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

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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
  o 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
  o Uncomfortable bodily sensations experienced as a strong urge-to-tic
Neuropathological basis for TS

Cortico-striatal-thalamic-cortical ‘motor’ circuit

Striatal disinhibition

Thalamus released from tonic inhibition

Cortical hyper-excitability

Generation of tics

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 (\( \geq 2 \) 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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>DBS</th>
<th>Medication</th>
<th>Behavioral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline YGTSS</td>
<td>80.0 (9.8)</td>
<td>54.1 (9.8)</td>
<td>48.2 (2.3)</td>
</tr>
<tr>
<td>% improvement</td>
<td>49.9 (17.5)</td>
<td>22.5 (15.2)</td>
<td>20.0 (11.3)</td>
</tr>
</tbody>
</table>


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 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?
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 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?
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.

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?
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 tic 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
<table>
<thead>
<tr>
<th>Reason for withdrawing</th>
<th>/143</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulation too uncomfortable</td>
<td>10</td>
<td>7.0</td>
</tr>
<tr>
<td>Other reasons (no time, holiday, etc.)</td>
<td>14</td>
<td>9.8</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Active</th>
<th>Sham</th>
<th>Waitlist</th>
<th>F-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>23.5</td>
<td>24.0</td>
<td>24.4</td>
<td>0.04</td>
<td>0.96</td>
</tr>
<tr>
<td>Tic onset (years)</td>
<td>7.0</td>
<td>8.4</td>
<td>7.5</td>
<td>1.59</td>
<td>0.21</td>
</tr>
<tr>
<td>Total tics (YGTSS)</td>
<td>40.1</td>
<td>39.5</td>
<td>38.9</td>
<td>0.35</td>
<td>0.71</td>
</tr>
<tr>
<td>Motor tics (YGTSS)</td>
<td>21.1</td>
<td>20.4</td>
<td>20.8</td>
<td>0.49</td>
<td>0.62</td>
</tr>
<tr>
<td>Phonic tics (YGTSS)</td>
<td>19.0</td>
<td>19.1</td>
<td>18.1</td>
<td>0.49</td>
<td>0.62</td>
</tr>
<tr>
<td>Impairment (YGTSS)</td>
<td>25.5</td>
<td>29.8</td>
<td>30.1</td>
<td>1.51</td>
<td>0.23</td>
</tr>
<tr>
<td>Premonitory urges (PUTS-R)</td>
<td>17.9</td>
<td>19.3</td>
<td>17.6</td>
<td>0.40</td>
<td>0.67</td>
</tr>
<tr>
<td>OCD (CYBOCS)</td>
<td>14.8</td>
<td>15.7</td>
<td>16.1</td>
<td>0.25</td>
<td>0.78</td>
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</table>

<table>
<thead>
<tr>
<th>Medication</th>
<th>N</th>
<th>%</th>
<th>Active</th>
<th>N</th>
<th>%</th>
<th>Sham</th>
<th>N</th>
<th>%</th>
<th>Waitlist</th>
<th>N</th>
<th>%</th>
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<tbody>
<tr>
<td>Taking any medication</td>
<td>49</td>
<td>41</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Tic medication</td>
<td>29</td>
<td>24</td>
<td>14</td>
<td>11.6</td>
<td>9</td>
<td>7.4</td>
<td>6</td>
<td>7</td>
<td>5</td>
<td>5.8</td>
<td></td>
</tr>
<tr>
<td>Other medication</td>
<td>29</td>
<td>24</td>
<td>12</td>
<td>9.9</td>
<td>10</td>
<td>8.3</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5.8</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>Total</th>
<th>Active</th>
<th>Sham</th>
<th>Waitlist</th>
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</thead>
<tbody>
<tr>
<td>Attention deficit hyperactivity disorder (ADHD)</td>
<td>27</td>
<td>22</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Obsessive–compulsive disorder (OCD)</td>
<td>37</td>
<td>31</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>Autism spectrum disorders (ASD)</td>
<td>19</td>
<td>16</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>32</td>
<td>26</td>
<td>9</td>
<td>7</td>
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</table>

### Multiple comorbidities

<table>
<thead>
<tr>
<th>Total</th>
<th>N</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>No co-occurring neuropsychiatric diagnosis</td>
<td>52</td>
<td>43</td>
</tr>
<tr>
<td>One co-occurring neuropsychiatric diagnosis</td>
<td>36</td>
<td>30</td>
</tr>
<tr>
<td>Two co-occurring neuropsychiatric diagnoses</td>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td>Three co-occurring neuropsychiatric diagnoses</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Four co-occurring neuropsychiatric diagnoses</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Key Results

Reduction in YGTSS-TTSS by Week 4

Mean reduction in tic severity

Reduction in YGTSS-TTSS by Week 4

Active  Sham  Waitlist

25 percentile reduction

Effect of active vs. sham stimulation

Mean tics per minute

Effect of active vs. sham stimulation

Pre  During  Post

Active  Sham

25 percentile reduction
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.

<table>
<thead>
<tr>
<th>YGTSS-TTSS</th>
<th>Responders</th>
<th>Non-responders</th>
<th>Odds ratio</th>
<th>low CI</th>
<th>high CI</th>
<th>RRR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N /39</td>
<td>%</td>
<td>N /39</td>
<td>%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>23</td>
<td><strong>59.0</strong></td>
<td>16</td>
<td>41.0</td>
<td>2.9</td>
<td>1.1</td>
</tr>
<tr>
<td>Sham</td>
<td>13</td>
<td>33.3</td>
<td>26</td>
<td><strong>66.7</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- 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

University of Nottingham
Precision Imaging

Tourette Association of America

Tourettes Action

National Institute for Health Research

Team members

Barbara Morera
Postdoc

Mairi Houlgreave
PhD Student

Georgina Jackson
Professor

NEUPULSE
Giving control to people with Tourette syndrome and tic disorders
Questions?