Transcranial Magnetic Stimulation for Adolescent depression

Professor Steven Marwaha, UoB

Consultant Psychiatrist: Severe Mood Disorders Clinic (BSMHT)

26 September 2025

UNIVERSITY OF BIRMINGHAM

NIHR | National Institute for Health and Care Research

Midlands Translational Centre
Mental Health Mission

Conflicts of interest

- I don’t hold shares in pharma or neurostimulation companies
- I don’t hold copyright for any psychological treatments or co-author on manuals
- I don’t give drug or psychological therapy sponsored talks
- I have received research funding from the National Institute of Health Research, Medical Research Council and the Wellcome Trust.

Work in the CYP space

- Disclosure
- Epidemiology-Data from ALSPAC Birth Cohort Study
- rTMS
- TRIDENT trial

Depression in CYP

- Depression and anxiety are the largest contributors to the health burden experienced by children and adolescents.
- According to a meta-analysis, 12.3% meet criteria for anxiety disorder in middle childhood and 11.0% in adolescence
- Major depression has an estimated prevalence of 4% in school-aged children and 7.5% in adolescents.
- Global Burdens of Disease study: among young people aged 10–24 years in Europe, anxiety and depressive disorders contributed to a substantial amount of years lived with disability, reporting 655 912 and 626 008 years, respectively.
- Some longitudinal studies suggest that when left untreated, anxiety and depression can put children and adolescents at risk for long-term adverse outcomes.

Factors associated with chronic depressive symptoms across adolescence and young adulthood: a UK birth cohort study

B. B. Durdurak[1], B. Williams[1], A. Zhigalov[2], A. Moore[3], P. Mallikarjun[4], D. Wong[5], S. Marwaha[1,6] and I. Morales-Muñoz[1]

[1]Institute for Mental Health, University of Birmingham, Edgbaston, Birmingham, UK; [2]School of Engineering and Technology, Aston University, Birmingham, UK; [3]Department of Psychiatry, University of Cambridge Herchel Smith Building for Brain & Mind Sciences, Cambridge, UK; [4]Early Intervention Service, Birmingham Women's and Children's NHS Trust, Birmingham, UK; [5]Leeds Institute of Health Sciences, School of Medicine, University of Leeds, Leeds, UK and [6]Specialist Mood Disorders Clinic, The Barberry Centre for Mental Health, Birmingham and Solihull NHS Trust, Birmingham, UK

UNIVERSITY OF BIRMINGHAM

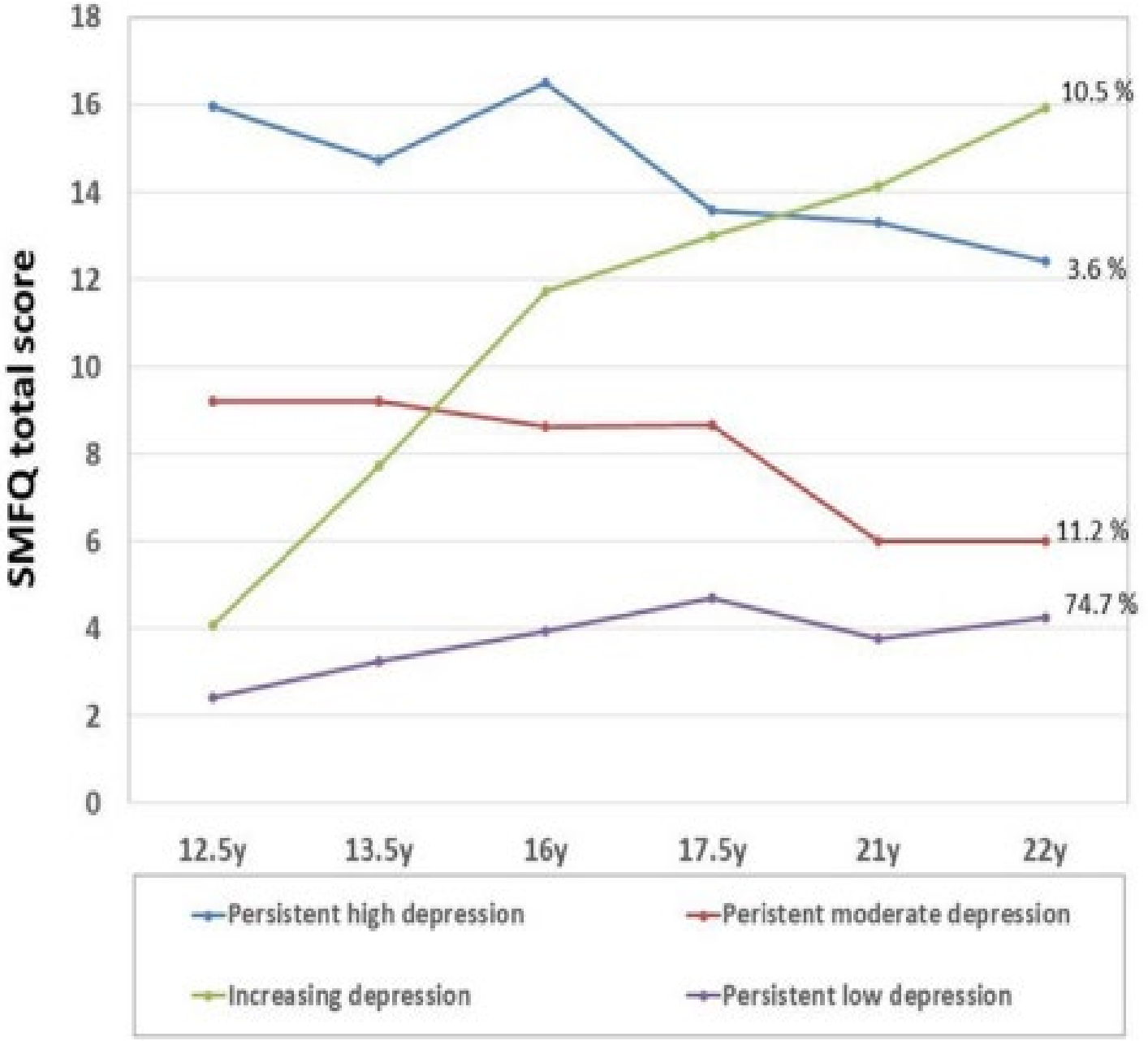


Table 4. Associations between combined factors and persistent high levels of depressive symptoms

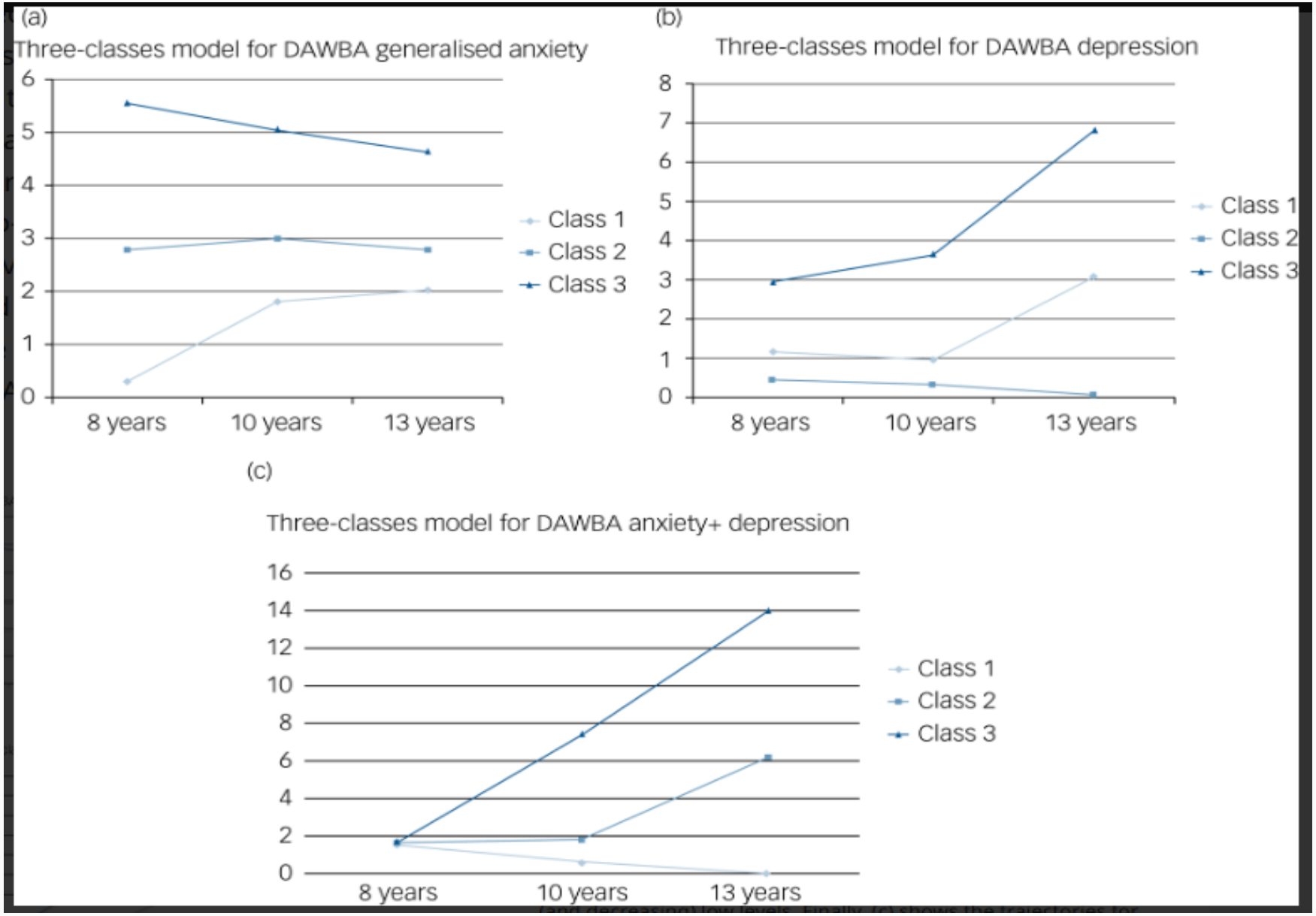
	Persistent high levels of depressive symptoms					
	Unadjusted model			Adjusted model*		
	OR	95% CI	*p*	OR	95% CI	*p*
Male parenting score at 81 months**	1.00	0.97–1.03	0.825	1.00	0.97–1.03	0.924
Friendship at 8 years**	0.98	0.87–1.11	0.763	0.96	0.84–1.08	0.478
WISC—total IQ at 8 years	0.99	0.97–1.01	0.240	0.99	0.97–1.02	0.625
Total sleep during night at 9 years	1.62	0.60–4.33	0.340	1.68	0.59–4.74	0.329
Bedtime at 9 years	1.81	0.62–5.33	0.281	1.60	0.51–5.03	0.418
Loneliness at 10 years	**2.25**	**1.30–3.89**	**0.004**	**2.02**	**1.11–3.67**	**0.022**
School connectedness at 11 years**	**1.24**	**1.13–1.36**	**<0.001**	**1.29**	**1.16–1.43**	**<0.001**
School enjoyment at 11 years**	**0.75**	**0.60–0.94**	**0.011**	0.81	0.62–1.03	0.112

OR = odds ratio.

*Adjusted model controlled for sex, ethnicity, SES, temperament at 2 years, preterm and maternal postnatal depression at 8 months.

**These variables were invertedly coded, with higher scores indicating worse outcomes, and lower scores better outcomes. Note 1: The selection of these factors was done based on lived experience involvement. Here, all the factors were included together within the same regression analyses model.

Childhood anxiety and depression and long-term outcomes



Impact of anxiety and depression across childhood and adolescence on adverse outcomes in young adulthood: a UK birth cohort study

Isabel Morales-Muñoz, Pavan K. Mallikarjun, Joht S. Chandan, Rasiah Thayakaran, Rachel Upthegrove and Steven Marwaha

UNIVERSITY OF BIRMINGHAM

Any mental health problem at age 24 years

Outcomne	OR	95% CI	*P*
Any mental health problem at 24 years			
DAWBA anxiety			
Anxiety Class1 (ref)	–	–	–
Anxiety Class2	1.07	0.91 to 1.26	0.417
Anxiety Class3	**2.09**	**1.63 to 2.69**	**<0.001**
Gender	**0.48**	**0.42 to 0.56**	**<0.001**
Gestational age	0.97	0.93 to 1.09	0.083
FAI total score	**1.04**	**1.03 to 1.06**	**<0.001**
Ethnicity	1.08	0.67 to 1.73	0.758
Maternal age birth	0.99	0.98 to 1.01	0.994
DAWBA depression			
Mood Class2 (ref)	–	–	–
Mood Class1	0.93	0.75 to 1.15	0.490
Mood Class3	**2.07**	**1.50 to 2.87**	**<0.001**
Gender	**0.52**	**0.46 to 0.60**	**<0.001**
Gestational age	0.97	0.94 to 1.01	0.111
FAI total score	**1.04**	**1.04 to 1.06**	**<0.001**
Ethnicity	1.01	0.63 to 1.62	0.969
Maternal age birth	0.99	0.98 to 1.01	0.336
DAWBA Anxiety + Depression			
A + D Class2 (ref)	–	–	–
A + D Class1	1.17	0.95 to 1.44	0.148
A + D Class3	**1.99**	**1.49 to 2.65**	**<0.001**
Gender	**0.52**	**0.45 to 0.59**	**<0.001**
Gestational age	0.98	0.95 to 1.02	0.289
FAI total score	**1.04**	**1.03 to 1.05**	**<0.001**
Ethnicity	1.01	0.63 to 1.62	0.959
Maternal age birth	0.99	0.98 to 1.01	0.376

UNIVERSITY OF BIRMINGHAM

Any physical health problem at age 24 years

UNIVERSITY OF BIRMINGHAM

Gender	**0.46**	**0.42 to 0.50**	**<0.001**
Gestational age	1.00	0.98 to 1.03	0.827
FAI total score	**0.98**	**0.97 to 0.99**	**<0.001**
Ethnicity	1.07	0.77 to 1.48	0.693
Maternal age birth	**1.01**	**1.00 to 1.02**	**0.006**
Child's health 4 weeks	0.00	0.00 to 0.00	0.998
Child's health 8 years	**1.83**	**1.12 to 3.01**	**0.016**
Child's health 10 years	**2.88**	**1.91 to 4.37**	**<0.001**
Child's health 13 years	**1.92**	**1.13 to 3.25**	**0.015**
DAWBA depression			
Mood Class2 (ref)	–	–	–
Mood Class1	**1.23**	**1.02 to 1.48**	**0.033**
Mood Class3	**1.27**	**1.09 to 1.48**	**0.002**
Gender	**0.47**	**0.43 to 0.52**	**<0.001**
Gestational age	1.00	0.98 to 1.03	0.743
FAI total score	**0.98**	**0.97 to 0.99**	**<0.001**
Ethnicity	0.99	0.72 to 1.37	0.973
Maternal age birth	**1.01**	**1.00 to 1.02**	**0.010**
Child's health 4 weeks	0.00	0.00 to 0.00	0.998
Child's health 8 years	**1.92**	**1.17 to 3.14**	**0.009**
Child's health 10 years	**2.81**	**1.86 to 4.27**	**<0.001**
Child's health 13 years	**1.93**	**1.14 to 3.28**	**0.015**
DAWBA anxiety + depression			
A + D Class2 (ref)	–	–	–
A + D Class1	**1.28**	**1.04 to 1.56**	**0.017**
A + D Class3	**1.40**	**1.21 to 1.62**	**<0.001**
Gender	**0.48**	**0.44 to 0.52**	**<0.001**
Gestational age	1.01	0.98 to 1.03	0.580
FAI total score	0.98	0.97 to 0.99	<0.001
Ethnicity	0.95	0.69 to 1.30	0.732

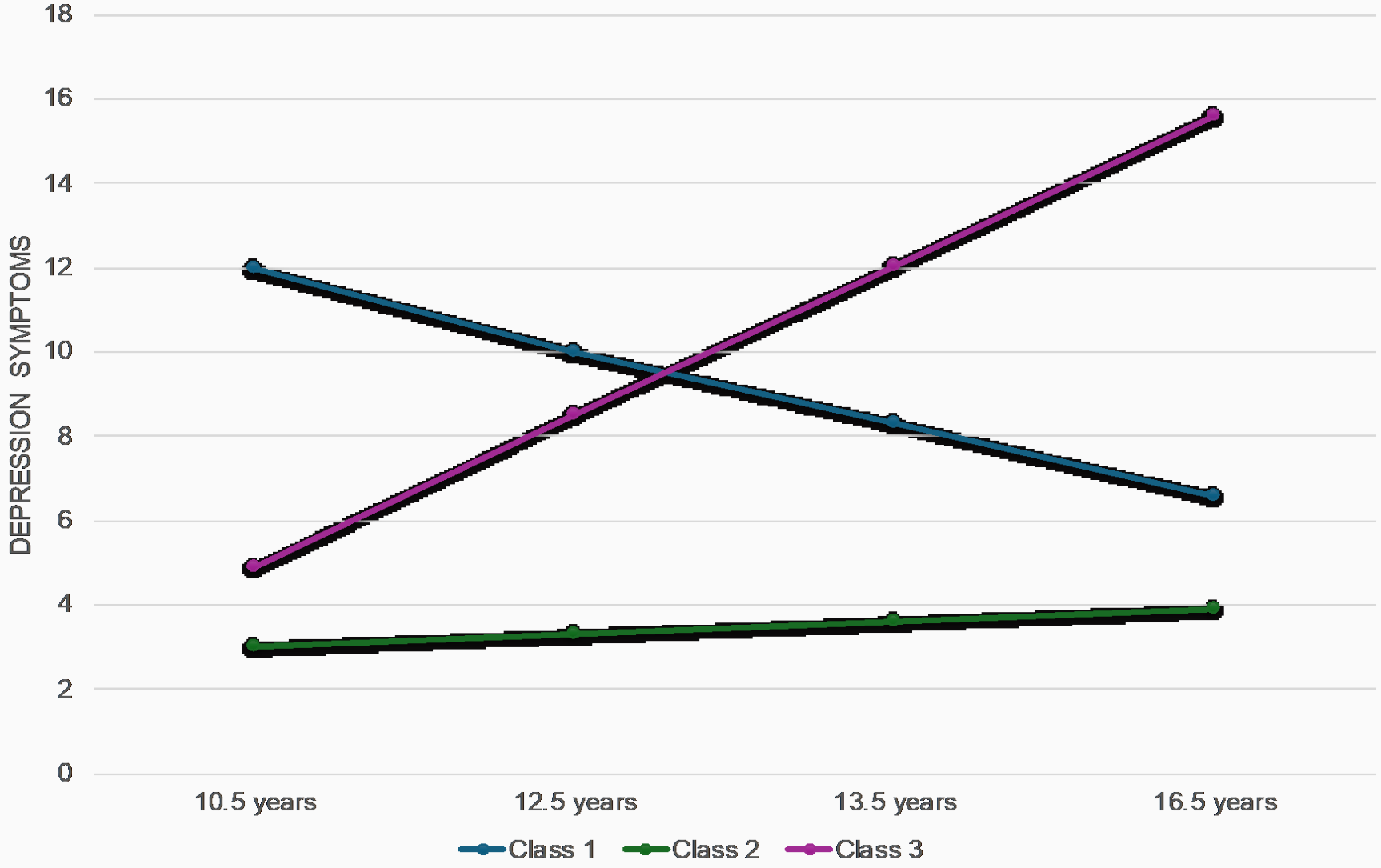
Education and employment at age 24 years

UNIVERSITY OF BIRMINGHAM

Any education/employment problem at 24 years			
DAWBA anxiety			
Anxiety Class1 (ref)	–	–	–
Anxiety Class2	**1.27**	**1.10 to 1.47**	**0.001**
Anxiety Class3	**1.56**	**1.20 to 2.03**	**0.001**
Gender	0.89	0.78 to 1.01	0.083
Gestational age	**0.94**	**0.91 to 0.98**	**0.001**
FAI total score	**1.03**	**1.02 to 1.04**	**<0.001**
Ethnicity	0.92	0.57 to 1.50	0.747
Maternal age birth	1.10	0.99 to 1.12	0.207
DAWBA depression			
Mood Class2 (ref)	–	–	–
Mood Class1	**1.77**	**1.47 to 2.12**	**<0.001**
Mood Class3	**1.38**	**1.00 to 1.91**	**0.047**
Gender	**0.86**	**0.76 to 0.98**	**0.026**
Gestational age	**0.94**	**0.91 to 0.98**	**0.001**
FAI total score	**1.03**	**1.01 to 1.04**	**<0.001**
Ethnicity	1.04	0.66 to 1.65	0.854
Maternal age birth	1.01	0.99 to 1.03	0.114
DAWBA anxiety + depression			
A + D Class2 (ref)	–	–	–
A + D Class1	**1.68**	**1.40 to 2.01**	**<0.001**
A + D Class3	**1.48**	**1.07 to 2.05**	**0.018**
Gender	**0.86**	**0.76 to 0.98**	**0.022**
Gestational age	**0.96**	**0.92 to 0.99**	**0.009**
FAI total score	**1.03**	**1.02 to 1.04**	**<0.001**
Ethnicity	1.02	0.64 to 1.62	0.926
Maternal age birth	1.01	0.99 to 1.02	0.198

Depression symptom trajectories across adolescence and risk of hypomanic symptoms in young adulthood

Buse Durdurak et al
(in peer review)



UNIVERSITY OF BIRMINGHAM

Associations of Latent Classes of SMFQ and Risk of Clinically Significant Hypomanic Symptoms at 21-23 Years

	Unadjusted Model			Adjusted Model		
	OR	95% CI	P Value	OR	95% CI	P Value
Hypomanic symptoms at 21-23 Years						
SMFQ persistent low levels class (Reference)	-	-	<0.001	-	-	<0.001
SMFQ increasing class	4.48	2.64-7.58	<0.001	3.30	1.78-6.12	<0.001
SMFQ decreasing levels class	0.00	0.00	0.993	0.00	0.00	0.993
Child's sex	-	-	-	0.89	0.50-1.58	0.679
Child's ethnicity	-	-	-	0.00	0.00	0.996
Family Adversity Index	-	-	-	1.19	1.13-1.25	<0.001
Any Childhood psychopathology at 8 years	-	-	-	4.03	2.00-8.08	<0.001
BPD symptoms at 11 years	-	-	-	1.27	1.08-1.51	0.005

UNIVERSIT
BIRMINGH

In summary

- Chronic depressive symptoms in children and adolescents appear to be associated with multiple poor outcomes, including transition to bipolar disorder
- What new treatments could help this population
- Focus on rTMS because of evidence base in adults

What is Transcranial Magnetic Stimulation (rTMS)

- It is a form of non-invasive brain stimulation in which a changing magnetic field alters the activity in neural circuits in the brain.
- TMS does not require anaesthesia or hospital inpatient admission
- There does not appear to be debilitating side-effects in adults
- Protocols that enable pulses of TMS to be delivered in short intervals are referred to as repetitive TMS (rTMS)
- High-frequency rTMS (> 1 Hz) is thought to have an excitatory effect on the cerebral cortex, low-frequency rTMS (≤ 1 Hz)-inhibitory effect
- rTMS believed to modulate the function of stimulated region beyond the period of stimulation.

Evidence in adults

- For depression LDLPF is typically repeatedly stimulated with high-frequency.
- rTMS: 30–45-min sessions/ day for at least 4 weeks.
- Placebo response is large, lower in severe depression, not associated with sex or age.
- Data from 9 SRs of the effectiveness of rTMS vs sham in adults with TRD. Absolute risk reduction is 23% (95% CI 15% to 32%) by treatment end, and NNT was 4.
- rTMS not as effective as ECT.
- With θ-burst stimulation 9 min sessions-Data suggest a pooled significant effect on response (ES 0·38; CI: 0·29–0·48) and on remission (ES 0·20, CI: 0·13–0·29).

UNIVERSITY OF BIRMINGHAM

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Repetitive Transcranial Magnetic Stimulation (rTMS) for the Treatment of Depression in Adolescence: A Systematic Review

Danielle Hett[a,b,*], Jack Rogers[a], Clara Humpston[a], Steven Marwaha[a,b,c]

Results: Fourteen studies were identified, which included 8 open-trial studies (N = 142 participants) and six studies which performed further post-hoc/follow-up analyses on these open-trial datasets. All studies suffered from multiple biases but reported that rTMS treatment reduced depression scores in adolescents. A single study on theta burst stimulation also found a positive effect. No study to date includes a sham control. Reported side effects of rTMS included scalp pain, headache and dizziness.

Limitations: Study methodologies precluded a meta-analysis.

Conclusions: The current literature signals that rTMS could reduce adolescent depressive symptoms. However, sham controlled randomized trials are needed. These findings suggest that rTMS may be a promising treatment option for adolescents with depression.

UNIVERSITY OF BIRMINGHAM

ARTICLE

Left prefrontal transcranial magnetic stimulation for treatment-resistant depression in adolescents: a double-blind, randomized, sham-controlled trial

Paul E. Croarkin[1], Ahmed Z. Elmaadawi[2], Scott T. Aaronson[3], G. Randolph Schrodt Jr[4], Richard C. Holbert[5], Sarah Verdoliva[6], Karen L. Heart[7], Mark A. Demitrack[8] and Jeffrey R. Strawn[9]

112 Antidepressant treatment resistant participants randomised

Table 1. Key demographics and clinical variables at baseline.

Variable	Treatment group		*P*-value[b]
	Sham ($n = 55$)[a]	Active ($n = 48$)[a]	
Sex, No. (%)			0.61
Female	37 (67.3)	30 (62.5)	
Male	18 (32.7)	18 (37.5)	
Age, *y*			0.34
Mean (SD)	17.1 (2.22)	17.6 (2.28)	
Median (range)	17.4 (12.1–21.4)	17.6 (12.2–21.8)	
Age group, No. (%), y			0.74
12–14	11 (20.0)	8 (16.7)	
15–17	24 (43.6)	19 (39.6)	
18–21	20 (36.4)	21 (43.8)	
QIDS-A_{17}-SR total score			0.76
Mean (SD)	20.8 (7.54)	20.4 (6.80)	
Median (range)	21.0 (1.0–36.0)	20.0 (6.0–35.0)	

UNIVERSITY OF BIRMINGHAM

No statistically significant differences in outcomes between active vs sham.

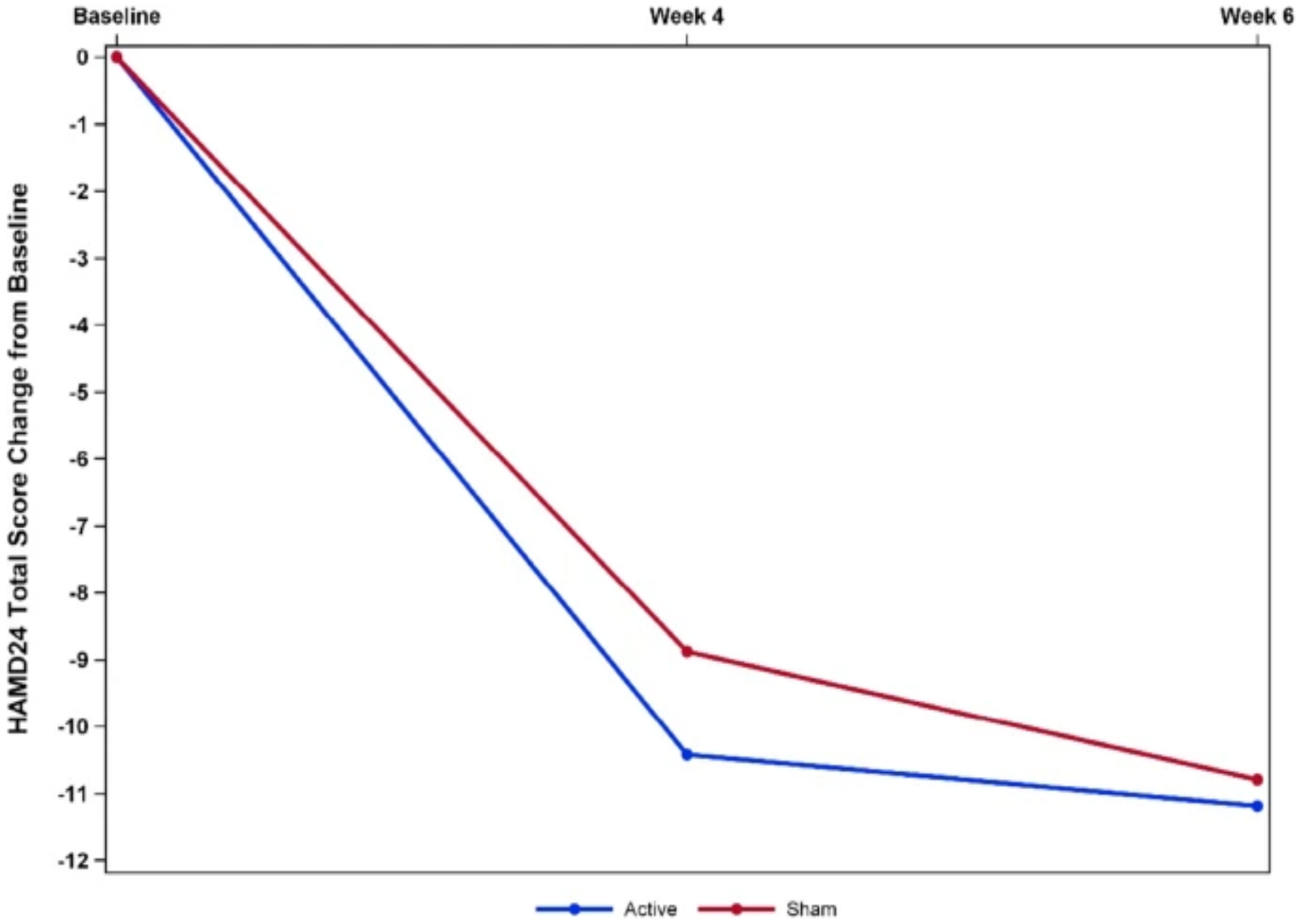
HAM-D-24 score in the treatment group decreased from 28.8 to 18.1vs 29.5 to 19.2 in the sham group.

Response rates active vs sham: 41.7% vs 36.4%

Increased separation between the active and sham groups as the ATR level increased.

UNIVERSITY OF BIRMINGHAM

Fig. 2: Primary efficacy outcome.



Week 4 and Week 6 primary effiacy outcomes (HAMD24) in depressed adolescents treated with active 10 Hz TMS or sham treatment.

NIHR | National Institute for Health and Care Research

NHS Birmingham and Solihull Mental Health NHS Foundation Trust

Midlands Translational Centre
Mental Health Mission

Theta buRst stImulation for aDolescent dEpressioN feasibiliTy study: The TRIDENT study

Funded by the NIHR-HTA

UNIVERSITY OF BIRMINGHAM

What is the trial?

Research question: Is it feasible to conduct a study to examine the effectiveness of iTBS for adolescents with depression that has not responded to at least one antidepressant and one psychological therapy?

Primary objective: To complete a double-blind feasibility trial including a sham arm to assess recruitment, adherence and outcome data completion at 8 weeks post-randomisation.

UNIVERSITY OF BIRMINGHAM

Secondary objectives

To evaluate:

A] acceptability of iTBS to patients, and family/carers across different ethnic and socioeconomic groups.

B] views and knowledge of CAMHS clinicians about the intervention.

C] capacity in NHS neuromodulation services to deliver a full trial.

D] change in depression, anxiety, psychological functioning, self-harm/suicidal acts, quality of life, social functioning, sleep quality and insomnia, relationships, other treatment, cognition, and adverse events at 8 weeks post randomisation.

E] and to optimise iTBS, sham and trial procedures maximising their feasibility, acceptability, and efficiency.

What is the trial

Trial design

A double-blind, 1:1 randomised parallel-group, sham-controlled multicentre feasibility trial.

The trial includes nested mixed-methods evaluations and a national survey of NHS TMS services.

Participant population and sample size

Fifty adolescents aged 14–19 years with moderate to severe unipolar depression which has not responded to at least one antidepressant and one psychological therapy.

UNIVERSITY OF BIRMINGHAM

What is the trial

Setting

- Participants will be recruited from:
- CAMHS and young people's mental health services
- Primary care (via GP practices)
- University wellbeing services
- Community mental health teams and the NHS Talking Therapies programme
- Inpatients
- The trial sites are: Birmingham, Nottinghamshire, North London, Oldham and Newcastle.

UNIVERSITY OF BIRMINGHAM

What is the trial - eligibility

Inclusion Criteria:

- Aged 14–19 years.
- DSM diagnosis of unipolar major depression confirmed using the MINI-KID for ages 14–17; MINI for ages 18–19.
- Moderate to severe depression, defined as a score of ≥18 on the HAM-D-24.
- Non-response to at least 1 antidepressant defined as prescribed for at least 6 weeks at BNF doses, or unable to tolerate at least 2 antidepressants or refusal of antidepressant medication AND not responded to at least 1 psychological treatment, defined as non-response to at least 4 sessions, unable to engage or refusal of psychological therapy.

What is the trial - eligibility

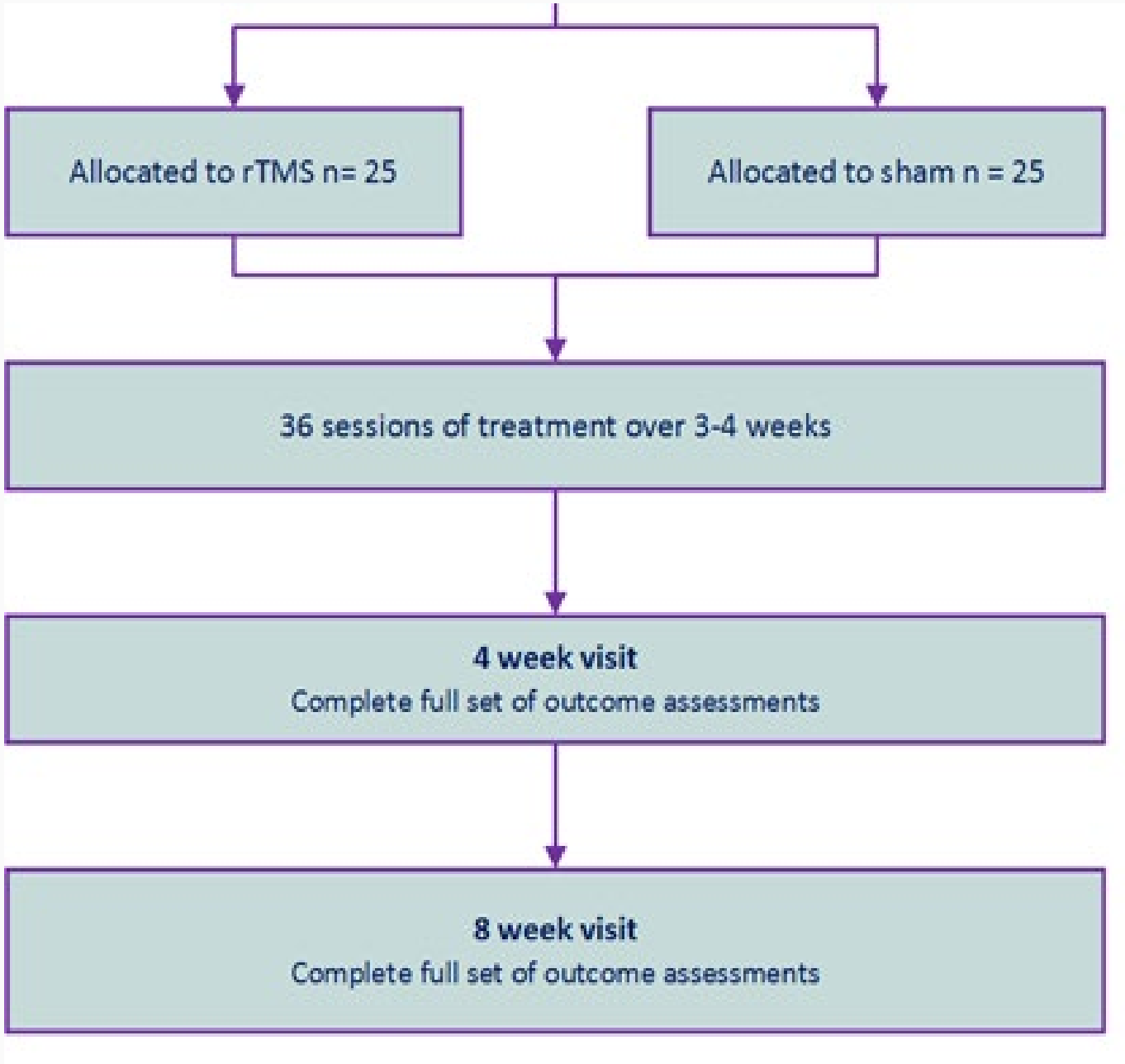
Exclusion Criteria:

- Depression secondary to physical health problems, eating disorders, or neurological conditions.
- Contraindication for TMS
- Detained under the Mental Health Act 1983 or hospitalised in general hospital wards.
- Prior TMS treatment.
- Primary diagnosis of psychosis

What is the trial

Outcomes:

- **Depression**
- **Anxiety**
- **Psychological functioning**
- **Social functioning**
- **Sleep**
- **Cognitive function**
- **Quality of Life**
- **Self-harm and suicidal acts**
- **Relationships**



UNIVERSITY OF BIRMINGHAM

NHS capacity to deliver a full trial

Aim: to understand the current provision of NHS TMS, the patient population being treated, and readiness to participate in a full scale trial evaluating TMS in adolescents with depression.

Method: We will complete a UK wide electronic survey of all mental health Trusts on their provision of TMS services.

i] patients treated / week;

ii] TMS set-up / equipment used;

iii] NHS or other provider

iv] whether they currently treat adolescents with depression, and what protocols;

v] referral pathways or local links and processes with CAMHS colleagues that would facilitate them being a centre in a full trial

vi] willingness to participate in a full trial and if not what would enable this.

Views and knowledge of rTMS amongst CAMHS clinicians

- Our aim is to understand and evaluate the views and knowledge of rTMS amongst CAMHS clinicians. We will use a mixed methods sequential explanatory approach.
- We will: a] design and distribute an electronic survey focussed on views and knowledge of TMS to CAMHS clinicians in our recruitment sites and then b] conduct qualitative focus groups with CAMHS clinicians (N=8-10).
- Aspects explored will be attitude to, knowledge and concerns about rTMS, potential to address unmet need, and facilitators and barriers to accessing the intervention.
- The survey results will be quantitatively analysed. A thematic analysis will be used to analyse the audio-recorded and transcribed focus group data.

Acceptability to participants and family / carers

- Our aim is to understand and evaluate the acceptability of iTBS to participants and family/carers.
- 8-10 parents/carers of trial participants who score within the lower (n = 4-5) and upper quartiles (n = 4-5) will also be recruited. Participants will be invited to individual qualitative interviews which will explore experiences of receiving iTBS (active and sham), dislikes, burden, how the intervention fits with their values, perceived effectiveness and reasons for continuing (or not) treatment.
- A thematic analysis will generate themes using a deductive and inductive approach. We will assess whether participants correctly guess whether they received sham or iTBS

PPIE

- The formation of a TRIDENT lived experience advisory panel (LEAP) which will be made up of young people aged 16-25 years from the YAG, and if needed additional young people with experience of mental health problems will be recruited.

- The TRIDENT LEAP will be focussed on meeting study objectives and will be embedded throughout each aspect of the work. The LEAP will be flexible in the frequency of meetings, but we would anticipate these will occur at least every 4 months throughout the study period.

Primary outcome to be reported

1. Recruitment rate per month: our target is randomisation of 50 participants over 12 months to demonstrate that randomisation to a sham controlled TMS study is feasible at a rate that would be sustainable to achieve a fully powered RCT of iTBS in this population.

2. Adherence to treatment protocol will be considered to have been achieved if participants have received at least 36 treatment sessions.

3. Data return and completion of the HAM-D at 8 weeks post-randomisation, our proposed primary outcome in a full RCT.

Secondary outcomes to be reported

- Acceptability. Mean total score on the PPI developed acceptability score used for our proposed progression criteria. Qualitative data will be used to gain insights on how to best facilitate a full trial, trial procedures, patients trial knowledge, and outcome data collection.

- A mixed methods analysis integrating a quantitative analysis of survey results of CAMHS clinicians' views with a thematic analysis from the focus group.
- We will produce an NHS TMS services map addressing our objective of the capacity of NHS services to deliver a full trial.
- Reduction of depressive symptoms at 8 weeks. We will also report the data collection rates and acceptability of these outcomes.
- Optimising treatment and procedures for a full trial.

UNIVERSITY OF BIRMINGHAM

Major milestones

- Sponsor submission: end of August 2025
- First participant: end of January 2026
- 50th participant: end of December 2026

Thank you for listening

s.marwaha@bham.ac.uk

UNIVERSITY OF BIRMINGHAM