External Trigeminal Nerve Stimulation in youth with ADHD: a randomized, sham-controlled, phase 2b trial

Dr Aldo Alberto Conti

Department of Child & Adolescent Psychiatry, Institute of Psychiatry, Psychology & Neuroscience; Florence Nightingale Faculty of Nursing, Midwifery & Palliative Care, Division of Care in Long Term Conditions, King's College London

JOINTLY FUNDED BY

Medical Research Council

NIHR | National Institute for Health and Care Research

Email: Aldo.conti@kcl.ac.uk

Background

- ADHD affects ~5% of school-age children
- Stimulant medications are first-line but have side effects and poor long-term adherence
- Families often prefer non-pharmacological treatments
- External Trigeminal Nerve Stimulation (TNS) received FDA clearance in 2019 as the first non-pharmacological treatment for ADHD
- The evidence for FDA clearance was based on a pilot double-blind randomized controlled trial (RCT) in 62 unmedicated children, showing that four weeks of nightly real versus sham TNS significantly decreased parent-rated ADHD symptoms on the ADHD Rating Scale (ADHD-RS), with medium effect size (Cohen's d = 0.5) (McGough et al., 2019)

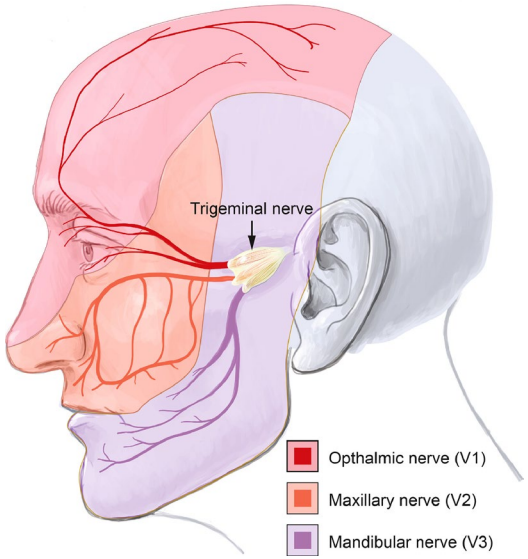
Proposed TNS mechanisms

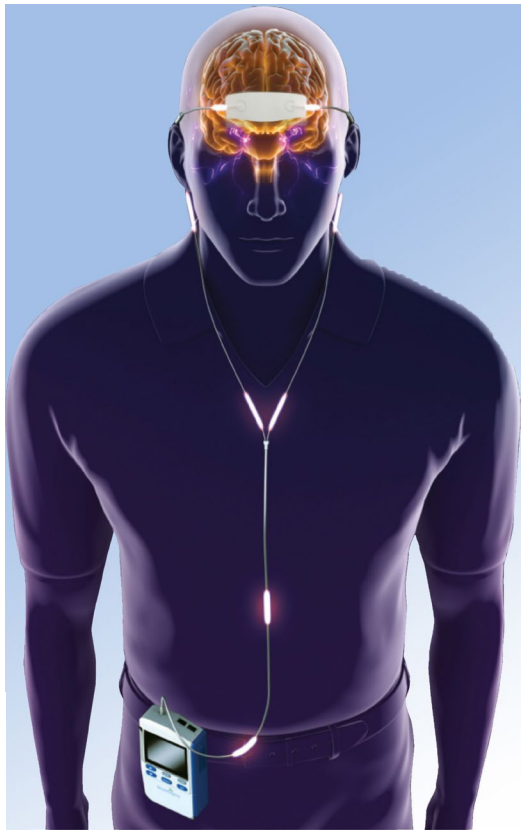
- Non-invasive brain stimulation technique that targets the supraorbital branches (V1) of the trigeminal nerve by delivering an electric current through electrodes placed on the forehead

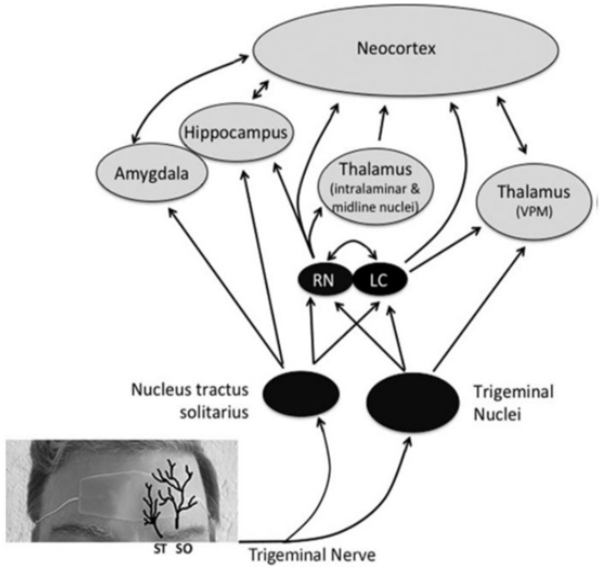
- Sensory inputs from the trigeminal nerve fibres activate the LC, RN, and NTS thought to activate in a bottom-up manner several thalamic, frontal and limbic brain regions

- The effects of TNS on the LC and brainstem are thought to enhance attention and arousal mechanisms by stimulating the release of norepinephrine which is important for arousal, attention, and emotion regulation (possibly also other NTs like dopamine, glutamate, GABA, and serotonin)

- A meta-analysis found TNS to be safe and effective in reducing migraine pain intensity (combined with medication) and depression symptoms (Westwood et al., 2023), only one study was done on ADHD (McGough et al., 2019)







Objectives and study design

- Confirm clinical efficacy of TNS in children and adolescents with ADHD in a larger multi-center double blind-confirmatory phase 2b RCT
- Multi-centre: London and Southampton
- Assess both short-term (4 weeks) and longer-term (6 months) TNS efficacy
- Evaluate TNS efficacy on secondary clinical, cognitive, and physiological measures

Outcome measures

- Primary outcome: Researcher-scored parent-rated ADHD-RS total score at week 4
- Secondary outcomes:
  - ADHD-RS total score at 6 months
  - Anxiety and Depression (RCADS-25)
  - Emotion regulation (ARI)
  - Mind Wandering (MEWS)
  - Sleep (SDSC)
  - Cognition: vigilance, sustained attention, motor & interference inhibition (Go/no-Go, Simon, time estimation)
  - Objective hyperactivity during 3-4 hr testing (Empatica wristband device)
  - Pupil diameter (arousal) during rest, GNG task
  - Safety (Side effects; adverse events)
  - fMRI activation (MOA) London only

Rubia et al., (2024) BMC Psychiatry 24(1):326.

Participants

- **Inclusion criteria:**
  - Children and adolescents (8-18 years) with ADHD
  - ADHD diagnosis (clinical or research K-SADS)
  - Score > 24 on ADHD-RS; score > cut-off for ADHD on K-SADS
  - Either unmedicated or on stable stimulant medication (for 4 weeks RCT)

- **Exclusion criteria:**
  - IQ < 70
  - Any major comorbid psychiatric disorder except for CD/ODD, mild anxiety or mild depression
  - Neurological abnormalities, TBI
  - Counterindication for TNS (implanted cardiac, neurostimulation, metallic or electronic device, dermatitis)
  - Receiving non-medication treatment
  - Non-stimulant medication (as similar MOA on LC and norepinephrine to TNS)

Rubia et al., (2024) BMC Psychiatry 24(1):326.

Intervention

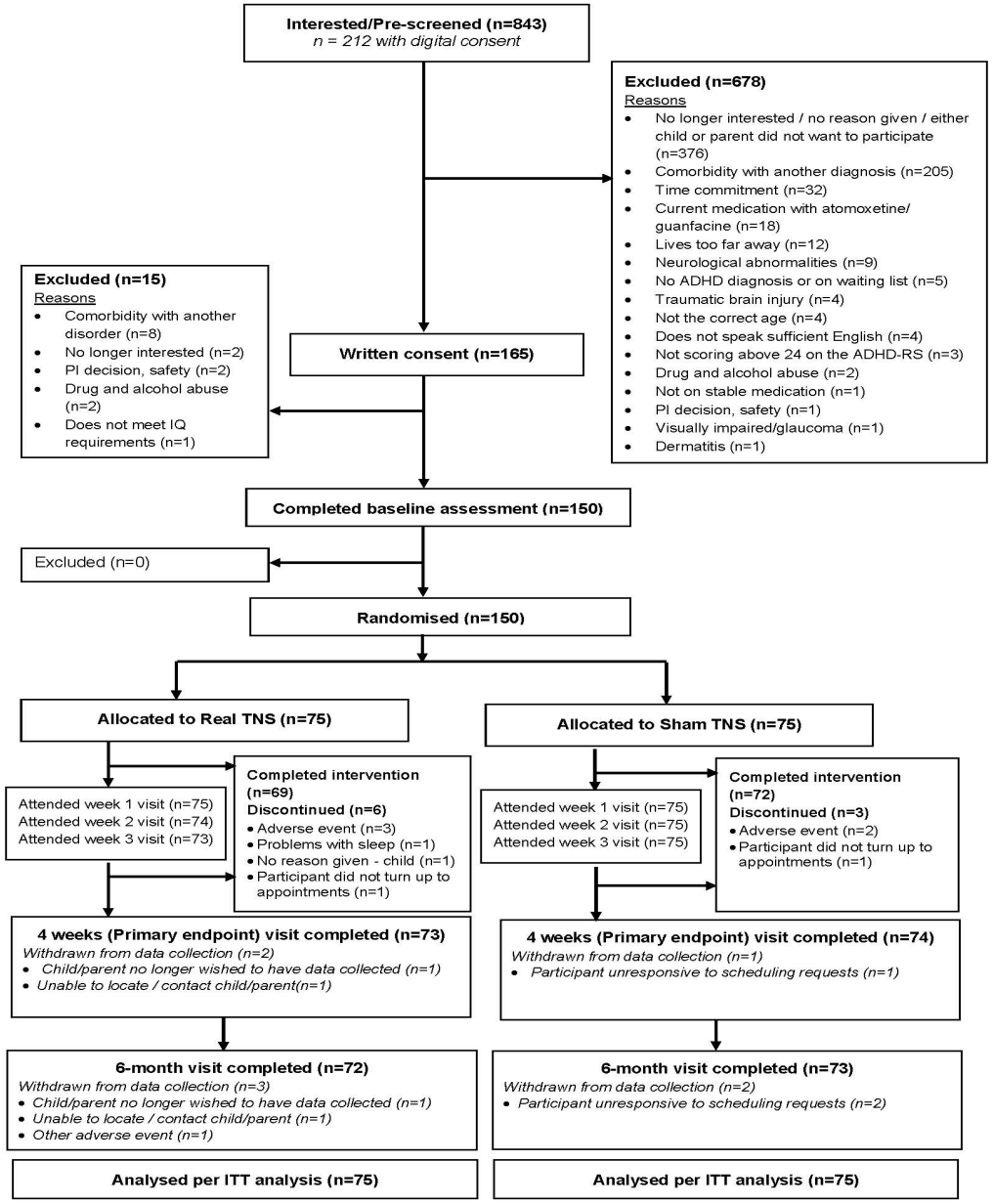
- Monarch TNS system; NeuroSigma Inc, LA

Details of the stimulation parameters and settings for the active and sham TNS devices		
	Active TNS	Sham TNS
Frequency of stimulation	120 Hz	2 Hz
Pulse width	250 µs	50 µs
Pulse interval	8 ms	8 ms
Maximum stimulus intensity	10 mA	10 mA
Net charge per pulse at maximum stimulus intensity	2.5 µC	2.5 µC
Maximum output voltage at maximum stimulus intensity	5.36 V	5.36 V
Current increment	0.2 mA	0.2 mA
Cycling	30 sec on/30 sec off	30 sec on/(1hr-30s) off
Hours of use	8 hrs during sleep	8 hrs during sleep
Stimulation time (8 hrs of use)	240 min	4 min
Number of pulses (8 hrs of use)	~1.7 million	~480
Note. Hz=Hertz; µs=microsecond; ms=millisecond; mA=milliampere; µC=microcoulombs; V=volt; hr=hours; min=minutes; sec=seconds.		

Rubia et al., (2024) BMC Psychiatry 24(1):326.

Results

- Compliance: 93%
- Adherence: 93.3%
- Blinding: successful (both sham and real TNS participants thought to be in the real group)
- Safety: good, no SAE, no diffs in SE
- Most common side effects in real TNS were mild headaches (21%) sleep problems (20%)
- Acceptability: 82% no or mild burden



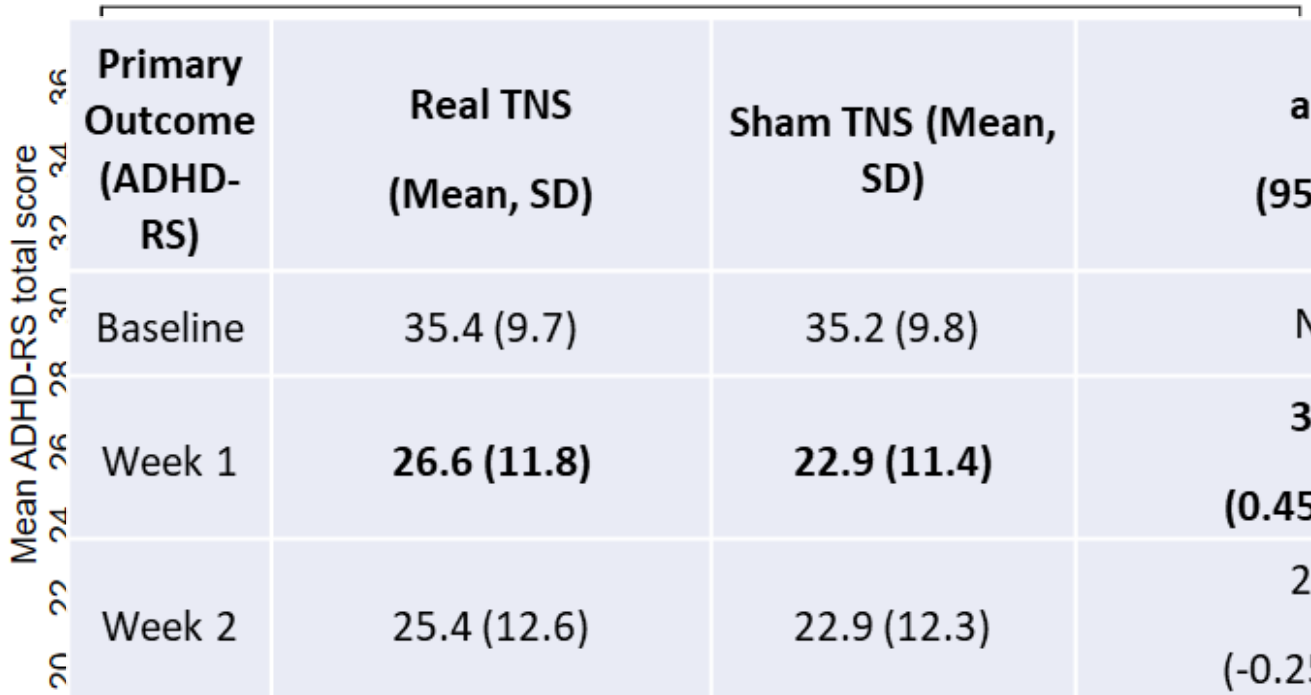
Conti et al., (2025), Nature Medicine, in press

Participants' characteristics at BL

Baseline characteristics (n,%)	Real TNS (n=75)	Sham TNS (n=75)	Overall (n=150)
Age (Mean, SD)	12.6 (2.8)	12.6 (2.8)	12.6 (2.8)
Male	49 (65.3)	48 (64.0)	97 (64.7)
Female	26 (34.7)	27 (36.0)	53 (35.3)
ADHD diagnosis per KSADS			
Combined presentation	66 (88.0)	67 (89.3)	133 (88.7)
Inattentive presentation	8 (10.7)	8 (10.7)	16 (10.7)
Hyperactive/impulsive presentation	1 (1.3)	0 (0.0)	1 (0.7)
Oppositional Disorder per KSADS	26 (34.7)	28 (37.3)	54 (36.0)
Conduct Disorder per KSADS	4 (5.3)	0 (0.0)	4 (2.7)
Current stimulant medication status			
On stable medication	29 (38.7)	30 (40.0)	59 (39.3)
Off medication/ Naive	46 (61.3)	45 (60.0)	91 (60.7)
WASI FSIQ-4 score (Mean (SD))	105.5 (13.8)	109.8 (13.5)	107.6 (13.8)

Conti et al., (2025), Nature Medicine, in press

Primary outcome



Primary Outcome (ADHD-RS)	Real TNS (Mean, SD)	Sham TNS (Mean, SD)	aMD (95% CI)	Cohen's d (95% CI)	p-value
Baseline	35.4 (9.7)	35.2 (9.8)	N/A	N/A	
Week 1	**26.6 (11.8)**	**22.9 (11.4)**	**3.03 (0.45, 5.61)**	**0.31 (0.05,0.58)**	N/A
Week 2	25.4 (12.6)	22.9 (12.3)	2.30 (-0.25,4.84)	0.24 (-0.03,0.50)	N/A
Week 3	24.1 (11.9)	22.5 (12.0)	1.56 (-1.24, 4.37)	0.16 (-0.13,0.45)	N/A
Week 4	**26.1 (12.3)**	**25.0 (12.3)**	**0.83 (-2.47,4.13)**	**0.09 (-0.26,0.43)**	**0.622**

Conti et al., (2025), Nature Medicine, in press

Secondary outcomes	Mean (SD)					
	Baseline		Week 4		Stats	
	Real TNS (75)	Sham TNS (75)	Real TNS (73)	Sham TNS (74)	aMD	p-value
SDQ Hyperactivity/impulsivity/ inattention score (child rated)	7.5 (2.0)	7.5 (2.1)	6.8 (2.3)	7.0 (2.1)	-0.30	0.308
ARI-P total score (parent rated)	5.5 (3.3)	5.0 (3.2)	3.8 (3.2)	3.9 (3.1)	-0.36	0.374
ARI-S total score (child rated)	4.2 (3.4)	4.0 (3.3)	2.9 (3.2)	3.4 (3.2)	-0.63	0.052
MEWS total score (child rated)	16.7 (8.1)	17.3 (8.2)	13.4 (8.9)	15.9 (9.8)	-2.17	0.049*
RCADS-25 total score (child rated)	41.6 (9.0)	42.7 (10.4)	36.9 (7.1)	39.1 (9.1)	-1.56	0.121
RCADS-25 total score (parent rated)	58.5 (12.6)	56.9 (13.7)	50.3 (10.1)	50.7 (11.7)	-1.07	0.453
Mackworth Vigilance Task (% OM)	45.8 (23.8)	41.4 (21.7)	36.3 (21.1)	30.1 (21.8)	3.62	0.103
Mackworth Vigilance Task (% COM)	6.8 (8.6)	5.9 (6.6)	4.7 (5.5)	6.8 (12.8)	0.95[1]	0.573
SDSC total score (parent rated)	49.2 (12.1)	44.0 (9.7)	43.2 (10.0)	39.6 (8.9)	1.00	0.417
Objective hyperactivity composite score	-0.1 (1.7)	0.1 (1.7)	-0.2 (1.8)	0.2 (1.7)	-0.25	0.319
Average pupil diameter at rest	9.5 (1.5)	9.5 (1.6)	9.0 (1.3)	9.3 (1.6)	-0.25	0.134
Average pupil diameter at task	9.9 (1.6)	10.1 (1.5)	9.5 (1.3)	9.8 (1.6)	-0.17	0.349
Side effects score (child rated)	12.5 (10.1)	12.3 (9.3)	10.7 (9.5)	11.9 (10.5)	-1.11	0.410
Side effects score (parent rated)	10.8 (7.9)	8.9 (6.5)	8.7 (6.0)	9.0 (6.8)	-1.09	0.210
Weight (Kg)	46.7 (13.8)	47.4 (14.4)	47.2 (14.1)	48.1 (14.8)	-0.39	0.080
Pulse (bpm)	78.4 (13.7)	78.5 (14.2)	78.0 (12.5)	79.4 (13.7)	-1.32	0.477

Conti et al., (2025), Nature Medicine, in press

Conclusions

- TNS is a safe intervention but it does not demonstrate clinical efficacy for paediatric ADHD

- These negative findings extend largely negative findings using other neurostimulation techniques in children with ADHD, including TMS and TDCS

- Previous positive findings may reflect a neurotechnology-induced placebo effect or “neuro-enchantment” or “neuro-suggestion”

- Other possible explanations: Regression to the mean, baseline severity symptom inflation, non-specific effects of staff interaction

- Future neurostimulation studies should employ rigorous sham control conditions and explicit expectation management to minimise placebo effects.

Conti et al., (2025), Nature Medicine, in press

Acknowledgments

Thank you to all participants and their parents!

Institute of Psychiatry, Psychology & Neuroscience

MRC Medical Research Council

NHS South London and Maudsley NHS Foundation Trust

NIHR | National Institute for Health and Care Research

NIHR | Maudsley Biomedical Research Centre

King's College London Founded 1829

University of Southampton

Prof Katya Rubia (PI)
Prof Samuele Cortese
Prof Paramala Santosh
Dr Natali Bozhilova
Dr Irem Eranydin
Prof Mitul Metha
Mrs Lena Johansson
Dr Federico Fiori
Dr Robert Marhenke
Prof Ben Carter
Mr Dominic Stringer
Mr Sahid El-Masri
Mrs Andrea Bilbow OBE
Dr Giovanni Giaroli
Dr Holan Liang
Mr Joshua Hyde

THANK YOU!

Any questions?