Developing a novel therapy for Tourette syndrome based upon wearable median nerve stimulation

Stephen Jackson,

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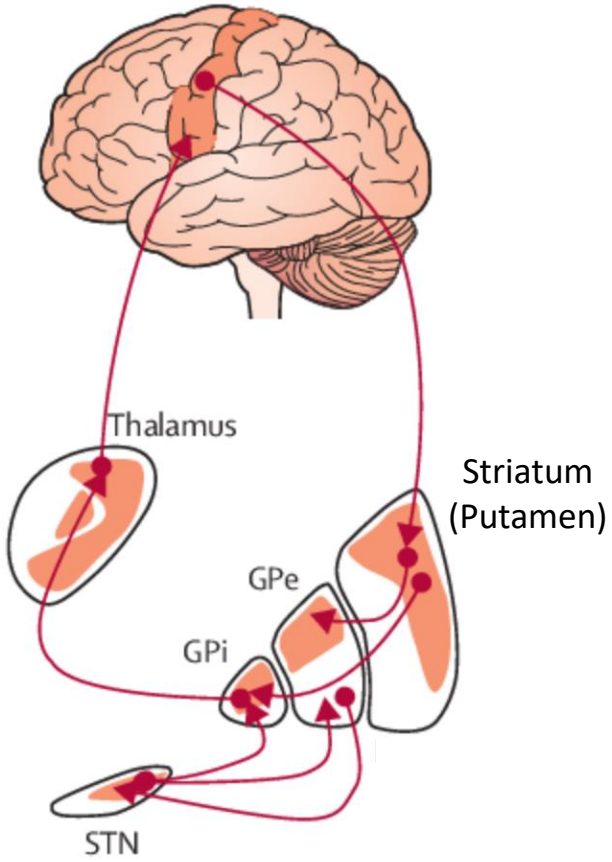
University of Nottingham, UK

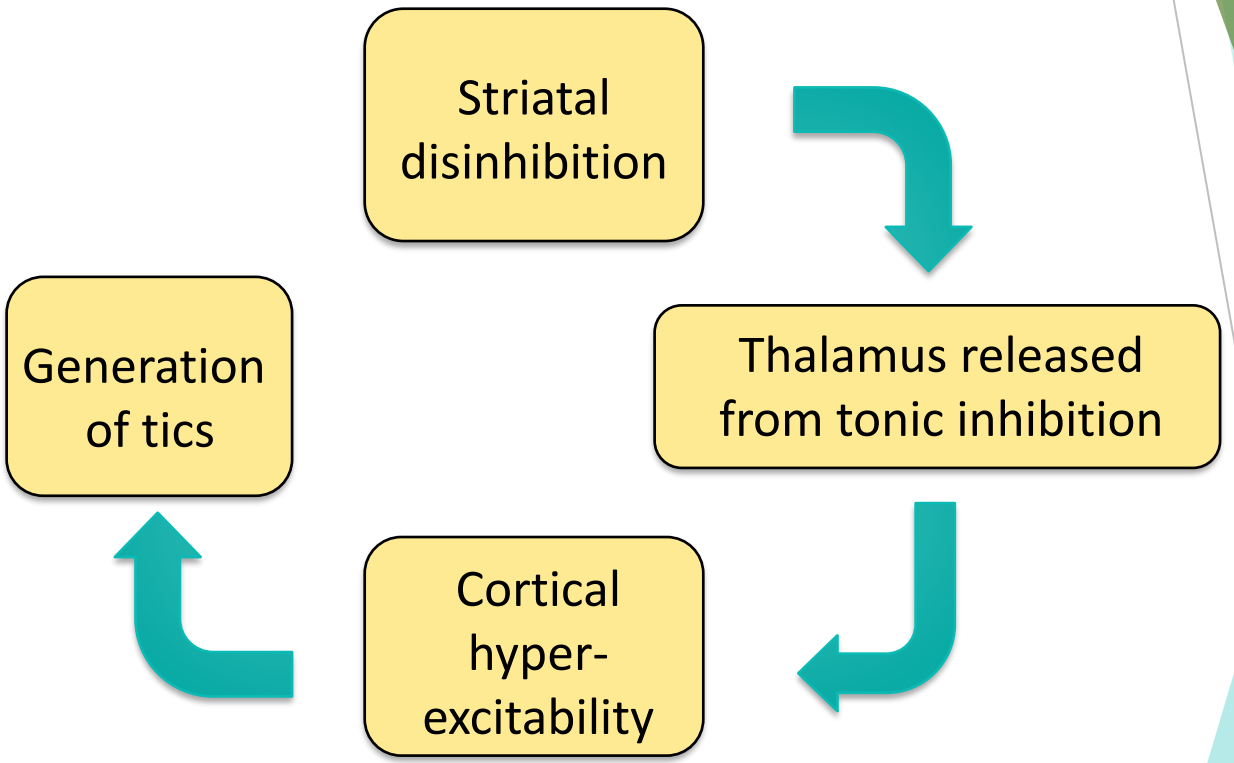
Tourette syndrome and tic disorders

- Neurological condition of childhood onset
- Characterised by unwanted movements and vocalisations known as tics.
- Linked to dysfunction in brain networks controlling movements
  - Specifically, hyper-excitability and altered brain network dynamics
- Tics can sometimes be suppressed but this can be uncomfortable and difficult to sustain
- When suppressed, tics often associated with so-called ***premonitory urges***
  - Uncomfortable bodily sensations experienced as a strong *urge-to-tic*

Neuropathological basis for TS

Cortico-striatal-thalamic-cortical 'motor' circuit





Albin & Mink (2006) *TRENDS in Neurosciences*

Current treatments for Tourette syndrome

- **Behavioural therapy**:
  - First line treatment for TS
  - But, often difficult to access. Few centres in the UK. Long waiting times to access (>= 2 years). Often not available on the NHS.

- **Medication**:
  - Readily available and frequently effective
  - But, often not popular, with poor adherence. Issues with tolerability and adverse effects

- **Deep-brain stimulation**:
  - Demonstrated to be effective
  - But, classed as experimental medicine in the UK, so not available outside of small number of trials. Not suitable for children or young people

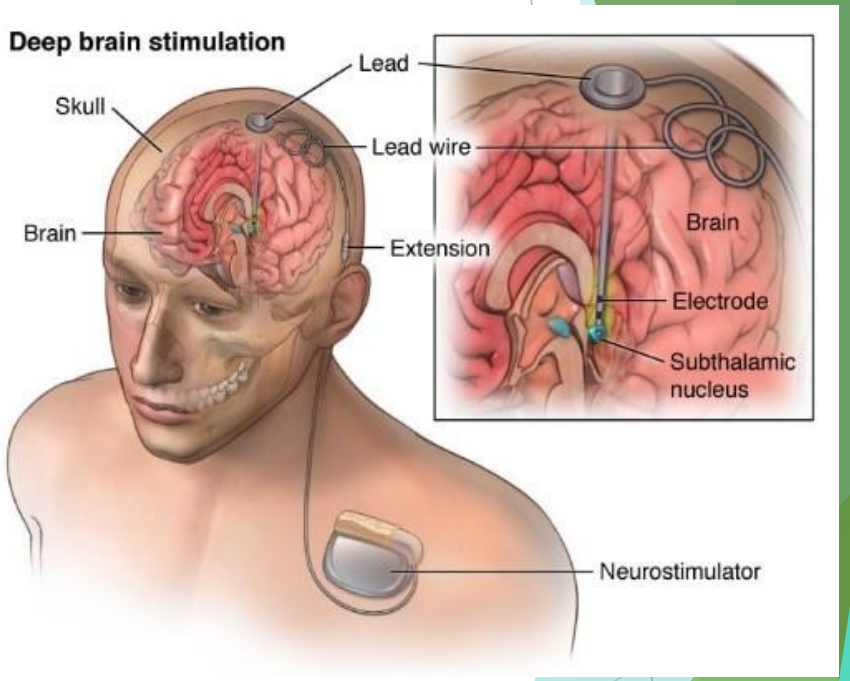
Deep-brain stimulation (DBS) in TS:

Meta-analytic comparison of DBS, medication, and behavioural treatments for TS

Treatment	DBS	Medication	Behavioral	
Baseline YGTSS	80.0 (9.8)	54.1 (9.8)	48.2 (2.3)	/100
% improvement	49.9 (17.5)	22.5 (15.2)	20.0 (11.3)	/100

Mahajan et al., (2020) *Stereotactic and Functional Neurosurgery.*

Efficacy of DBS in reducing tics in TS clearly demonstrates the 'proof-of-concept' that targeted modulation of brain movement networks can be an effective treatment for TS



Limitations of DBS

- Invasive surgical procedure that carries some risk of adverse response (e.g., infection, lead migration requiring further surgery)
- In the UK is is not available as an NHS treatment, but is an experimental treatment
- Typically, only given to individuals with intractable TS
- Not considered suitable for children and adolescents

So, is non-invasive brain stimulation an alternative?

Research priority identified by TS patients

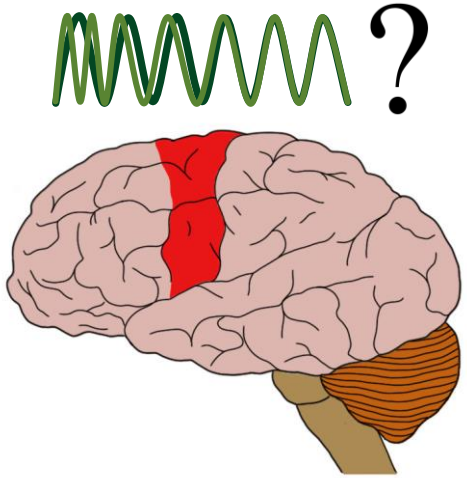
Develop a low-cost, safe and effective, non-drug treatment that can be used by the individual to give them control over their tics - ideally outside of the clinic

Research question:

- Could we use the peripheral nervous system to modulate the cortical brain sensorimotor networks linked to the generation of tics in TS?
- Specifically, could we utilize rhythmic median nerve stimulation (MNS) to ***entrain*** those brain oscillations linked to the suppression of movement, and reduce the urge-to-tic and tic frequency in TS?

- Can we use non-invasive brain stimulation (NIBS) techniques to influence the movement-related brain oscillations?
- Can we reduce the the occurrence of tics and/or the experience of premonitory urges in Tourette syndrome?
- Can we use a NIBS approach that is suitable for use by the patient unsupervised and outside of the clinic?

Electrical stimulation of peripheral nervous system



Is rhythmic median nerve stimulation effective in reducing PU and/or suppressing tics in TS

Participants

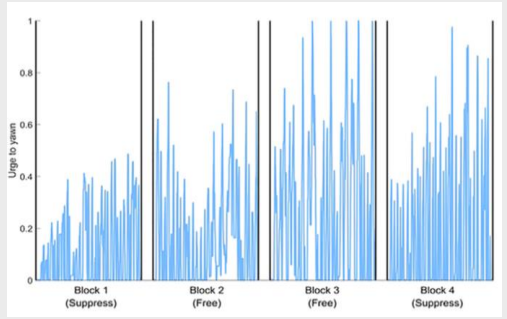
19 adults with Tourette syndrome.

- 3 withdrew as they found MNS uncomfortable.
- Remaining 16 individuals (9 males, aged 14–51, mean age = 22) subject to blind video analysis of tic frequency and tic intensity

Study design

- Random 1 minute periods of MNS vs. no stimulation
- Participants continuously rated their self-estimated urge-to-tic using a slider device.
- Tics frequency and intensity were rated for the final 40 seconds of each epoch.

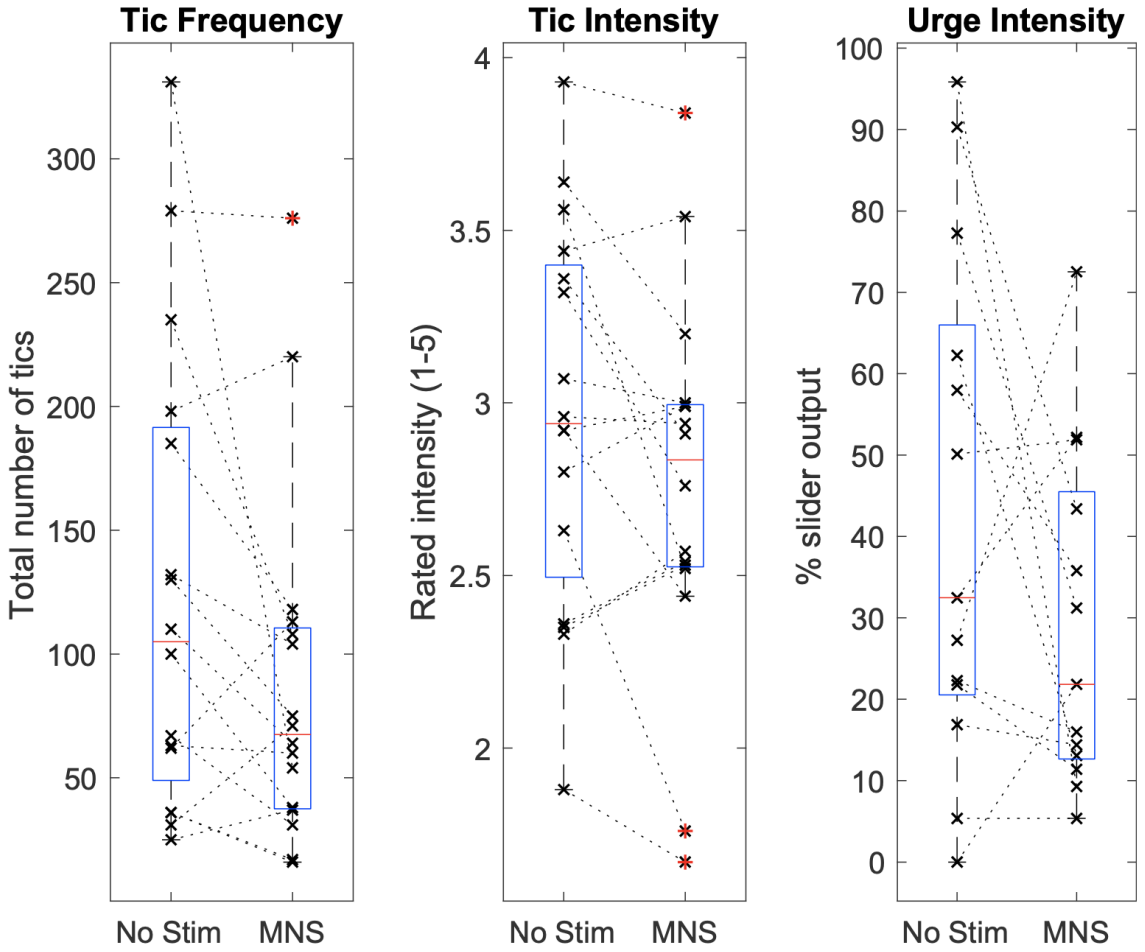
Slider device



Morera Maiquez , et al. (2020) *Current Biology*.

Rhythmic MNS reduces tic frequency and suppresses the urge-to-tic in TS

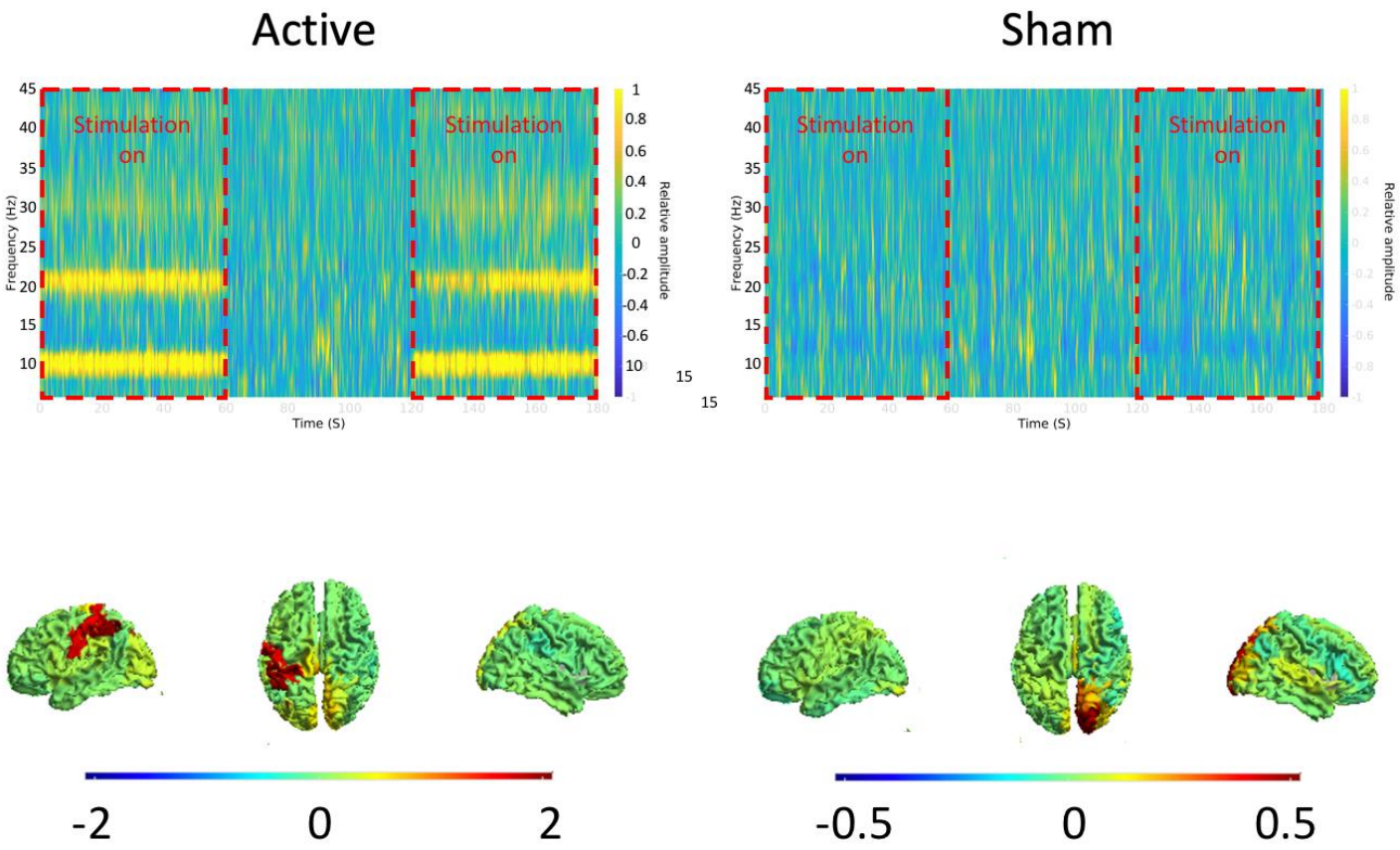
Rhythmic Mu-band MNS is sufficient to suppress the urge-to-tic and reduce tic frequency in TS



Morera Maiquez , et al. (2020) *Current Biology*.

Pre-registered UK-wide double-blind sham-controlled clinical trial commenced March 2022

Neurotherapeutics Ltd have developed a prototype wearable device for the trial



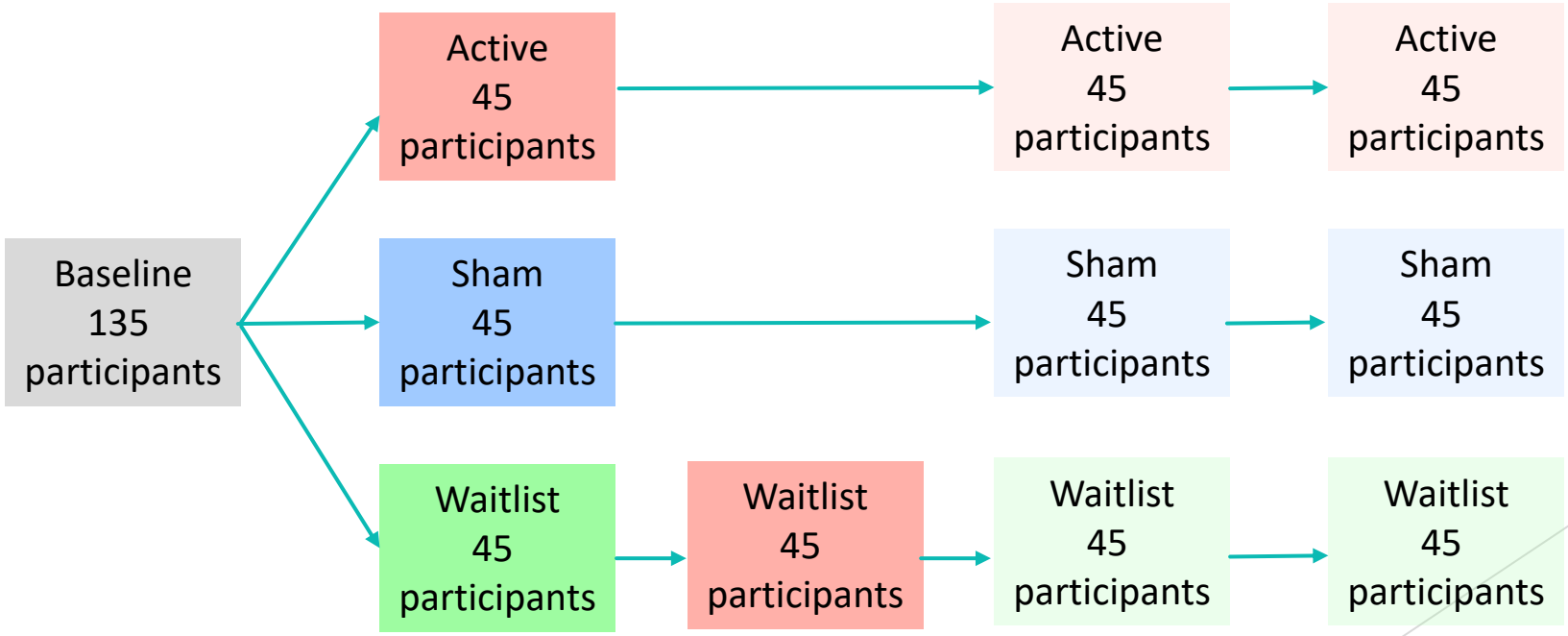
Research questions

- **Q1**. Does rhythmic MNS (rMNS) lead to a reduction in tic frequency during stimulation?

- **Q2**. Do repeated periods of rMNS lead to a sustained reduction in clinical symptoms that outlast any periods of stimulation?

Proposed study design

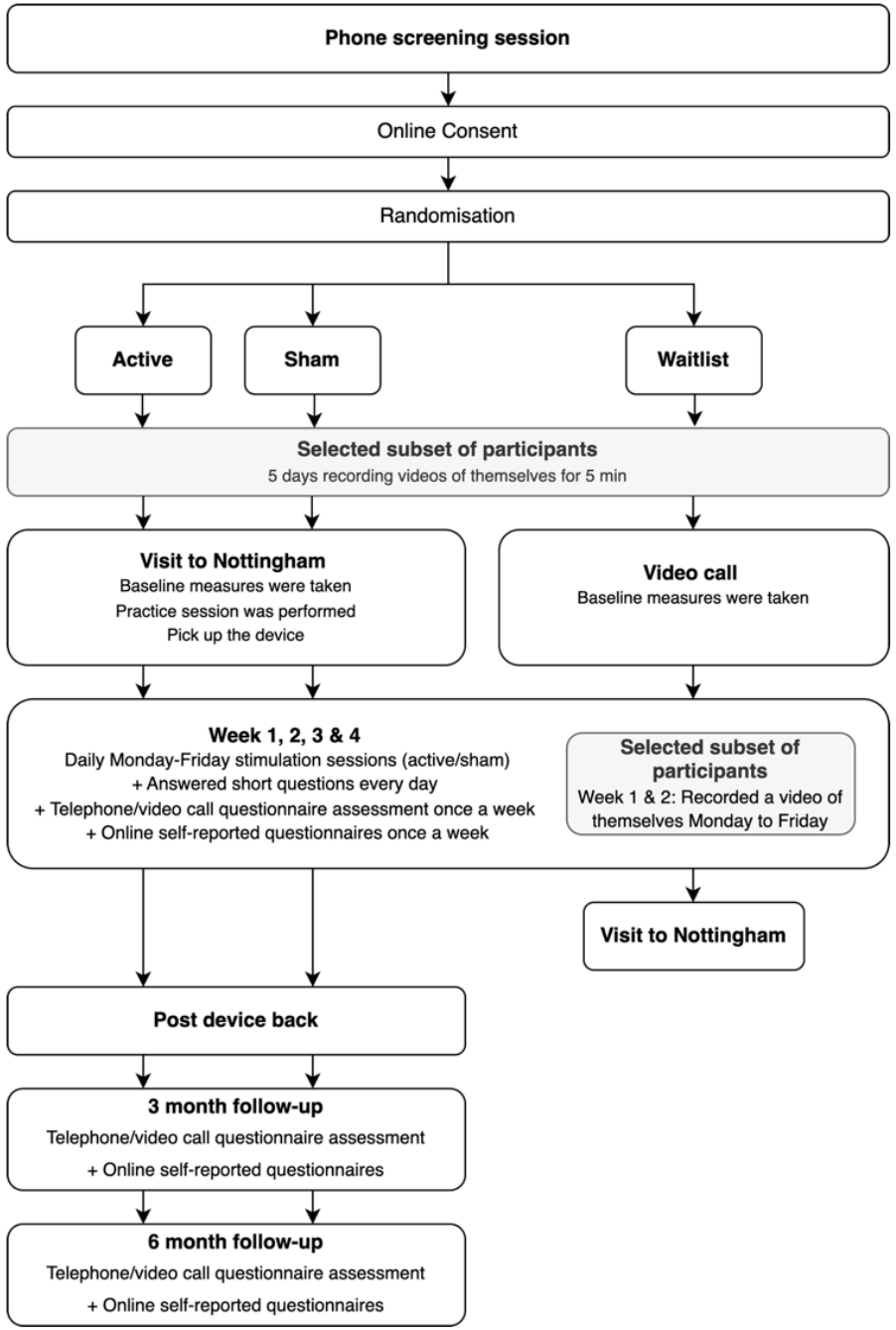
- 135 participants recruited who all exhibit a tic disorder
- Pseudo-random allocation to three groups: **Active** stimulation; **Sham** stimulation; **Waitlist** (treatment as usual).
- Participants in each group matched for **sex**, **age**, and baseline t**ic severity** score.



Study protocol

Key elements:

1. Initial phone screening
2. Recruitment and informed consent
3. Stratified randomization to condition
4. Four weeks of daily use of Neupulse device
5. 3-month follow-up
6. 6-month follow-up



Withdrawals from study

Reason for withdrawing	/143	%
Stimulation too uncomfortable	10	7.0
Other reasons (no time, holiday, etc.)	14	9.8

Study variables

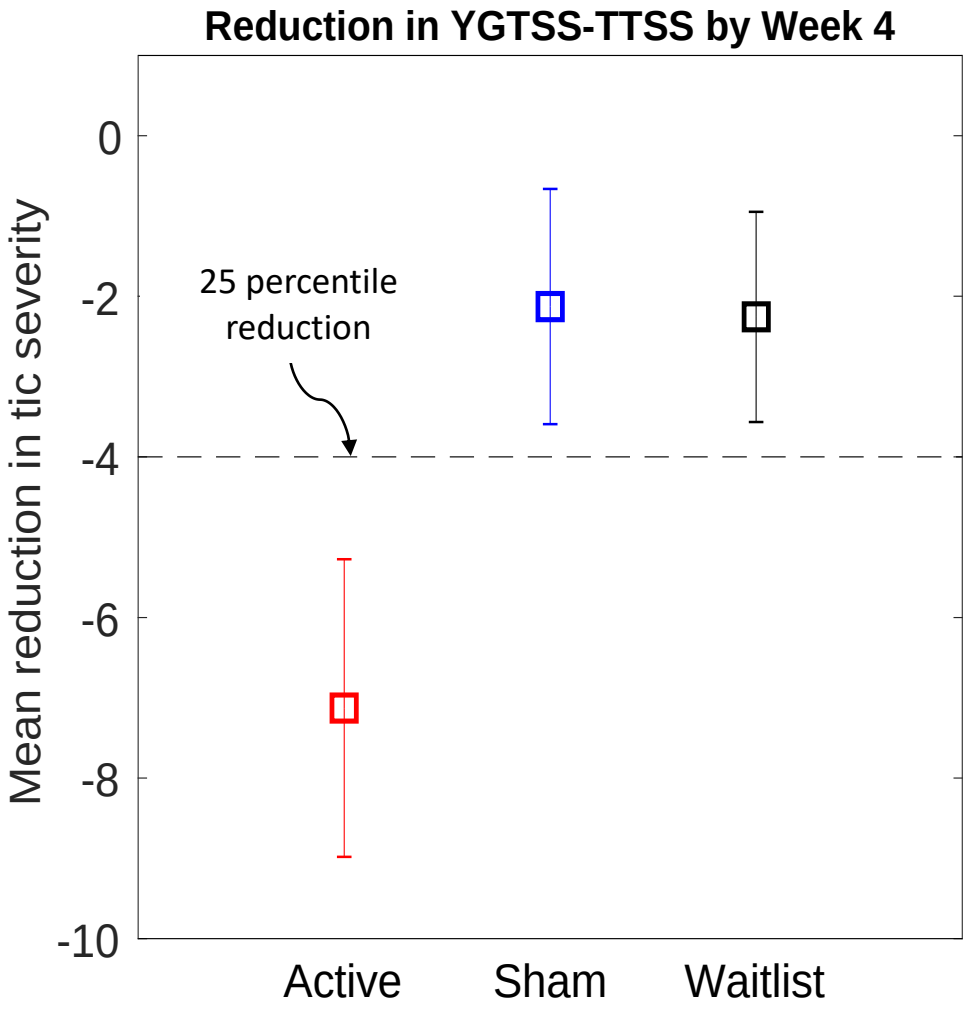
- **Static variables**: age at baseline; sex; IQ, time since tic onset; ADHD score; anxiety score, etc.
- **Dynamic variables**:
  - tic frequency scores before, during and after stimulation (from daily videos)
  - Weekly clinical assessments YGTSS, PUTS-R, Y_BOCS, etc.

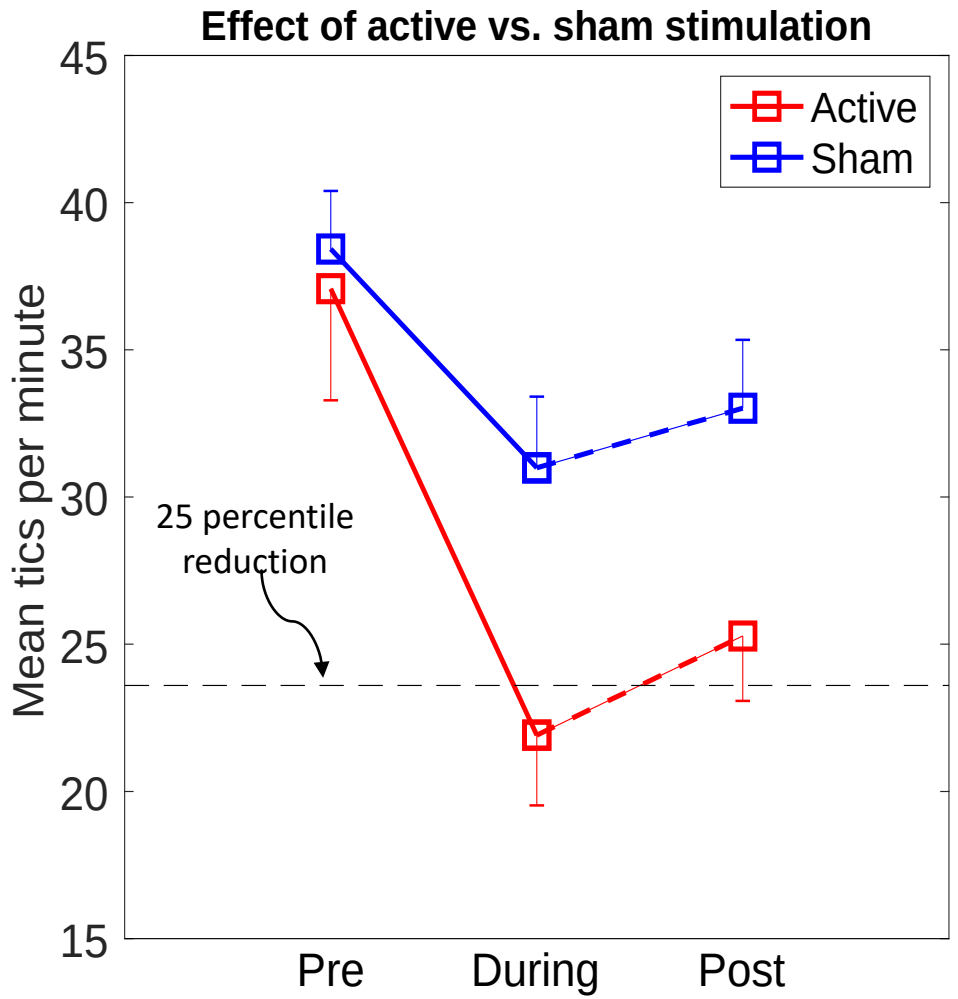
Sample characteristics

	Active		Sham		Waitlist			
Variable	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**F-value**	**p-value**
Age (years)	23.5	12.6	24.0	13.4	24.4	12.6	0.04	0.96
Tic onset (years)	7.0	3.5	8.4	3.8	7.5	3.3	1.59	0.21
Total tics (YGTSS)	40.1	7.0	39.5	6.3	38.9	6.9	0.35	0.71
Motor tics (YGTSS)	21.1	3.2	20.4	3.5	20.8	3.1	0.49	0.62
Phonic tics (YGTSS)	19.0	4.7	19.1	4.7	18.1	4.7	0.49	0.62
Impairment (YGTSS)	25.5	13.7	29.8	13.5	30.1	12.9	1.51	0.23
Premonitory urges (PUTS-R)	17.9	8.8	19.3	8.5	17.6	8.6	0.40	0.67
OCD (CYBOCS)	14.8	8.9	15.7	7.2	16.1	9.2	0.25	0.78

	Total							
Medication	**N**	**%**	**Active**		**Sham**		**Waitlist**	
Taking any medication	49	41	**N**	**%**	**N**	**%**	**N**	**%**
Tic medication	29	24	14	11.6	9	7.4	6	7
Other medication	29	24	12	9.9	10	8.3	5	5.8
Comorbidities	**Total**		**Active**		**Sham**		**Waitlist**	
Attention deficit hyperactivity disorder (ADHD)	27	22	10	8	9	7	8	7
Obsessive–compulsive disorder (OCD)	37	31	17	14	8	7	12	10
Autism spectrum disorders (ASD)	19	16	8	7	9	7	2	2
Anxiety disorder	32	26	9	7	12	10	11	9
Multiple comorbidities	**Total**							
No co-occurring neuropsychiatric diagnosis	52	43						
One co-occurring neuropsychiatric diagnosis	36	30						
Two co-occurring neuropsychiatric diagnoses	20	17						
Three co-occurring neuropsychiatric diagnoses	13	11						
Four co-occurring neuropsychiatric diagnoses	0	0						

Key Results


Reduction in YGTSS-TTSS by Week 4
Mean reduction in tic severity
0
-2
-4
-6
-8
-10
25 percentile reduction
Active
Sham
Waitlist


Effect of active vs. sham stimulation
Mean tics per minute
45
40
35
30
25
20
15
Active
Sham
25 percentile reduction
Pre
During
Post

Example video uploaded by one of the trial participants

Number of responders

i.e., number of individuals who have at least a 25 percentile reduction in tic severity by week 4.

	Responders		Non-responders					
YGTSS-TTSS	N /39	%	N /39	%	Odds ratio	low CI	high CI	RRR (%)
Active	23	**59.0**	16	41.0	**2.9**	1.1	7.2	67
Sham	13	33.3	26	**66.7**				

Where next? Co-creation of a commercially available Neupulse device. Current thoughts.

- Non-invasive *user-controlled* median nerve stimulation
- Wearable delivers rhythmic pulses of electric stimulation to reduce tics and premonitory urges
- Stimulation turned on/off at the press of a button
- Pulse strength adjustable to personal requirements
- Monthly delivery of certified gel pads

For people who tic and who seek:

- the option to control their tics when they choose
- Stimulation controlled by an app on their phone
- Increased autonomy over their tics
- non-invasive, drug-free solution, accessible without prescription

Research funding

Nottingham Biomedical Research Centre

NHS National Institute for Health Research

University of Nottingham Precision Imaging

Tourette Association of America

Tourettes action

Team members

Barbara Morera
Postdoc

Mairi Houlgreave
PhD Student

Georgina Jackson
Professor

NEUPULSE

Giving control to people with Tourette syndrome and tic disorders

Questions?