2) improve performance on a battery of cognitive tasks relevant to ADHD 3) will increase activation in rIFC in a Stop fMRI task 4) Will increase the activation of an entire functional network connected with the rIFC 5) has no side effects 6) will improve clinical and cognitive measures longer-term, 6 months after training
Trial Design:	Randomised controlled double-blind trial
Endpoints:	1) Performance on a cognitive task battery of cognitive control tasks 2) Parent ratings on the ADHD Rating scale
Sample Size:	100 ADHD children, 10-18 years
Summary Of Eligibility Criteria:	Meeting clinical diagnosis for Attention-Deficit Hyperactivity Disorder (ADHD); male; age range 10-18 years; stable medication or non-medicated; no comorbid conditions other than oppositional defiant and conduct disorder; IQ > 80.
Intervention (Description, frequency, details of delivery)	Participants will undergo four hourly fMRI scans with feedback of their activation of rIFC. They will be asked to modulate this activation via a video-game that is connected to the activity of the rIFC.
Comparator Intervention:	Sham real-time fMRI neurofeedback
Maximum Duration Of Treatment Of A Subject:	2 weeks
Version And Date Of Final Protocol:	Version 2 27/10/2017
Version And Date Of Protocol Amendments:	

3. Revision History

Document ID - (Document Title) revision X.Y	Description of changes from previous revision	Effective Date

4. Glossary of terms (Optional)

ADHD = Attention Deficit Hyperactivity Disorder

fMRI= functional magnetic resonance imaging

NF= Neurofeedback

rIFC = right inferior frontal cortex

IOPPN = Institute of Psychiatry, Psychology & Neuroscience

KCL = King's College London.

5. Protocol Contents

6. Background & Rationale

Attention deficit hyperactivity disorder (ADHD) children have age-inappropriate problems with inattention, hyperactivity and impulsiveness. The most efficacious current treatment is with psychostimulants, which is effective in 70% of children. However, psychostimulants are associated with long-term adverse effects such as reduced growth, irritability, loss of appetite, tremor, sleep and vegetative disturbances (Greenhill et al., 2001; Jensen et al., 2007). There is also some addictive potential of psychostimulants. Furthermore, nothing is known on the long-term effects of psychostimulants. The last decade has shown an escalating rate of stimulant prescription for ADHD with a net drug costs to the NHS in 2010 of £25m and about £30m for health professional, social and educational time. This escalating prescription rate has raised concerns about the unknown long-term effects on the developing brain. Importantly, recent studies have shown limited long-term effects of psychostimulants beyond 1-2 years, despite the fact that currently stimulants are given to ADHD patients long-term, well into adolescence and adulthood. We and others have shown that the brain adapts to the medication which would explain the limited longer-term effects. In conclusion, adverse effects of psychostimulants, lack of evidence for long-term benefits, and potentially long-term negative effects on brain development make the development of a non-pharmacological treatment for ADHD with no side effects highly desirable to parents, clinicians and patients.

ADHD affects 5-10% of school aged children in the UK. ADHD causes symptoms such as difficulty in focussing attention, impulsiveness and hyperactivity and can seriously impact life, both at home and at school. Underlying their impulsiveness, children with ADHD have problems with self-control, timing and attention. Over the last two decades of brain imaging we and others have shown that these cognitive problems are due to reduced activity in the right inferior frontal part of the brain. Furthermore, one of the main mechanisms of action of stimulant medication, which works in 70% of the cases, is to increase the activity of this brain region. We argue that a therapy that is based on the neuroscience of ADHD, i.e. on the main brain abnormality in ADHD and on the main mechanism of action of stimulant medication, but without side effects, is likely to be successful. We therefore aim to train patients to self-regulate this region of their brain which is underfunctioning, by providing them feedback of their own brain activity.

Patients can be treated by self-regulation of the underlying pathological networks directly, through Neurofeedback (NF). It has been shown that modulating brain function via NF can change behaviour and improve cognitive functions (Birbaumer, et al., 2009). NF is an operant conditioning procedure that allows subjects to achieve volitional and conscious self-control over otherwise unconscious brain activation (and associated processes) mainly through real-time audio/visual feedback. This is achieved by continuously updating subjects with representations of their brain activity on a PC and training them to modulate these representations, usually through trial and error. Changes in the desired direction are rewarded. Since NF can be run as a computer game it is attractive to children. Given that Neurofeedback teaches participants self-regulation of their brain and ADHD is typified by poor self-control, it is the psychiatric disorder where NF has been most applied, using electrophysiology Neurofeedback (EEG-NF).

However, blinded randomised controlled studies of EEG-NF only show trend-level efficacy. Real-time functional magnetic resonance imaging neurofeedback (fMRI-NF) acts more rapidly, presumably due to its superior spatial resolution, allowing more specific targeting of brain regions. Furthermore, it can target deep cortical and subcortical regions such as the rIFC that are most consistently impaired in ADHD. fMRI-NF studies have been promising in other disorders in remediating key neurofunctional substrates and improving

associated behaviours. Our pilot feasibility RT-fMRI-NF study showed that ADHD children can learn to self-regulate rIFC within 11 fMRI-NF sessions of 8.5 minutes each, with significant transfer effects (i.e., after the training they are asked to self-regulate their brain without the NF to show they have learned it) and that this is associated with improved clinical symptoms, cognitive improvements and enhanced rIFC activation during a fMRI task of self-control. However, potential placebo effects cannot be ruled out as we did not include a sham control condition. We therefore plan here a larger and more definite data-driven proof of concept study to test the efficacy of 15 sessions of 7.5 minutes of fMRI-NF of rIFC in 100 children with ADHD, randomised into active and sham control groups, on improving ADHD behaviour, brain function and cognition.

7. Trial Objectives and Design

7.1 Trial Objectives

Aim of the study

We plan to test whether fMRI-NF of rIFC will reduce ADHD symptoms and improve their cognitive performance. For this purpose, 100 boys with ADHD aged 10 to 18 years will undergo 4 fMRI scans of 60 min over 2 weeks, where they will be trained to enhance the activity of the rIFC. This will be achieved in a playful way, by playing a videogame of a rocketeer that is connected to their brain activity in rIFC. The goal is for the children to manage to fly the rocketeer into the sky where he will see some planets and asteroids etc, etc. Half of the children will be a control group who will receive a sham NF where they will obtain non-contingent NF from the NF data of one of the active participants. We will test in a well powered study whether fMRI NF in ADHD boys will improve their clinical symptoms, their brain activation and their cognitive problems after the treatment as well as after 6 months to test for longer-term effects. The study will be a first step towards the development of a new, brain-based, non-drug treatment for ADHD which could benefit many young people affected by this condition.

Objectives of the study:

The proposal is for a suitably powered proof of concept experimental randomized placebo-controlled double-blind trial to test the mechanism and clinical efficacy of rt-fMRI-NF of rIFC compared to sham fMRI-NF in ADHD children.

7.1.1 Primary endpoints

1) ADHD symptoms as measured on the ADHD-Rating Scale (ADHD-RS). (Dupaul et al. 1999).
2) Monotonic increase in inferior frontal lobe activation across the 14 neurofeedback sessions in the active group.

7.1.2 Secondary endpoints

1) The ADHD Index of the Conners Parent Rating Scales (CPRS).
2) Stop fMRI task performance and related brain activation.
3) A cognitive task battery we have developed for ADHD that measures key functions including inhibition, attention, timing and motivation and which lasts 30min (Rubia, Smith, & Taylor, 2007).
4) Other clinical measures:

    a. the Affective Reactivity index (ARI) (Stringaris et al., 2012) (2min)

b. the Columbia Impairment Scale (CIS) (Bird, et al., 1003) (5min)
c. The Mind excessive wandering scale (MEWS) (Mowlem et al., 2016)

4) Side effect scale (Hill & Taylor, 2001). (5min)
5) Long-term effects will be assessed 6 months after training in the primary outcome measure (ADHD-RS for parent-ratings), the ARI, the MEWS and in the performance on the cognitive task battery.

7.2 Trial Design

Double-blind, parallel-group, randomised placebo-controlled trial.

We will test the superiority of the real-time fMRI neurofeedback of rIFC over the sham-NF.

7.3 Trial Flowchart

Please include a time/event matrix (flow chart) of trial procedures and stages. This desirable is it is particularly useful for determining activities involved during each clinic visit (e.g. blood tests or scans, treatment, diary completion, adverse event monitoring, physical examination etc).

	Baseline	Visit A NF-training	Visit B NF-training	Visit C NF-training	Visit D NF-training	Endpoint	6-month Follow-up
Date							
Start / End time							
Researcher administered							
Eligibility checklist							
K-SADS							
DSM-5 ADHD criteria							
NF Scan Training Form							
Self-administered							
Background Information (P)							
Edinburgh Handedness (C)							
SCQ (P)							
Medication form (P or C)							
Conners 3-PL (P)							
ADHD-RS (P)							
CIS (P)							
WREMB-R (P)							
ARI (C)							
ARI (P)							
MEWS (P)							
Side effects (P)							
Adverse effects (P)							
NF Questionnaire (C)							
NF Effectiveness questionnaire (P)							
Mood before & during NF (C)							
Blindness form (P and C)							
Neurocognitive measures							
WASI (40-60min)							
Go-no go task (5min)							
Continuous performance task (8min)							
Interference inhibition (Simon Task) (5min)							

Wisconsin Card Sort Task (5min)							
Working memory (6min)							
Vigilance task (5min)							
fMRI Stop task (6min)							
Forms							
Consent form child							
Consent form parent							
MRI safety form							
MRI request form							
Receipt of payment							

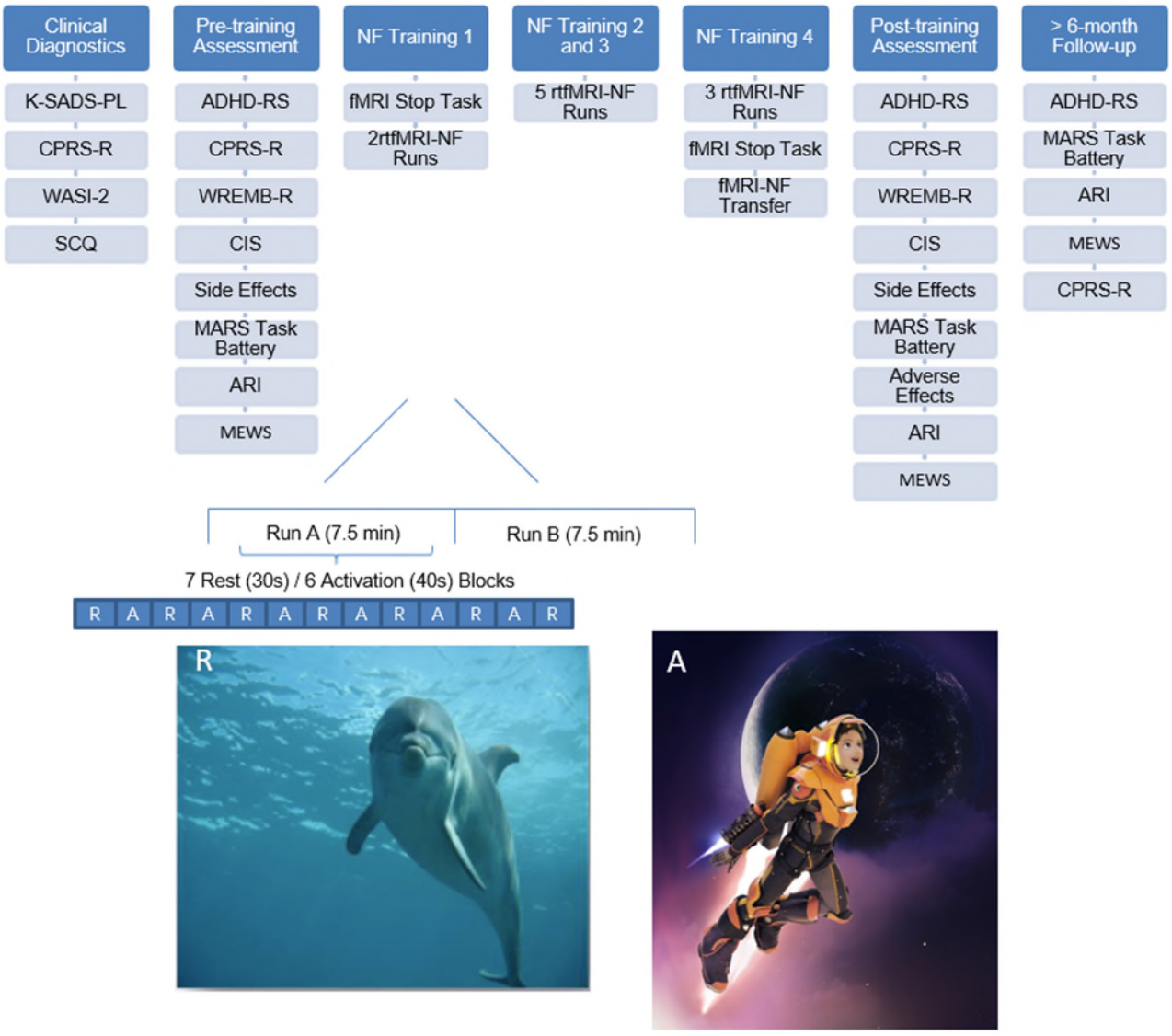

Figure 1. Schematic overview of the design of the rtfMRI-NF study. ADHD-RS, Attention Deficit Hyperactivity Disorder-Rating Scale; CIS, Columbia Impairment Scale; CPRS-R, Conners' Parent Rating Scale - Revised; K-SADS-PL, Kiddie-SADS-Present and Lifetime Version; MARS, Maudsley Attention and Response Suppression task battery; NF, Neurofeedback; SCQ, Social Communication Questionnaire (Lifetime); Wechsler Abbreviated Scale of Intelligence, 2nd Edition (WASI-II); WREMB-R, Weekly Rating of Evening and Morning Behavior-Revised; ARI, Affective Reactivity index; MEWS; Mind Excessive Wandering Scale. Adapted from Alegria et al., 2017, Human Brain Mapping, in press.

8. Trial Intervention

8.1 Therapy/Intervention Details

The electronic version of this document is the latest version. It is responsibility of the individual to ensure that any paper material is the current version. Printed material is uncontrolled documentation.

Participants will be scanned 4 times in a new GE MR750 3T scanner (General Electrics Milwaukee, USA) for 60 min. Patients will be randomly allocated to active (N = 50) or control groups (N = 50), stratified by age and medication status. The active group will be trained to upregulate right inferior frontal lobe activation throughout 14 fMRI-NF sessions (7 min 30sec each, 2-5 sessions per scan), totalling 4 fMRI scan hours over two weeks. The first of the 4 visits will contain the 6min fMRI task and 2 NF sessions. Visit 2 and 3 will contain 5 NF sessions each followed by a transfer session without feedback. Visit 4 will contain 3 NF sessions, the Stop fMRI task, and a transfer session. The control group will have the exact same procedure, but will obtain non-contingent NF from the NF data of one of the active participants.

NF sessions (1hr) will consist of either 2 (visit 1) or 5 (visit 2-3) and 3 (visit 4) runs of each of six activation (upregulation) blocks (40s each), separated by 7 baseline blocks (relaxation/no upregulation, 30s), starting and ending with a baseline block (ABABABABABA). The RT-fMRI interface system (provided by Dr Jerzy Bodurka, Laureate Institute for Brain Research, USA) transfers the images from the MRI scanner to an external workstation as soon they are reconstructed. Images are then pre-processed using AFNI (afni.nimh.nih.gov/afni), which has built-in real-time capacities. An image mask composed of pre-selected regions of interest (ROIs) is then applied to the pre-processed images in order to extract the mean neural activity in each selected region. As a new brain volume is acquired every repetition time (2s in this study), AFNI calculates a new set of values for each ROI. The values for each ROI are then sent to a second PC, where they are combined to generate a running time-series for the feedback signal. Finally, this feedback signal is displayed within the scanner in a child-friendly manner. We will present as feedback to the participants their brain activation of rIFC, using a graphical representation of a rocketeer that flies up in the sky (with increasing activation) or does not move (no activation/rest) and we will ask the subjects to try to make the rocketeer fly, thus increasing their brain activation in the ROIs. The rocketeer movie is done by a professional videogaming artist and is highly engaging and fun. Participants cannot easily verbalise the most efficient strategies for successful NF and it is hence more efficient to let participants find their own strategy rather than prescribing one (Birbaumer et al., 2009). The activation will be evaluated in real-time, after each fMRI acquisition, by using the latest reconstructed dataset, i.e. the brain activation during the last 2 seconds.

8.2 Frequency and duration of intervention

Subjects are expected to visit the IOPPN for 4 hourly MRI scans of neurofeedback (see flowchart and Figure 1) which will take about 60 minutes each. On the first and the last NF session, the participants will perform a stop signal task to test motor response inhibition. In addition to these 4 visits, they will also have to come to the IOPPN for pre-assessment where they will perform a task battery of cognitive tests (30 min), and which they will have to repeat after the 4 NF sessions at the post-assessments and again after 6 months follow-up. In total, this will require 7 visits. The parents will also have to fill in some behavioural questionnaires about the behaviour of their child and about side effects at the pre-assessment (~ 2 hours) and post assessments (~ 50 min) as well as the follow-up assessment (about 45min). If they agree to it, the parents and the patient will be audio-recorded during their interviews with the Kiddie-SADS. This will be done to assist us in the reliability of the assessment, in case a diagnosis is questioned later on. Their refusal of the recording will influence not their inclusion in the study.

8.3 Intervention records

n/a as this is not a drug trial

8.4 Subject Compliance.

n/a as this is not a drug trial

8.5 Study adherence

n/a as this is not a drug trial

8.6 Concomitant Medication

Those patients who are on stimulant medication, may be asked to be taken off their psychostimulant medication 24-hours before the pre-, post-, and follow-up assessment, if it is feasible and if the clinical needs do not override this. (I.e. not to take the medication on the day of the assessments) However, this is not mandatory, this decision will be made by the patient and the parent/guardian, and the patient's clinical needs will override this option. If the patient cannot be taken off medication for the assessments, they can still participate in the study.

For ADHD children to take the medication off for a day is perfectly safe and is commonly done in ADHD research, as the drug wears off within 24 hours and can easily be taken off for a day for this reason. It is common practice in the UK to give children who are on stimulant medication a "drug holiday" over the weekend or on holidays, and it is even recommended as it may prevent the child to develop a tolerance to the drug (when it no longer works). However, as stated above, we will only ask those families who already occasionally take the child off drugs and who know that the child is perfectly manageable without his medication to do this.

For all other timepoints (i.e. the treatment itself), they do not have to come off their medication, but they will be asked to not change their usual medication regime for the duration of the 2 weeks of the NF training. Patients on non-stimulant medication for ADHD will not be asked to be taken off medication at any stage of the study (because, unlike for stimulant medication where the washout is 24 hours, the wash-out of non-stimulant medication is over two weeks and this would not be feasible).

9. Research environment

The study will be conducted at an academic institution, the Institute of Psychiatry, Psychology and Neuroscience, at King's College London, UK.

10. Selection and Withdrawal of Subjects

10.1 Inclusion Criteria

One hundred male children/adolescents with ADHD, 10-18 years, medication-naïve or on stable medication, recruited from local clinics, meeting DSM-5 criteria for ADHD using ADHD Diagnostic Interview and rating scales.

- Age range: 10-18 years
- Gender: male
- Meeting DSM-5 diagnosis of ADHD, combined type or inattentive type.
- Score above clinical cut-off for ADHD/ADD on the Schedule for Affective Disorders and Schizophrenia, ADHD module (K-SADS) (Kaufman et al., 1996).
- Score about clinical cut-off for ADHD/ADD on the short forms of the Conners Parent Rating Scales (CPRS/CTRS) (Conners et al., 1998a, b).

- Patients will be either non-medicated (or medication naïve) or on their usual stable medication without change in regime during the 2 weeks of NF training. Only for the pre-post and follow-up assessments, if they have agreed to it, they will be taken off stimulant medication.
- 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.
Comorbidity with other disorder will be allowed except the ones outlined below under exclusion criteria

10.2 Exclusion Criteria

- IQ < 80 (Wechsler et al., 1999).
- Comorbidity with schizophrenia, Bipolar disorder, autism, learning disability, severe depression with current suicidal behaviour (as assessed by clinician). Problems with mood, anxiety and depression will be allowed as long as they are not the primary diagnosis.
- Neurological problems, i.e. a history of severe neurological illness, e.g. brain tumour, epilepsy or a history of symptomatic seizures, polyneuropathy etc.
- Substance abuse history
- Contraindication to fMRI. i.e., previous implantation of metallic material, pacemaker, implanted medication pumps, neural stimulators, claustrophobia.
- Unable to give informed consent by the patient or the parent/primary caregiver.

10.3 Selection of Participants

Patients will be recruited through Child and Adolescent Mental Health Services, via advertisement, social media, parent support groups, community paediatrics, and paediatrics and general practitioner settings as well as via Trust Consent for Contact mechanisms.

10.4 Randomisation Procedure / Code Break

The ADHD children (non-medicated or on stable medication) will be randomized to sham or real fMRI-NF of rIFC, 50 in each group. Stratification factors will include medication status (non-medicated/stable) and age. Patients will be randomly assigned in a 1:1 ratio with varying block size to either the experimental (real fMRI-NF) or the control (sham-fMRI-NF) groups. This assignment will be realized by a computer-generated, web-based tool provided by the Clinical Trials Unit of the IOPPN, KCL.

10.5 Withdrawal of Subjects

There is no evidence for side or adverse effects of the therapy, hence withdrawal due to adverse effects are not expected. Therapy will be discontinued if

- *the participant decides they no longer wish to continue*
- *recommended by the investigator*

Should a patient decide to withdraw from the study, the reason for withdrawal will be recorded as detailed as possible.

Participants who wish to withdraw from therapy will be asked to confirm whether they are still willing to provide the study specific data at visits that were completed.

10.6 Expected Duration of Trial.

Specify the expected clinical participation and define the end of the trial. This can be the full study duration e.g. first patient first visit to last patient last visit including follow up.

The first participant is expected to start the trial around 1st November 2017 and the last participant will be tested by 1st January 2021.

11. Trial Procedures

The following procedure will be followed in this study:

1. The participant will express interest in the study either in response to an advertisement (attached to this proposal), or through information provided by their clinicians at CAMHs or through Trust Consent for Contact (C4C) mechanisms.

2. The participant and the parents will then be sent a copy of the information sheet describing the research study and additional information on the methodologies used. They will receive comprehensive information about the study and the type of screening questions that they will be required to answer on a consent form on the day of the study at least 24 hours before the appointment.

3. If the participant or the parent contacts one of the researchers (by telephone, email, or in person) to receive further information, s/he will be given the opportunity to ask any questions about the study, and to take more time to think about it if they so wish. If they express interest in participating in the study, we will take their contact details to arrange a convenient appointment time.

4. In the week prior to the first testing session, participants will come to the Institute of Psychiatry, Psychology and Neuroscience to complete the IQ testing and to fill in any questionnaires that relates to the main experiment (clinical questionnaires will be filled out by the parents). This visit will also provide the volunteer and his/her parent with an opportunity to ask questions about the study and to familiarise themselves with the study protocol and the facilities. The children will also have to perform a computer test battery that measures attention, inhibition and timing skills.
All participants will be randomly allocated to an experimental (fMRI-NF) and a control group (sham fMRI-NF). The two groups will be matched for age and medication status.

5. At the beginning of any experimental session, the researcher will explain the procedure in detail. Participants will be scanned 4 times in a new GE MR750 3T scanner (General Electrics Milwaukee, USA) for 60min.
Patients will be randomly allocated to active (N = 50) or control groups (N = 50) stratified by age and medication status.
The active group will be trained to upregulate right inferior frontal lobe activation throughout 14 RT-fMRI-NF runs (7.5 min each, 2-5 sessions per scan), totalling 4 fMRI sessions of 60 minutes over two weeks. In order to prove specificity of NF effects, the control group will have the exact same procedure, but will obtain non-contingent NF from the NF data of one of the active participants.

6. NF sessions (60 min) will consist of 4 runs of each of six activation (upregulation) blocks (40s each), separated by 7 baseline blocks (relaxation/no upregulation), starting and ending with a baseline block (ABABABABABA). The fMRI interface system (provided by Dr Jerzy Bodurka, Laureate Institute for Brain Research, USA) transfers the images from the MRI

scanner to an external workstation as soon they are reconstructed. Images are then preprocessed using AFNI (afni.nimh.nih.gov/afni), which has built-in real-time capacities. An image mask composed of preselected regions of interest (ROIs) is then applied to the preprocessed images in order to extract the mean neural activity in each selected region. As a new brain volume is acquired every repetition time (2s in this study), AFNI calculates a new set of values for each ROI. The values for each ROI are then sent to a second PC, where they are combined to generate a running time-series for the feedback signal. Finally, this feedback signal is displayed within the scanner in a child-friendly manner. We will present as feedback to the participants their brain activation of rIFG (sham-feedback in controls), using a graphical representation of a rocketeer moving towards the sky, passing through clouds, and ultimately reaching some planets every time they managed to increase the activation of the target region.
Participants cannot easily verbalise the most efficient strategies for successful NF and it is hence more efficient to let participants find their own strategy rather than prescribing one (Birbaumer et al., 2009). The activation will be evaluated in real-time, after each fMRI acquisition, by using the latest reconstructed dataset, i.e. the brain activation during the last 2 seconds.

7. After the last session, the children will be asked to do again the computerised tests of attention, inhibition and timing to test whether they have improved in these skills after the training. The parents also will have to fill in the clinical questionnaires and the side effects scale.

8. After 6 months (after the training) the parents will be asked to fill in (or answer by telephone) the ADHD severity questionnaire and the child will have to repeat the cognitive test battery one more time.

9. The participants will receive up to £180. We will give them tokens for each visit throughout the 2 week training. They will receive money in exchange for the tokens at the end of the training and at the follow-up assessment. We will also reimburse their travel costs.

11.1 Laboratory Tests

None

12. Assessment of Efficacy

The ADHD Rating scale is the primary efficacy measure which is a standard measure used in ADHD to measure effects of pharmacological and non-pharmacological treatment. The ADHD index of the Conners Parent Rating Scale is a commonly used secondary efficacy measure for behavioural improvement in ADHD.

12.1 Primary Efficacy Parameters

ADHD symptoms as measured on the ADHD-Rating Scale (ADHD-RS). (Dupaul et al. 1999).

12.2 Secondary Efficacy Parameters

The ADHD Index of the Conners Parent Rating Scales (CPRS).

12.3 Procedures for Assessing Efficacy Parameters

The efficacy measures are parent rated behaviour scales for ADHD behaviours which will be filled in by the parents before and after the treatment and at follow-up assessment.

13. Assessment of Safety

13.1 Specification, Timing and Recording of Safety Parameters.

MRI is considered safe and non-invasive and there are no side effects are usually recorded.

We will measure side effects before and after the treatment as well as adverse effects. However, we do not expect any side or adverse effects as the methodology is safe in children and we found no side or adverse effects in our pilot study.

However, there is a slight risk that the scanner is sometimes perceived as unpleasant and uncomfortable. The researchers will be sensitive to this possibility and will suspend testing sessions at the request of the participant or at the first signs of distress and discomfort. The participant will be informed that he/she is free to terminate the scanning session whenever he/she wants to. Alerting mechanisms ensure easy communication and radiographers will constantly check that the participant is content to remain in the scanner.
Adolescents are sometimes anxious about the scanner − they will be shown the "mock scanner" to familiarise them with the scanner beforehand and they will be able to tell in the first scan whether they are happy to be scanned 4 times. Every effort will be made to ensure that they do not feel anxious or claustrophobic. However, if they feel that the scanner is frightening to them, they will not have to participate. The same applies for adolescents who feel claustrophobic in the scanner.
The scanner is also noisy and this may be unpleasant for some children. We will therefore expose them to the noise beforehand in the mock scanner. If the children feel that they dislike the noise, they do not have to participate. Also, in order to minimize the discomfort of the noise, we will provide all participants with headphones that are specifically designed for MRI scanners to reduce the noise level. This is standard procedure for all scanning subjects at the IOP.

13.2 Procedures for Recording and Reporting Adverse Events

We will measure side effects before and after the treatment as well as adverse effects. However, we do not expect any side or adverse effects as the methodology is safe in children and we found no side or adverse effects in our pilot study.

13.2.1 Adverse events that do not require reporting

None are expected.

13.3 Stopping Rules

Changes in safety rules are very unlikely and there are no particular reasons why the trial should be stopped.

14. Statistics

Behavioral data and fMRI analysis will be conducted using statistical techniques with a primary focus on repeated measures ANOVAs (within-subject factor TIME; between subject factor GROUP). Supplementary analyses may include parametric correlation analyses (for example Pearson’s correlation tests).
The named researchers have substantial and proven experience in these types of analyses, having published and taught extensively.

14.1 Sample Size

100 ADHD adolescents will be enrolled in the study, randomised into the fMRI-NF of rIFC (N = 50) and the sham NF (N = 50).

The estimates of a clinically relevant effect size were calculated from our IOPPN pilot study on fMRI-NF in ADHD adolescents using the exact same outcome measures. ES for clinical efficacy in our pilot study was around 0.6. For a mean ES of 0.6 and a power of 80% with a $p < 0.05$, we would need 45 children in each group. We hence powered the study to include 50 children in each group accounting for a generously estimated potential drop-out rate of up to 10%. Our pilot study was well tolerated by ADHD children who liked the Neurofeedback "game" and we had a drop-out rate of only 5%, which is lower than the 6-10% drop-out rate we have had for studies of repeated fMRI scans under several medication conditions.

14.2 Randomisation

The ADHD children (non-medicated or on stable medication) will be randomized to sham or real fMRI-NF of rIFC, 50 in each group. Stratification factors will include medication status (non-medicated/stable) and age. Patients will be randomly assigned in a 1:1 ratio with varying block size to either the experimental (real fMRI-NF) or the control (sham-fMRI-NF) groups. This assignment will be realized by a computer-generated, web-based tool provided by the Clinical Trials Unit of the IOPPN, KCL.

14.3 Analysis

A description of the statistical methods to be employed, including timing of any planned interim analyses should also be provided The level of significance that is to be used in each trial analysis must be stipulated, together with the procedure(s) for accounting for any missing, unused, and spurious data. Procedures for reporting any deviation from the original statistical plan should be described and justified. The data set for any analysis must be clearly stipulated (e.g. "all subjects", "randomised subjects", "intent to treat") and the population(s) should be clearly defined. Define the trial stopping rules if appropriate.

For all analyses, repeated measures ANOVAs will be conducted with TIME as within-subject factor and GROUP as between subject factor. Supplementary analyses may include parametric correlation analyses (for example Pearson's correlation tests).
The named researchers have substantial and proven experience in these types of analyses, having published and taught extensively.

For missing data, imputations will be used. The individual estimates from the multiply-imputed datasets will then be used to calculate a combined estimate by applying Rubin's Rules [Little and Rubin, 2002].

15. Trial Steering Committee

n/a

16. Data Monitoring Committee

As this is not a drug trial we will not have an external data monitoring committee. The CIs of the study will form a data monitoring committee and assess the trial progress and all other aspects of the trial. They will meet once every 6 months.

17. Direct Access to Source Data and Documents

The Investigator(s) will permit trial-related monitoring, audits and REC review by providing the Sponsor(s), and REC direct access to source data and other documents (eg patients' case sheets, blood test reports, X-ray reports, histology reports etc).

18. Ethics & Regulatory Approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Mental Capacity Act 2005.

This protocol and related documents will be submitted for review to the South London Research Ethics Committee (REC)

The Chief Investigator will submit a final report at conclusion of the trial to the funder, the REC and the Sponsor.

19. Quality Assurance

Monitoring of this trial will be to ensure compliance with Good Clinical Practice and scientific integrity will be managed by the study team.

20. Data Handling

The Chief Investigator will act as custodian for the trial data. The following guidelines will be strictly adhered to:

Patient data will be anonymised.

- All anonymised data will be stored on a password protected computer.
- All trial data will be stored in line with the Data Protection Act.
- and archived in line with Sponsor requirements

21. Data Management

The data will be behavioural data, cognitive performance data, and fMRI data in electronic format and password protected.

The data to be analysed will be inputted into an SPSS datasheet in a linked-anonymised format.

Data management will follow KCL guidelines.

Give details of whether paper or electronic CRF will be used, describe the proposed database etc

22. Publication Policy

It is intended that the results of the study will be reported and disseminated at international conferences and in peer-reviewed scientific journals.

23. Insurance / Indemnity

A professional indemnity policy is in place from the sponsor (KCL) for all studies conducted at KCL. The policy is part of the NHE01CA250013.

24. Financial Aspects

Funding to conduct the trial is provided by Medical Research Council.

25. Signatures

.

Katya Rubia 27/10/2017

Chief Investigator Date

Print name

Statistician (if applicable) Date

Print name

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