The Future of Neurosurgery for Severe Mental Illness: Deep Brain Stimulation and Ablation

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Neurosurgery for Neuropsychiatric Disorders: The Past

Frontal leucotomy - Moniz 1936

Following observation of calming effect in two non-human primates

Leucotome
Frontal leucotomy - Moniz 1935

N=20; Reported

35% recovered
35% partial recovery
30% no change
Transorbital Lobotomy - Freeman 1935

Avoided need for anaesthetic
ECT seizure
No aseptic technique
Performed on a large scale
Transorbital Lobotomy (‘ice pick lobotomy’) - Freeman

1936-1967

Used to treat all forms of mental illness - unselected
Long–term postoperative results unacceptable
Introduction of chlorpromazine in 1955 reduced frequency procedure
Last patient 1967
Ablation Neurosurgery

• 1949, Tailarach, Paris

Developed stereotactic neurosurgery with pneumoencephalography to guide neurosurgeons

Described anterior capsulotomy in one patient

• 1952, Leskell, Sweden

Anterior capsulotomy of 117 cases of all types of mental illness

OCD particularly benefited with good outcome in 78%
Anterior Capsulotomy for Severe Mental Illness

Methods:
- knife cut
- radiofrequency thermocoagulation

Used for OCD and depression; NHS procedure - tightly regulated
Anterior Capsulotomy for Severe OCD

Outcomes
Brown et al 2017
8 studies, follow up >12 months
N=105

Mean 55% reduction in YBOCS
• 54% full response (35% decrease in YBOCS)
• 18% partial response
• Reduction severe to moderate
• 13% adverse effects
• incontinence of urine, weight gain and lethargy

N=19: 47% (9) responder or partial responder
D’Astous et al., 2013
Anterior Capsulotomy for Treatment Resistant Depression

54% full response

Confusion 24/45
Incontinence 24/45
Apathy and fatigue 20/45
Usually transient

Subramian et al 2017
Anterior Cingulotomy for Severe Mental Illness

Methods:
• knife cut
• radiofrequency thermocoagulation

Used for OCD and depression; NHS procedure - tightly regulated
Anterior Cingulotomy for OCD

38% response maintained over 5 years
25% partial response
One lesion
Few adverse effects

59% long term response in those with second lesion
19% partial response

Sheth SA et al 2013
Anterior Cingulotomy for Treatment Resistant Depression

Shields et al 2008
N=33
30 month follow up
50% second procedure
75% at least partial response

Steele et al 2008
N=8
12 month follow up
63% response
Ablation Neurosurgery – The Future?

MRI guided gamma knife capsulotomy for OCD

- Dedicated system
- High energy radioactive emitting isotope 60Co focussed stereotactically in ‘shots’
- Dose related side effect: oedema, radiation necrosis induced cysts, and clinical evidence of frontal lobe syndrome
- N=55, 56% 3 year follow up

Rasmussen et al 2018
Ablation Neurosurgery – The Future?
MRI guided focussed ultrasound capsulotomy for OCD

Conducted in an MRI machine; U/S delivered through a helmet
Lesion size and position checked during the procedure
Few adverse effects
11 patients 24 month follow-up
6 full responders, 55%

Jung et al. 2015; Kim et al 2018
Deep Brain Stimulation

- Used for Parkinson's disease >20 years
- Modifiable: 4 contact points enabling stimulation adjustment
- Reversible: can be turned off and mechanism removed
OCD: Ventral Capsule/Ventral Striatum Target
Greenberg et al 2010

Site of capsulotomy
- 4 open label studies
- N=26; YBOCS severe
- 62% response
- 11% partial response
- Sustained response over 3 years


Simultaneous improvement in OCD, mood, anxiety and function
OCD: Anteromedial Subthalamic Nucleus Target
Mallet et al 2008

Following observation of patients with PD and OCD

- N= 16 YBOCS severe
- Randomised double blind cross over design
- 3 months off, 3 months on (or vice versa)
- 56% response
- No improvement in mood

Boundary of association and limbic territory
DBS for severe OCD: outstanding questions

Which target?
VC/VS or amSTN?

What are the mechanisms of action?
VC/VS site - improvement in mood?
amSTN site - directly affect on obsessions and compulsions?
Direct Comparison of Subthalamic Nucleus and Ventral Capsule/Ventral Striatum Targets

National Hospital for Neurology & Neurosurgery Queen Square
Functional Neurosurgery: Marwan Hariz, Ludvic Zrinzo
Functional Neurology: Tom Foltynie, Patricia Limousin
Neuropsychiatry: Eileen Joyce

Specialist OCD Clinicians Network
NHS Highly Specialised OCD Service: patient identification - Lynne Drummond, Naomi Fineberg
NHS Advanced Intervention Service: assessment of suitability for ablation - Keith Matthews

Cognitive assessments: Cambridge
Trevor Robbins
Barbara Sahakian

Researchers: Himanshu Tyagi, Annemieke Apergi, Harith Akram
Tyagi et al, 2019
ventral capsule/ ventral striatum

Anteromedial STN

Baseline 3T MRI for tractography
Pre-op 1.5T MRI - to plan target
Post-op 1.5T MRI - verify target

N=6
**amSTN v VC/VS DBS**

**OCD:** YBOCS significantly reduced by amSTN and VC/VS DBS

**Mood:** MADRS significantly reduced by VC/VS DBS; significantly more so than by amSTN DBS

**Cognitive flexibility:** significantly improved by amSTN; not VC/VS DBS

**Same effect on OCD symptoms; dissociated effect on mood and cognitive flexibility**
Post-op 1.5T MRI images of electrode placement and identification of active contacts

Volumes of tissue activation calculated from active contacts and optimum stimulation amplitudes
Preop diffusion weighted 3T MRI: ventral capsule tractography from volumes of tissue activation

Ventral capsule VTAs connected to:
- medial orbitofrontal cortex
- mediodorsal thalamus
- amygdalofugal pathway
- hypothalamus
- habenulo-interpeduncular tract

AmSTN VTAs connected to:
- lateral orbitofrontal cortex
- dorso-anterior cingulate cortex
- dorsolateral prefrontal cortex
- medial forebrain bundle
DBS target connectomes

Harith Akram
The Future: DBS or Ablation?

DBS very effortful for patients and clinicians
Refined ablation techniques reduce adverse effects and require a single intervention

Pepper et al. 2015
Deep Brain Stimulation for Treatment-Resistant Depression
Subcallosal Cingulate Gyrus (area Cg25)

Mayberg et al., 2005
6 patients

Hamani C, Mayberg H et al. 2011
Cg25 – hyperactive in depression; normalised with treatments
Subcallosal Cingulate Gyrus DBS for Depression

Findings from the first 67 patients from 6 centres

• Initial 6 month response rate of 41% - 66% and remission rate of 18%-50%

• With longer follow up the response and remission rates increased

• With 2-6 years of follow-up, response rates were 64%-92% and remission rates 42% - 58%

• Patients reaching remission with SCC DBS stayed well over time

• Antidepressant effects were robust as long as stimulation was maintained

• Slow but predictable loss of effect is seen with stimulation discontinuation, such as with battery depletion, even after more than 5 years of sustained remission.

• Chronic SCC stimulation was usually well tolerated, there are no significant side effects related to increase in current settings and the neurocognitive profile remains intact, even improving on certain domains
The BROADEN Study 2012-2017

- BA 25 DBS, 15 centres
- Planned for 200, staggered start for 6 months in 1/3
- Needed 40% to reduce depression scores by 40%

Analysis when 90 reached 6 months in trial

- 20% reached outcome criterion
- 5% in remission with active DBS
- 17% and 7% in remission with inactive DBS
- Trial halted

Holtzheimer et al Lancet Psychiatry 2017
A Randomized Sham-Controlled Trial of Deep Brain Stimulation of the Ventral Capsule/Ventral Striatum for Chronic Treatment-Resistant Depression

Dougherty et al 2015

20% responded following the trial
The Future of DBS for depression

- Neurosurgical accuracy in different centres
- Inability to optimise DBS settings
- Too short a time frame to demonstrate efficacy
- Affective circuitry too widespread?

External Modulation may be more effective?

Left dorsolateral prefrontal cortex is hypoactive in depression
Affects widespread subcortical circuitry

Rodney et al 2016
Clinical Neurophysiology
The Future - External Brain Modulation: Transcranial Magnetic Stimulation

- Potent brief magnetic field to induce electric current flow in neurones
- High (excitatory) and low (inhibitory) frequency
- Treatment refractory depression - introduced as an alternative to ECT
- Left dorsolateral prefrontal frontal cortex (DLPFC) – clinically significant outcomes
- L DLPFC 4-6 weeks, 5 days a week
- Standard HF rTMS 10 Hz protocol: 37 minutes

Developments for the future
- Intermittent theta burst TMS protocol: 3 minutes is as effective as standard rTMS
- Can time be shortened with more frequent sessions?
- Home TMS systems

Rodney et al 2016
Clinical Neurophysiology
The Future - External Brain Modulation: Transcranial Direct Current Stimulation (TDCS)

- **Weak direct current** (1–2 mA) between two electrodes placed on the scalp
- **No action potential triggered** - may strengthen or weaken synaptic transmission – synaptic plasticity

- Electrodes placed according to the EEG montage
- **Anodal TDCS** - positive current causing depolarisation and increases cortical excitability
- **Cathodal TDCS** - negative current causing hyperpolarisation and decreases cortical excitability

- **Depression**: Anodal tDCS over prefrontal cortex improves depression; small-moderate effect size

- Home treatment possible
The Future - External Brain Modulation: Transcranial Magnetic Stimulation

Realistic head model with coils (a) Double cone coil, (b) H-coil, (c) HCA coil and (d) Fo8 coil.

OCD – Problems with target

Figure 8 - DLPFC
Double cone – OFC
H coil – dACC – deep TMS
Effective for OCD
Summary

Brain Modulation for Severe Mental Illness is mainly for OCD and Depression

• Ablation: cingulotomy and capsulotomy, highly regulated as an NHS treatment
• Deep Brain Stimulation: experimental therapy only in UK, restricted to regulated clinical trials
• Restricted to very severe unremitting symptoms
• Will only ever be available for the few: studies consistently show roughly 50-66% respond

External Brain Stimulation

• rTMS and TDCS promising treatments for depression
• Studied patients who have not responded to antidepressants but less severely ill
• Effect sizes low-moderate but can be clinically effective
• Influence superficial cortical areas only
• Deep TMS being developed

Bright Future