ISRCTN82129325 https://doi.org/10.1186/ISRCTN82129325

Effects of external trigeminal nerve stimulation in ADHD and mechanisms of action

Submission date	Recruitment status
11/05/2021	No longer recruiting
Registration date	**Overall study status**
02/08/2021	Ongoing
Last Edited	**Condition category**
19/01/2026	Mental and Behavioural Disorders

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

Plain English summary of protocol

Background and study aims
Attention Deficit Hyperactivity Disorder (ADHD) affects 7% of children worldwide; it consists of problems with poor attention, impulsivity, and hyperactivity. Most have problems in adulthood where ADHD is associated with poor social and employment outcomes. Children with ADHD also struggle with cognitive (thinking) skills (e.g., attention) and self-control. Treatment is with stimulant medication. However, this has side effects, does not work for everyone, and has limited longer-term effects. Non-drug treatments with fewer side effects would be preferred but most have shown little effects.
The first non-drug ADHD treatment device was approved in 2019 by the USA Food and Drug Administration (FDA), called external trigeminal nerve stimulation (eTNS). eTNS is a battery charged device that sends small electrical pulses or currents under the skin on the forehead and can be applied during sleep. eTNS activates the trigeminal nerve on the forehead which leads to the activation of the brain stem and frontal brain regions that are important for arousal and attention.
A pilot study in 62 children with ADHD showed an improvement of ADHD symptoms after 4 weeks of eTNS compared to placebo eTNS (fake, with no electrical currents) after it was used every night with children by their parents for 4 weeks, with minimal side effects. An earlier smaller study with 22 ADHD children showed that eTNS improved ADHD behaviours and cognitive abilities (e.g., inattention).
The aim of this study is to further confirm in a large group of 150 children and adolescents with ADHD whether eTNS improves ADHD symptoms, whether it improves academic abilities (e.g., attention), whether the effects are still observed 6 months later and how it works on the brain. The study is important as it will establish whether eTNS is an effective non-drug treatment for ADHD with minimal side effects that can be administered at home and would therefore be preferred by patients, parents, and clinicians. Such a treatment would improve healthcare and reduce the strain of the disease for patients.

Who can participate?
Children aged 8-18 years with a clinical diagnosis of ADHD

What does the study involve?
Participants are randomly allocated to eTNS or placebo eTNS treatment (with no electrical

currents) to test whether eTNS is better than placebo eTNS at improving parent and teacher-rated ADHD symptoms and cognitive performance in tests of self-control and attention. The treatment involves using the TNS device while the child is sleeping for 7-9 hours per night for 4 weeks; this is a disposable patch with a battery that can be attached to their pyjamas or placed under their pillow. It is not painful and has minimal side effects.
Participation in the study involves an assessment of the behaviour and cognitive functions of the child at the start of the study, after the treatment and at follow up. It will require four visits to the research centers and several online appointments. The researchers will also measure safety, pupil response and activity and heart rate and heart rate variability using a wrist-worn device at each centre visit.
The researchers also want to understand how eTNS works in the brain. Therefore, they will use functional magnetic resonance imaging (fMRI) to test the effects of eTNS on the brain function of ADHD children in a subgroup of 56 patients. Furthermore, they will test whether eTNS has side effects and whether effects continue 6 months after treatment.

What are the possible benefits and risks of participating?
It is very likely that the behaviour of the patients will improve with the TNS treatment if they are in the active group. Also, it is hoped that the information collected will establish whether TNS is a suitable treatment for ADHD and therefore help treat other young people with ADHD with TNS in the future. However, the researchers cannot guarantee that every patient gets better as this is a research study and there is no guarantee that every child gets better with the TNS treatment. In addition, the patient will also get some information about their intellectual performance which could be useful for school planning, and information about their clinical profile (i.e. the results of the questionnaires which will be an indicator of the severity of the patient's symptoms). It could potentially be a bit uncomfortable to sleep with the TNS device at night. However, in a previous study the sleep patterns of the children became better and not worse.
No serious side effects or adverse events have been reported in studies with TNS and the researchers do not expect any side effects. However, they cannot guarantee that the patients will not have any side effects and some have complaints about headache (that quickly goes away) or skin irritation (that goes away with cream).

Where is the study run from?
King's College London and University of Southampton (UK)

When is the study starting and how long is it expected to run for?
September 2021 to September 2026

Who is funding the study?
This project is funded by the Efficacy and Mechanism Evaluation (EME) programme, an MRC and NIHR partnership (project ref: NIHR130077)

Who is the main contact?
Prof. Katya Rubia
katya.rubia@kcl.ac.uk

Contact information

Type(s)
Scientific

Contact name
Prof Katya Rubia

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

Contact details
Department of Child Psychiatry/SGDP PO46
Institute of Psychiatry, Psychology & Neuroscience
De Crespigny Park
London
United Kingdom
SE5 8AF
+44 (0)7780611801
katya.rubia@kcl.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
299703

ClinicalTrials.gov (NCT)
Nil known

Central Portfolio Management System (CPMS)
49887

National Institute for Health and Care Research (NIHR)
130077

Protocol serial number
v.7.1 06.03.24

Study information

Scientific Title
A multi-centre, double-blind, randomized, parallel-group, Phase IIb study to compare the efficacy of real versus sham external trigeminal nerve stimulation on symptoms in youth with attention deficit hyperactivity disorder

Acronym
ATTENS

Study objectives

Four weeks of nightly administration of real versus sham trigeminal nerve stimulation (TNS) in attention deficit hyperactivity disorder (ADHD) children will significantly improve weekly investigator-assessed parent ratings of the ADHD-Rating Scale (ADHD-RS) (main hypothesis), as well as other clinical symptoms, cognitive functions and brain activation (secondary hypotheses).

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 10/03/2022, Medicines and Healthcare products Regulatory Agency (MHRA, 10 South Colonnade, Canary Wharf, London, E14 4PU, UK; Tel: not provided; Email: not provided), ref: CI/2022/0003/GB
2. Approved 20/09/2021, West Midlands - Solihull Research Ethics Committee (3rd Floor, Barlow House, 4 Minshull Street, Manchester, M1 3DZ, UK; +44 (0)207 104 8269; nabeelah.chothia@hra.nhs.uk), ref: 21/WN/0169
3. Approved 20/09/2021, Health Research Authority (2 Redman Place, Stratford, London, E20 1JQ, UK; +44 (0)207 1048000; solihull.rec@hra.nhs.uk), ref: 21/WM/0169

Study design
Multi-centre blinded randomized parallel-group phase IIb trial

Primary study design
Interventional

Study type(s)
Treatment

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

Interventions
Participants will be randomised 1:1 to receive either 4 weeks of 8 hours every night of:
1. Real TNS administered by the parents (or themselves if they have capacity). The TNS device will send stimulation 30 s on and 30 s off when in use
2. Sham TNS. The sham TNS device will send stimulation at a low frequency for 30 s at the start of every hour when in use

Intervention Type
Device

Phase
Phase II

Drug/device/biological/vaccine name(s)
-

Primary outcome(s)
Investigator-scored parent-rated ADHD symptoms measured on the well-validated ADHD-Rating Scale (ADHD-RS) at baseline, weekly during the 4-week trial and at 6 months follow-up

Key secondary outcome(s))

Current secondary outcome measures as of 16/08/2022:
1. Self-reported ADHD symptom severity measured using the Strength and Difficulties Questionnaire (SDQ) measured at baseline, after the 4 weeks trial and at 6 months follow-up
2. Side effects measured in parent and children completed side effects rating scales adapted for TNS, which will include open questions asking about general adverse events and their severity during the study period (5 min), measured at baseline, weekly during the 4 weeks trial and at 6 months follow-up
3. Sleep patterns of children with ADHD rated by parents measured using the parent-reported Sleep Disturbance Scale for Children (SDCS) measured at baseline, after the 4 weeks trial and at 6 months follow-up
4. Teacher-rated severity of ADHD symptoms assessed by the Conners Parent Rating Scale (CPRS) measured at baseline, after 4 weeks and at 6 months follow-up
5. Suicide risk measured using the Columba Suicide Severity Rating Scale (10 min) (C-SSRS) at baseline, post-treatment and at 6 months follow-up
6. Emotional dysregulation measured using the parent and child rated Irritability questionnaire (ARI) measured at baseline, after 4 weeks and at 6 months follow-up
7. The degree of mind-wandering assessed by the self-rated Mind Excessive Wandering Questionnaire (MEWS) measured at baseline, after 4 weeks and at 6 months follow-up
8. Depression and anxiety measured using the revised child and adolescent depression scale rated by children and by parents (RCADS-25 and RCADS 25-P) measured at baseline, after 4 weeks and at 6 months follow-up, measured at baseline, after 4 weeks and at 6 months follow-up
9. Cognitive performance in a range of executive functions including attention, inhibition, switching, working memory and timing measured using the Maudsley Attention and Response task battery, measured at baseline, after 4 weeks and at 6 months follow-up
10. Height, weight and vital signs measured using scale, height measure and blood pressure measurement device, measured at baseline, after 4 weeks and at 6 months follow-up
11. Physiological measures at baseline, post-treatment and at follow-up:
12. Heart rate, heart rate variability and objective hyperactivity measures measured using a wrist-hand device
13. Pupil diameter measured using Tobii eyetracker device during rest and one of the cognitive tasks

Previous secondary outcome measures:
1. Parent-rated ADHD symptom severity measured using the short form of the Conners Parent Rating Scale (CPRS), measured at baseline, weekly during the 4 weeks trial and at 6 months follow-up
2. Self-reported ADHD symptom severity measured using the Conners-Wells Adolescent Self-report form-short version (CASS-S), measured at baseline, weekly during the 4 weeks trial and at 6 months follow-up
3. Side effects measured in parent and children completed side effects rating scales adapted for TNS, which will include open questions asking about general adverse events and their severity during the study period (5 min), measured at baseline, weekly during the 4 weeks trial and at 6 months follow-up
4. Sleep patterns of children with ADHD rated by parents measured using the parent-reported Sleep Disturbance Scale for Children (SDCS) measured at baseline, weekly during the 4 weeks trial and at 6 months follow-up
5. Teacher-rated severity of ADHD symptoms assessed by the Conners Parent Rating Scale (CPRS) measured at baseline, after 4 weeks and at 6 months follow-up
6. Teacher-rated ADHD-related impairment in the classroom assessed using the web-based version of the T-SKAMP short form (i.e. the Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale),

which provides an additional objective measure of teacher-rated ADHD-related impairment in context-bound behaviours measured at baseline, after 4 weeks and at 6 months follow-up
7. ADHD severity measured using the investigator-completed Clinical Global Impression ADHD severity scale (CGI), measured at baseline, after 4 weeks and at 6 months follow-up
8. Emotional dysregulation measured using the parent and child rated Irritability questionnaire (ARI) measured at baseline, after 4 weeks and at 6 months follow-up
9. The degree of mind-wandering assessed by the self-rated Mind Excessive Wandering Questionnaire (MEWS) measured at baseline, after 4 weeks and at 6 months follow-up
10. Depression and anxiety measured using the revised child and adolescent depression scale rated by children and by parents (RCADS-25 and RCADS 25-P) measured at baseline, after 4 weeks and at 6 months follow-up, measured at baseline, after 4 weeks and at 6 months follow-up
11. Daily life executive function behaviour measured using the Behaviour Executive Function Questionnaire-Self-report measure (BRIEF) and the Behaviour Executive Function Questionnaire-parent-report measure (BRIEF), measured at baseline, after 4 weeks and at 6 months follow-up
12. Cognitive performance in a range of executive functions including attention, inhibition, switching, working memory and timing measured using the Maudsley Attention and Response task battery, measured at baseline, after 4 weeks and at 6 months follow-up
13. Height, weight and vital signs measured using scale, height measure and blood pressure measurement device, measured at baseline, after 4 weeks and at 6 months follow-up
14. Physiological measures at baseline, post-treatment and at follow-up:
14.1. Heart rate, heart rate variability and objective hyperactivity measures measured using a wrist-hand device
14.2. Pupil diameter measured using Tobii eyetracker device during rest and one of the cognitive tasks

Completion date
30/09/2026

Eligibility

Key inclusion criteria
Current inclusion criteria as of 12/08/2022:
1. Children and adolescents, aged 8-18 years at study entry
2. ADHD diagnosis (DSM-5; based on the K-SADS)
3. A score higher than 24 on the investigator-scored parent-rated ADHD-RS (DSM-5) (to include participants who still have relatively high symptoms)
4. Scoring above the clinical cut-off for ADHD (5 or above) on the combined summary score of the child and parent ratings Kiddie Schedule for Affective Disorders and Schizophrenia, for School-age Children- present and lifetime version, ADHD module (K-SADS) (Kaufman et al., 1996)
5. Both parent and child need to speak English (defined as sufficient to complete study assessments)
6. IQ above 70 as assessed on the Wechsler Abbreviated Scale of Intelligence (WASI-II) (Wechsler, 1999) (to exclude participants with a learning disability)
7. Patients should be either medication-naïve OR willing to come off their stimulant medication for one week before the trial OR willing to be on stable medication for the duration of the trial.

Previous inclusion criteria:
1. Children and adolescents, aged 8-18 years at study entry
2. ADHD diagnosis (Diagnostic and Statistical Manual of Mental Disorders, 5th Edition [DSM-5])
3. A score higher than 24 on the investigator-scored parent-rated ADHD-RS-5
4. Scoring above the clinical cut-off for ADHD on the Schedule for Affective Disorders and

Schizophrenia, ADHD module (K-SADS)
5. Scoring above the clinical cut-off for ADHD on the short forms of the Conners Parent Rating Scales (CPRS)
6. IQ above 70 as assessed on the Wechsler Abbreviated Scale of Intelligence (WASI-II)
7. Patients will be either medication-naïve, come off their stimulant medication for 2 weeks before the trial or be on stable medication for the trial duration. Patients on stable stimulant medication will come off for 24-48 hours prior to pre, post and follow-up assessments. The researchers will give priority to patients who are stimulant medication-naïve or not currently taking stimulant ADHD medication or other psychotropic medication or who are willing to come off their stimulant medication for 2 weeks before the trial and during the trial
8. Comorbidity with conduct/oppositional defiant disorder will be allowed

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
8 years

Upper age limit
18 years

Sex
All

Total final enrolment
150

Key exclusion criteria
Current exclusion criteria as of 12/08/2022:
1. Comorbidity with any other major psychiatric disorder (except conduct/oppositional defiant disorder, mild anxiety and depression- as assessed on the K-SADS, as these are commonly associated with ADHD)
2. Alcohol and/ or substance abuse (as assessed on the K-SADS) (potential confound)
3. Neurological abnormalities, such as epilepsy (potential confound)
4. Current medication with atomoxetine or guanfacine or in the past two weeks (as these have an effect on the arousal system to be improved with eTNS)
5. Participants who usually take drug holidays on weekends or holidays will not be able to participate in the study unless they are willing to take their stimulant medication in a stable way throughout the study or not at all throughout the study and 1 week before the study (Participants will be either on medication or off medication to decrease heterogeneity).
6. Implanted cardiac or neurostimulation systems (contraindication to eTNS)
7. Implanted metallic or electronic device in their head (contraindication to eTNS)
8. Presence of body-worn devices (e.g., insulin pumps and t-VNS) (contraindication to eTNS)
9. Currently receiving any non-medical treatment (e.g., psychotherapy, counselling, parent-training, cognitive rehabilitation, EEG neurofeedback) (potential confound)

10. Participants with dermatitis (could be sensitive to patches)
11. Traumatic Brain Injury (TBI) (potential confound)

Additional exclusion criteria for the 56 patients that will participate in the fMRI study
12. Under 10 years old
13. Have any MRI contra-indications (e.g., metal implants, pacemakers, braces, tattoos/piercings claustrophobia etc.) which would render them unsuitable for the fMRI sub-study
14. Be pregnant and/or breastfeeding if female

If patients are COVID positive, the participant's involvement in the trial will be delayed. If any patient develops COVID during the trial, arrangements will be made as required for the individual case.

Previous exclusion criteria:
1. Comorbidity with any other major psychiatric disorder (except conduct/oppositional defiant disorder (see above), mild anxiety and depression (as assessed on the K-SADS)
2. Alcohol and substance abuse (as assessed on the K-SADS)
3. Neurological abnormalities, such as epilepsy.
4. Medication with atomoxetine or guanfacine.
5. Implanted cardiac or neurostimulation systems (contraindication to TNS)
6. Implanted metallic or electronic device in their head (contraindication to TNS)
7. Presence of body-worn devices (e.g., insulin pumps and t-VNS) (contraindication to TNS)

Date of first enrolment
01/09/2022

Date of final enrolment
19/11/2024

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
King's College London
Department of Child Psychiatry/SGDP PO46
Institute of Psychiatry, Psychology & Neuroscience
De Crespigny Park
London
England
SE5 8AF

Study participating centre

Southampton University
Centre for Innovation in Mental Health (CIMH), School of Psychology
Highfield Campus, Building 44, Room 4059, University Rd
Southampton
England
SO17 1PS

Sponsor information

Organisation
King's College London

ROR
https://ror.org/0220mzb33

Organisation
South London and Maudsley NHS Foundation Trust

ROR
https://ror.org/015803449

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

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 are/will be available upon request from Prof. Katya Rubia (katya.rubia@kcl.ac.uk). Type of data: cognitive data, clinical data, fMRI data. Available for 10 years after study completion in anonymised form, shared on request for additional analyses; consent from participants will be obtained.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		16/01/2026	19/01/2026	Yes	No
Protocol article		30/04/2024	14/05/2024	Yes	No
Participant information sheet	Child aged 10 to 15 years version 7.0	24/08/2023	07/05/2024	No	Yes
Participant information sheet	Child aged over 16 years version 7.0	24/08/2023	07/05/2024	No	Yes
Participant information sheet	Child aged under 10 years version 6.0	05/07/2022	07/05/2024	No	Yes
Participant information sheet	Parent version 7.0	24/08/2023	07/05/2024	No	Yes
Participant information sheet	Teacher version 5.0	05/07/2022	07/05/2024	No	Yes
Statistical Analysis Plan			14/05/2024	No	No
Study website		11/11/2025	11/11/2025	No	Yes