Deep Brain Stimulation for Severe Mental Illness

- Used by NHS for Parkinson’s disease >25 years
- Modifiable: 4 contact points enabling stimulation adjustment
- Reversible: can be turned off and mechanism removed
Deep brain stimulation for severe OCD

Target 1:

Anterior Limb Internal Capsule (ALIC); Nuttin et al 1999, 2003

- Targets the same area as anterior capsulotomy
- Affects ventral fibres in ALIC connecting ACC and OFC with thalamus
- Additional connections with amygdala, hippocampus and limbic areas

Courtesy of Suzanne Haber

Tyagi et al 2019
Deep brain stimulation for severe OCDC

Target 2:

Anteromedial Subthalamic Nucleus, Mallet et al 2008

Based on observations of 3 patients with STN DBS for Parkinson’s disease and co-morbid OCD
Mallet et al 2002; Fontaine et al 2004

amSTN receives input directly from

- ventral anterior cingulate cortex
- medial orbitofrontal cortex
- dorsal anterior cingulate

Haber et al 2020

Mallet et al 2008
Deep brain stimulation for severe OCDC

Main Study Outcomes

**ALIC1**: Greenberg el 2010, 3 USA centres; 1 Belgium
26 patients YBOCS > 28-30
>35% reduction in YBOCS

**ALIC2**: Denys et al 2010, 1 centre Holland
Randomised double blind component
Response >35% reduction in YBOCS
YBOCS >28
16 patients

**amSTN**: Mallet et al 2008, 10 centres in France
Randomised double blind cross over design
16 patients: YBOCS>25
Response >25% reduction in YBOCS

<table>
<thead>
<tr>
<th></th>
<th>STN</th>
<th>ALIC1</th>
<th>ALIC2</th>
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<tbody>
<tr>
<td>Mean reduction in YBOCS scores</td>
<td>8.9</td>
<td>12.5</td>
<td>15.7</td>
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<tr>
<td>Response rate</td>
<td>56%</td>
<td>61.5%</td>
<td>56%</td>
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<tr>
<td>Reduction in YBOCS to mild/subclinical</td>
<td>25%</td>
<td>38%</td>
<td>50%</td>
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<tr>
<td>Reduction in depression scores</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
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Yale Brown Obsessive Compulsive Scale (YBOCS)

0–7 sub-clinical
8–15 mild
16–23 moderate
24–31 severe
32–40 extreme

Response: 35% reduction YBOCS
Deep brain stimulation for severe OCD

Main Outcomes: OCD, Mood and Cognitive Flexibility

amSTN v ALIC DBS: 6 patients, 4 electrodes

- OCD: YBOCS significantly reduced by amSTN and VC/VS DBS; no statistical difference
- Mood: MADRS significantly reduced by amSTN and VC/VS DBS; VC/VS statistically greater than amSTN DBS
- Cognitive flexibility: significantly improved by amSTN; not by VC/VS DBS

MRI Connectomics to define targets

Post-op 1.5 MRIT images of electrode placement and identification of active contacts

Volumes of tissue activation calculated from active contacts and optimum stimulation amplitudes

ALIC electrodes
• Dorsal contacts effective
• VAS confined to ventral anterior internal capsule
• Mean stimulation = 5.85V

amSTN electrodes
• Ventral contacts effective
• VAS centred on the anterior, inferior medial STN
• Mean stimulation = 1.56V
Preop diffusion weighted 3T MRI: ventral capsule tractography from volumes of tissue activation

ALIC VTAs connected to:
- medial orbitofrontal cortex
- mediodorsal thalamus
- amygdalofugal pathway
- habenulo-interpeduncular tract
Preop diffusion weighted 3T MRI: subthalamic nucleus tractography from volumes of tissue activation

amSTN VTAs connected to:

- lateral orbitofrontal cortex
- dorsal anterior cingulate cortex
- dorsolateral prefrontal cortex
- medial forebrain bundle
How do DBS findings fit with neurobiology of OCD?

Abnormal cortico-striatal-thalamic-cortical loops
Cortical and striatal areas are hypermetabolic
DBS thought to inhibit activity in OCD circuitry
DBS of ventral ALIC likely to dampen ACC/OFC loops

amSTN receives direct input from ACC, OFC and DLPFC
‘Limbic hyperdirect pathway’
Enables inhibition of programming in basal ganglia
STN DBS allows interruption of compulsions and obsessions
By improving cognitive flexibility
A unified connectomic target for deep brain stimulation in obsessive-compulsive disorder.

Li et al. 2020 Nat Commun

Is there a common pathway affected by DBS of ALIC and STN DBS related to clinical outcome?

Volumes of tissue activation calculated from active contacts and optimum stimulation amplitudes

Tractography from VTAs for each cohort

Used difference in YBOCS pre and post DBS To ‘weight’ each fibre
Fibre bundle associated with clinical improvement from either STN and ALIC sites. Madrid and London cohorts overlapped with this pathway.

Identified Tract predicting positive outcome:

Connects STN and mediodorsal nucleus of thalamus, traverses through ALIC to dorsal anterior cingulate cortex and ventrolateral prefrontal cortex.
Deep Brain Stimulation for Severe Treatment Resistant Depression

Mayberg et al., 2005, Neuron

Deep Brain Stimulation for Treatment-Resistant Depression

Cingulate Area 25

N=6

‘All patients spontaneously reported acute effects including “sudden calmness or lightness,” “disappearance of the void,” sense of heightened awareness, increased interest, “connectedness,” and sudden brightening of the room, including a description of the sharpening of visual details and intensification of colors’
Deep Brain Stimulation for Severe Treatment Resistant Depression

Mayberg et al. 1999

Cg25 – hyperactive in depression; normalised with treatments
Long-Term Outcomes of Subcallosal Cingulate Deep Brain Stimulation for Treatment-Resistant Depression
The BROADEN Study 2012-2017, Holtzheimer et al Lancet Psychiatry 2017

Brodman’s Area 25 DBS, 15 centres
Staggered start for 6 months in 1/3
Interim analysis when 90 reached 6 months
Needed 40% to reduce depression scores by 40%
20% reached outcome criterion, 5% in remission with active DBS
17% and 7% in remission with inactive DBS
Trial halted.

24 month follow-up: 77
Dougherty et al 2015, Biological Psychiatry

A Randomized Sham-Controlled Trial of Deep Brain Stimulation of the Ventral Capsule for Chronic Treatment-Resistant Depression

20% responded following the trial
Bergman et al, JAMA Psychiatry 2016

Deep Brain Stimulation of the Ventral Anterior Limb of the Internal Capsule for Treatment-Resistant Depression: A Randomized Clinical Trial

10/25 responders

Design: patients were optimised before DBS withdrawal
A systematic review and meta-analysis of deep brain stimulation for depression

190 patients: depression scores and response rate favours DBS
Scangos et al, 2021, Nature Medicine

Personalised approach

1 case report

10 stereoelectroencephalography electrodes (160 contacts) implanted in:

- orbitofrontal cortex (OFC)
- amygdala, hippocampus,
- ventral capsule/ventral striatum (VC/VS)
- subgenual cingulate (SGC)

stimulation at different sites alleviated anxiety,
boosting energy levels, restoring pleasure in everyday activities depended on the mental state at the time
Summary

DBS has been in use as a clinical procedures for severe Parkinson’s disease for several decades.

Despite successful application for severe OCD and depression this remains a research procedure in UK.

In USA OCD DBS has FDA exemption on compassionate grounds but insurance companies are not obliged to fund it.

In USA DBS for depression remains a research procedure.

Future work will refine network targets using procedures such as connectomics to improve outcomes.