Novel neurobiological therapies for OCD

- Transcranial Magnetic Stimulation (TMS)
- Deep Brain Stimulation (DBS)
- Psilocybin Assisted Psychotherapy (PAP)

- Scientific Evidence
- Clinical Efficacy
- Barriers in accessing treatment
- Progressions in the field

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NicAcevedo

Background- OCD outcomes

- Classified as one of the 10th most disabling illnesses[1]
- DSM-5- anxiety disorder, varying levels of insight
- 2-3% prevalence
- Onset- childhood or adolescence
- Chronic OCD: 5.9 hours on intrusions, 3.6 hours on compulsions per day
- First line therapies: CBT (ERP), and SSRIs.
- High treatment- resistant rates between 40-60%, and 80% relapse after pharmacological discontinuation[2]
- Majority (>95%) of patients experience moderate to severe symptoms, yet only a proportion of these receive specialized care (2.9-30.9%) and 65% experience serious disability[3]
- Treatment may alleviate OCD symptoms, yet significant symptoms and functional debilitation often remains (in responders)
- Progressions in the neurobiological and cognitive models of OCD
- Lack of integrated and specialized treatment options

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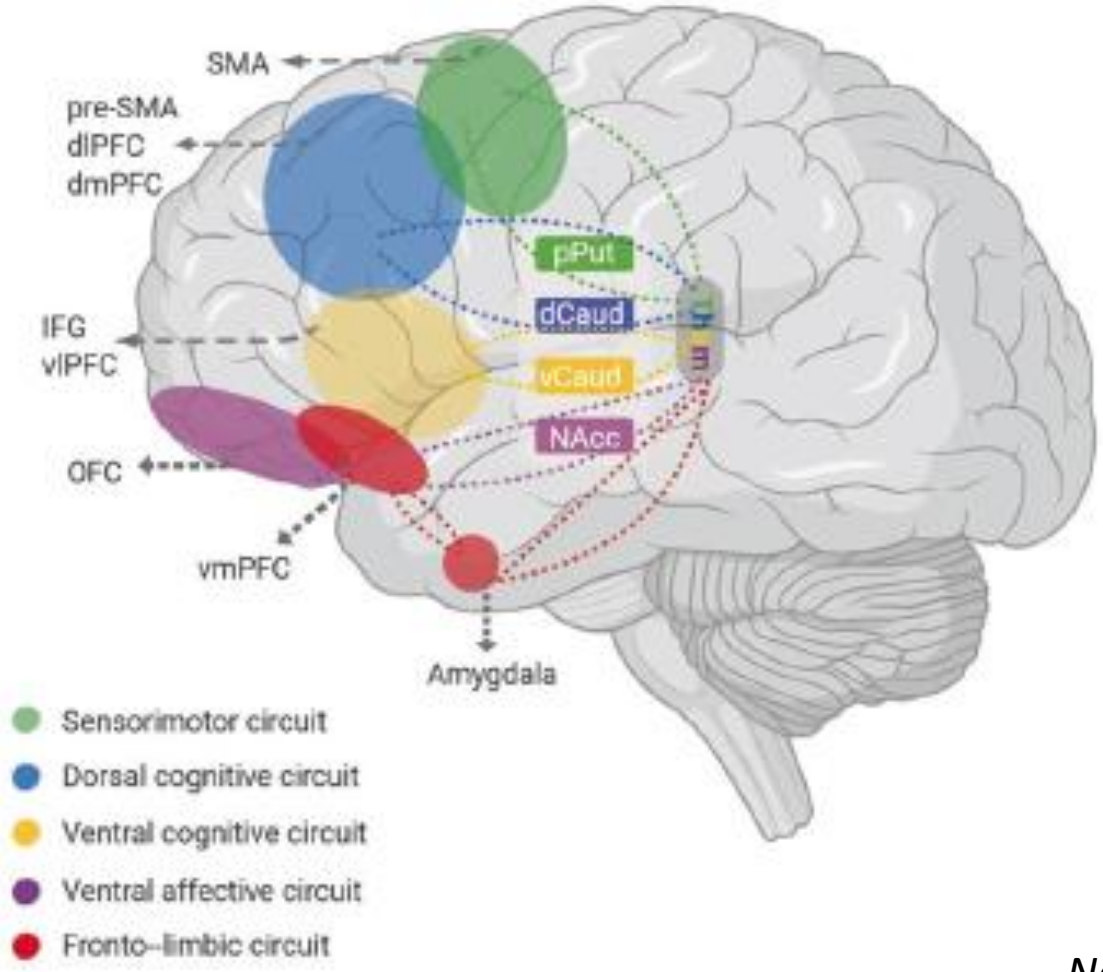
Background- Neurobiology of OCD

Cortico-stiato-thalamo-cortical (CSTC) circuits

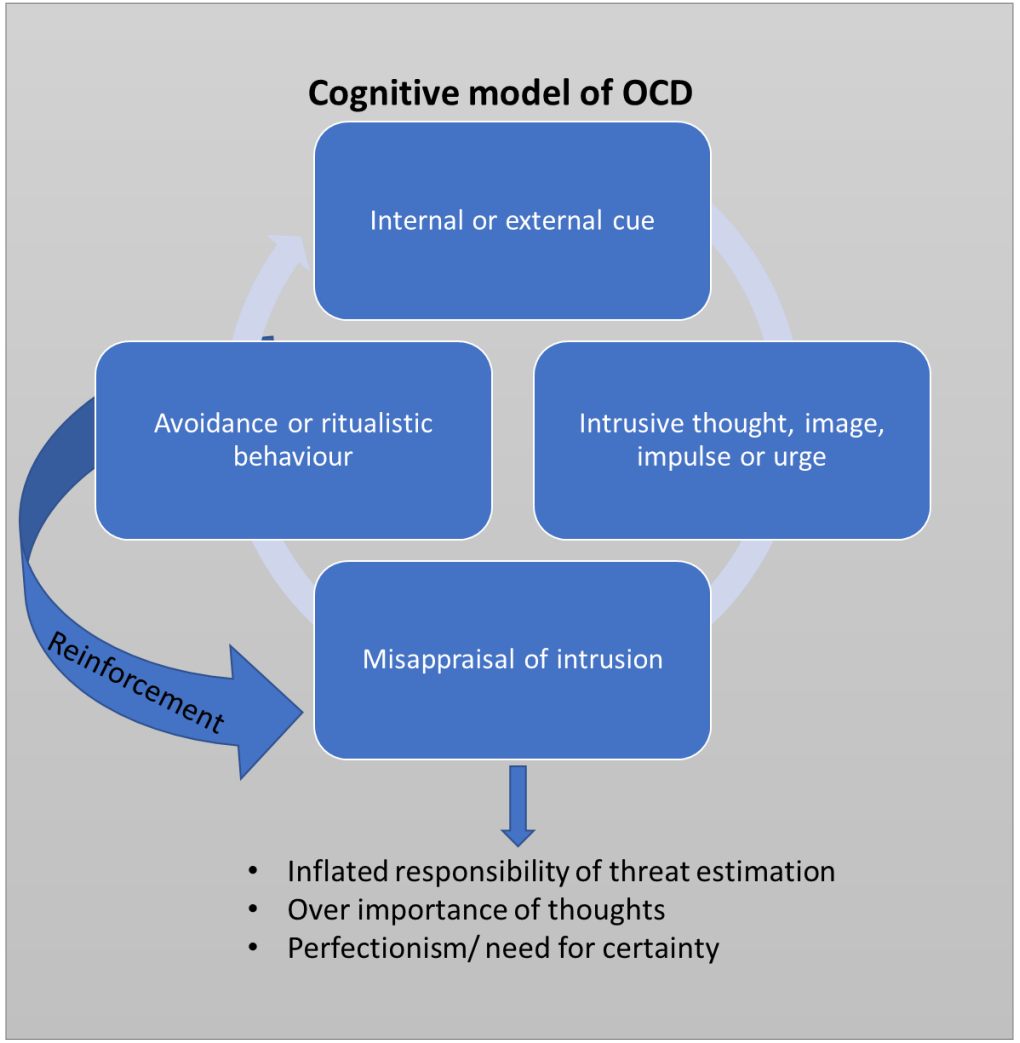


Nakao (2014) Psychiatry Clin Neurosci.

Background- Neurocognition and phenomenology of OCD

Cognitive deficits
- Flexibility
- Attention
- Inhibition
- Goal-directed behaviour

Ferreira et al., 2020,
Bijanki et al., 2021,
Fineberg et al., 2018



Phenomenological experiences
- Impaired agency
- Shame
- Guilt
- Self-ambivalence
- Feared self

de Haan et al., 2013
Abramowitz et al., 2017

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Background- OCD Treatments

CBT/ERP, SSRIs

↓

Clomipramine

↓

Antipsychotic augmentation

↓

In-patient program (ERP)

↓

ACT, MBCT, DBT, MCT

Approved

Investigational

Transcranial magnetic stimulation

↓

Magnetic resonance-guided focused ultrasound

↓

Deep brain stimulation, ablative surgery

Psilocybin assisted psychotherapy

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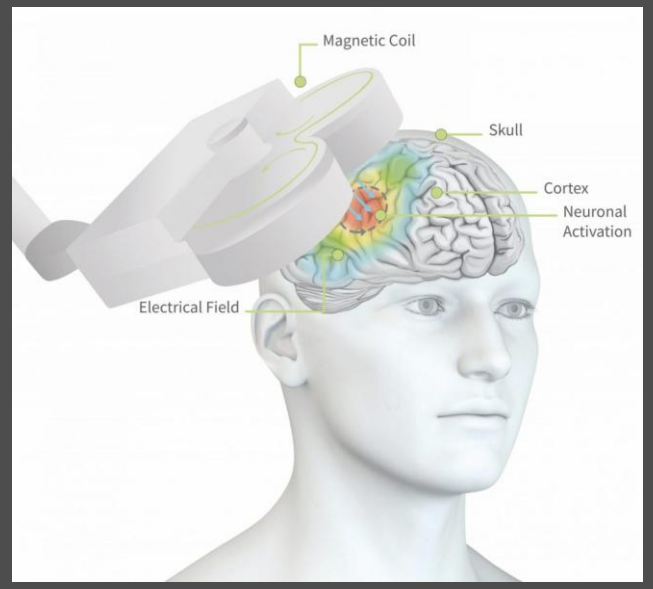
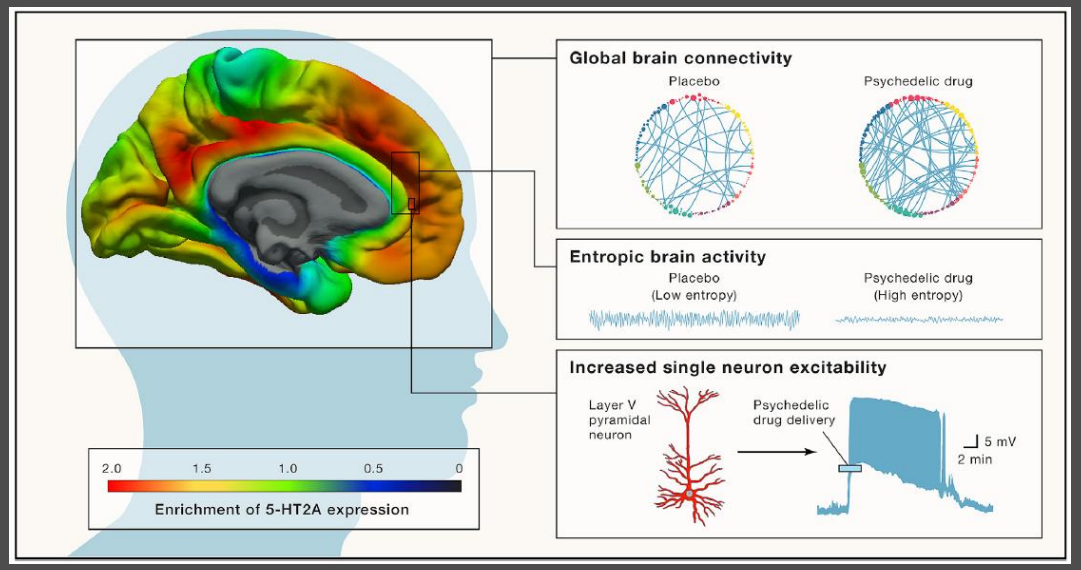
Background- Neuromodulation therapies

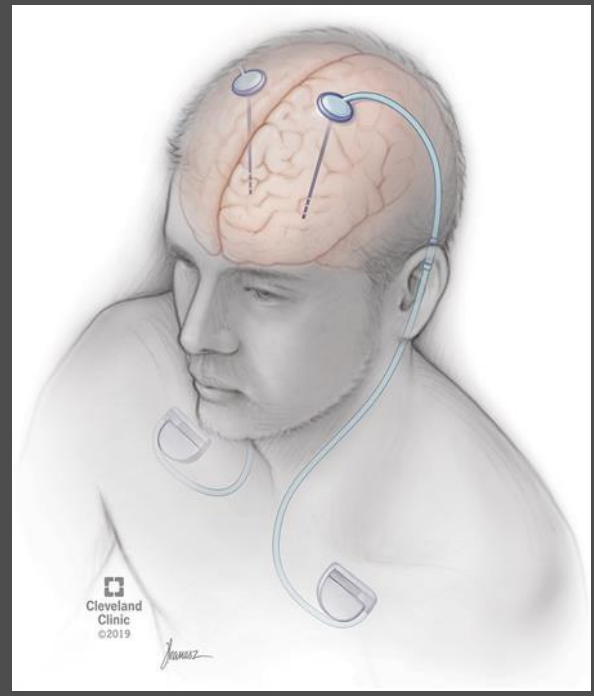
Transcranial Magnetic Stimulation (TMS)



Psilocybin Assisted Psychotherapy (PAP)



Deep Brain Stimulation (DBS)



- Tools to create a shift in the patient
- ‘Resetting’ of the circuitry
- Foster engagement in psychotherapy
- Combination with conventional therapies

1756 papers identified

886 abstracts screened

254 full texts screened

151 articles included

Techniques

Transcranial Direct Current Stimulation (tDCS)

- pre-SMA, SMA, DLPFC, OFC
  - *OCD (n=148)*
- pre-SMA/SMA
  - *Tourette's (n=8)*

Electroconvulsive Therapy (ECT)

- *OCD (n=46)*
- *Tourette's (n=4)*

Deep Brain Stimulation (DBS)

- NAc, ALIC, VC/VS, STN, BNST, ITP, MFB
  - *OCD (n=153)*
- GPi or thalamus targetted
  - *Tourette's (n=175)*
- *Body dysmorphic disorder (n=1)*
- VC/VS targeted

Transcranial Magnetic Stimulation (TMS)

- DLPFC, pre-SMA, SMA, OFC, mPFC, ACC
  - *OCD (n=952)*
- *Tourette's (n=92)*
  - pre-SMA/SMA
- *Skin picking (n=14)*
  - pre-SMA targeted
- *Hoarding disorder (n=1)*
  - right DLPFC targeted

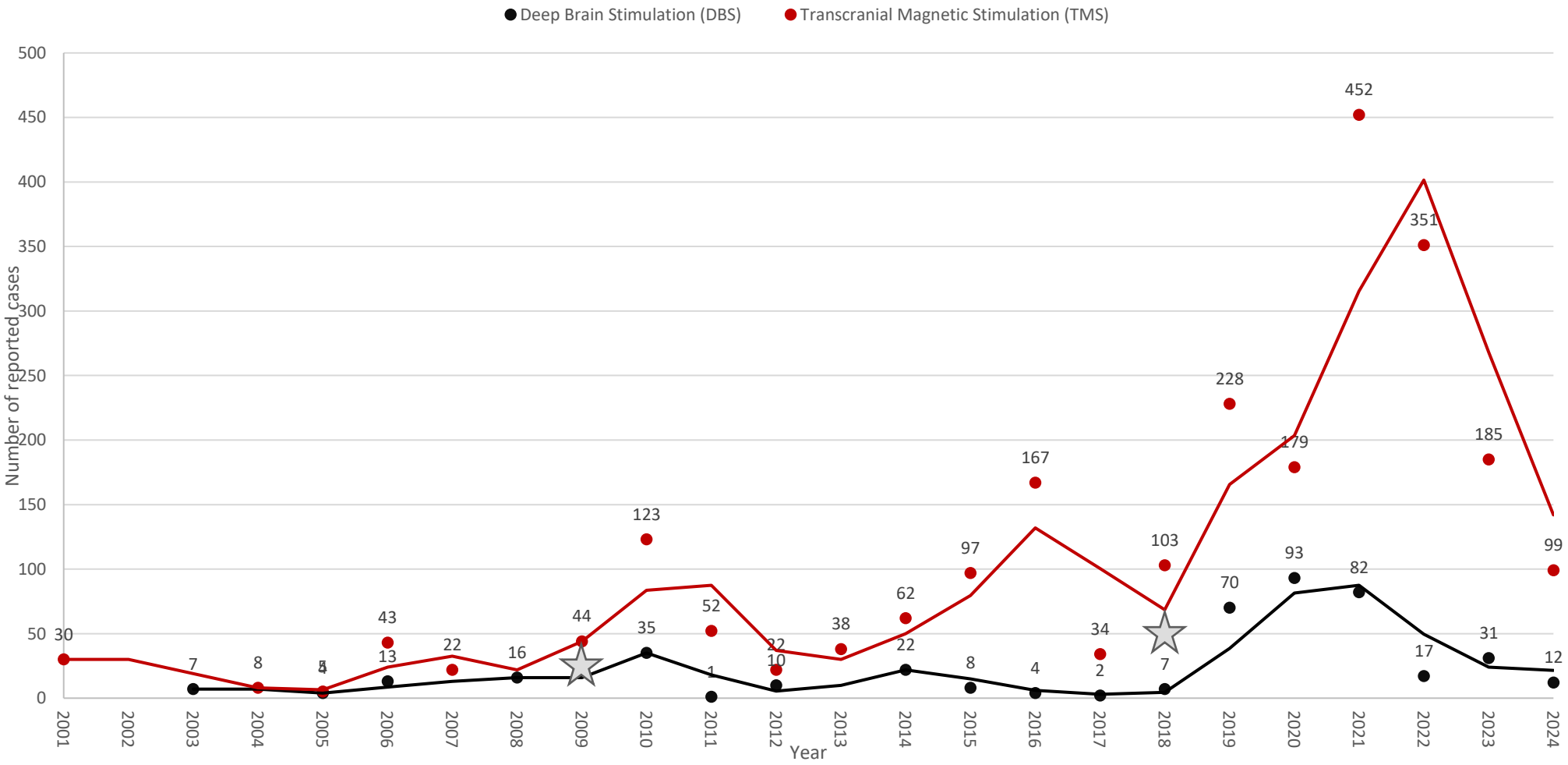
n= patients

Greatest evidence for DBS and TMS therapy for OCD and Tourette's Syndrome; standardised protocols and targetting of circuitry is necessitated.

Acevedo et al., (2021) Brain Sciences

Background

Timeline of reported OCD cases treated with DBS and TMS



Acevedo et al., (2024) Expert Review of Neurotherapeutics

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Patient management

TMS

Eligibility

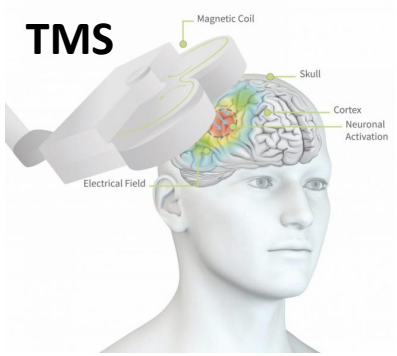
- Moderate symptom severity
- Low level treatment resistance
- Estimated 40% of OCD patients

Treatment access

- FDA approval
- Not approved in Australia

Cost- effectiveness

- TMS < antidepressants, CBT
- TMS > in-patient and intensive out-patient programs[7]



DBS

Eligibility

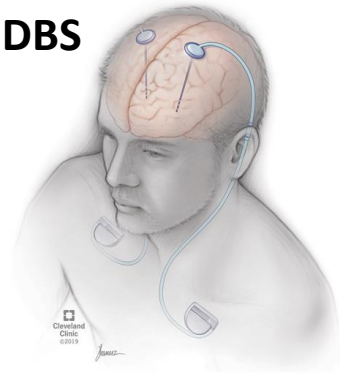
- Severe- extreme symptom severity
- Treatment refractory
- Chronicity
- Substantial functional impairment
- Estimated 10% of OCD patients

Treatment access

- FDA approval
- Not approved in Australia (prohibited in some states)
- MH tribunal approval

Cost- effectiveness

- ~$150,00 AUD
- DBS > TAU after 2 years[8]



Patient management

Treatment effect

- Between 15-30 sessions (3-6 weeks)
- Generally, a linear improvement, sustained at 3-month follow up

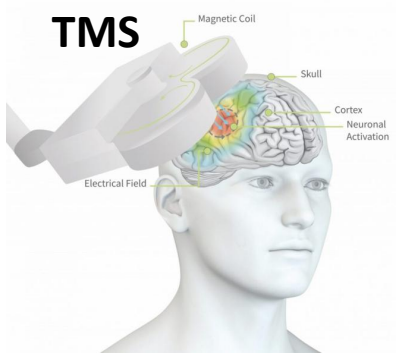
Treatment regime

- 5 sessions/ week for 3-10 weeks
- Prescribed medication generally continued

Side-effects

- Headaches (~35%)
- No serious side effects reported

TMS



Treatment effect

- Highly variable: within weeks or months, fluctuating improvement
- 25% reach clinical response within 1 month, 75% within 3 months (25% take 6-20 months)[9]

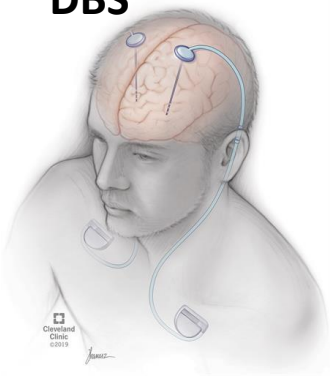
Treatment regime

- Pre-operative: screening, education, consent
- Surgery
- Post-operative: extensive programming adjustments, psychotherapy, psychosocial support, medication management.

Side-effects

- Surgical: ~5%
- Device: feeling of extension lead-10%, lead breakage- 3%
- Stimulation: anxiety-25%, hypomania-40-45%, memory complaints- 9%, dizziness/nausea-7%, disinhibition-7%[10,11]

DBS

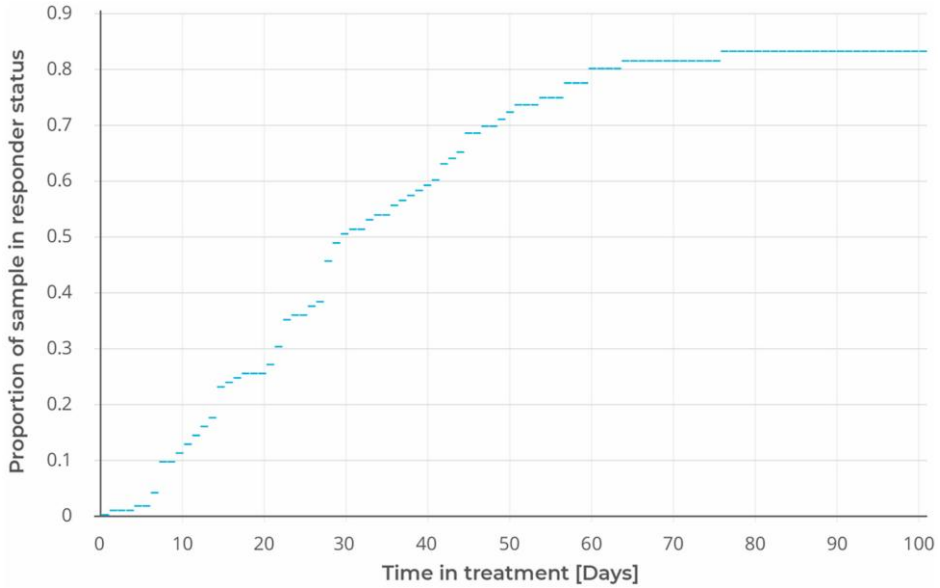


TMS: Current evidence

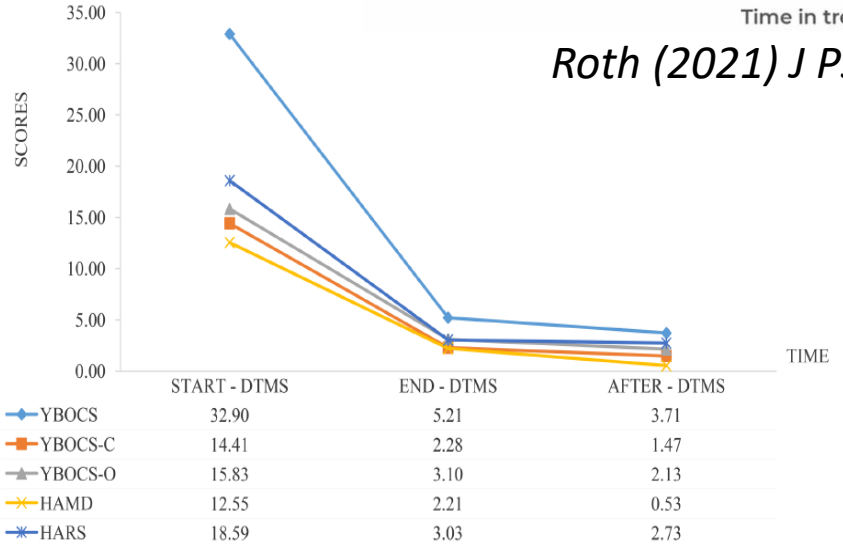
- 37 RCTs and 20 open label trials
- Inconclusive response rates- 14%-80% in RCTs
- Heterogeneity in stimulation protocols
- Low treatment sessions (10-20 sessions)
- High placebo effects
- RCT that led to FDA approval (n=100): 38% responders in active vs 11% in sham[12]

Naturalistic clinical evidence

- FDA approved deep rTMS protocol (29 sessions) + symptom provocation
- Response in 58% across 22 centres- increased to 78% at 2 month follow up [13]
- Response in 100% (n=29) [14]



Roth (2021) J Psychiatric Research



Y-BOCS= Yale-Brown Obsessive Compulsive Scale, O = Y-BOCS Obsession Scores, C = Y-BOCS Compulsion Scores. HDRS = 17-item Hamilton Depression Rating Scale. HARS = Hamilton Anxiety Rating Scale.

Arikan et al., (2022) Clinical EEG and Neuroscience

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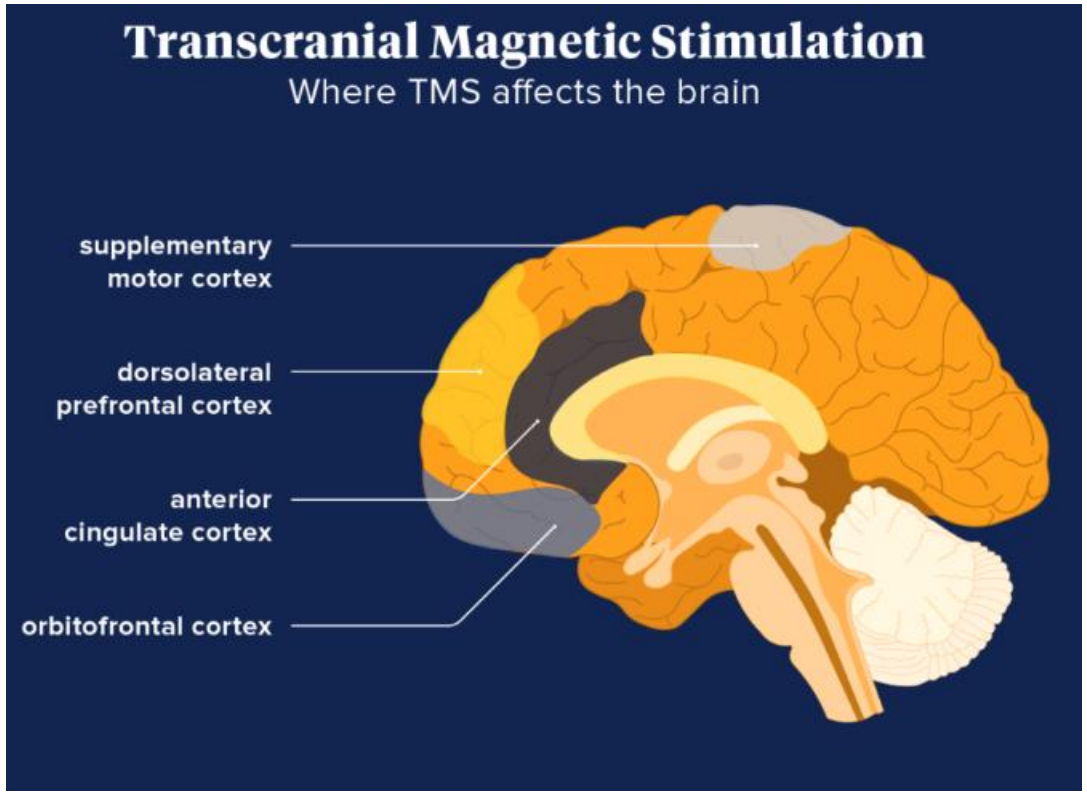
TMS: Current evidence



Meta-analysis and clinical recommendations

- Medium effect size (Hedges g= .47-.64)[16-18]
- Optimal targets: right DLPFC, bilateral DLPFC, SMA
- OCD treatment guidelines support TMS as an augmented treatment[19-21]
- TMS guidelines report inconclusive evidence for OCD [16-18, 22,23]

Clinical characteristics associated with response

- Younger age
- Less disease duration
- Less OCD and depression symptom severity
- Lower treatment resistance- Level of treatment resistance may be a driving factor in heterogeneity of outcomes[17]

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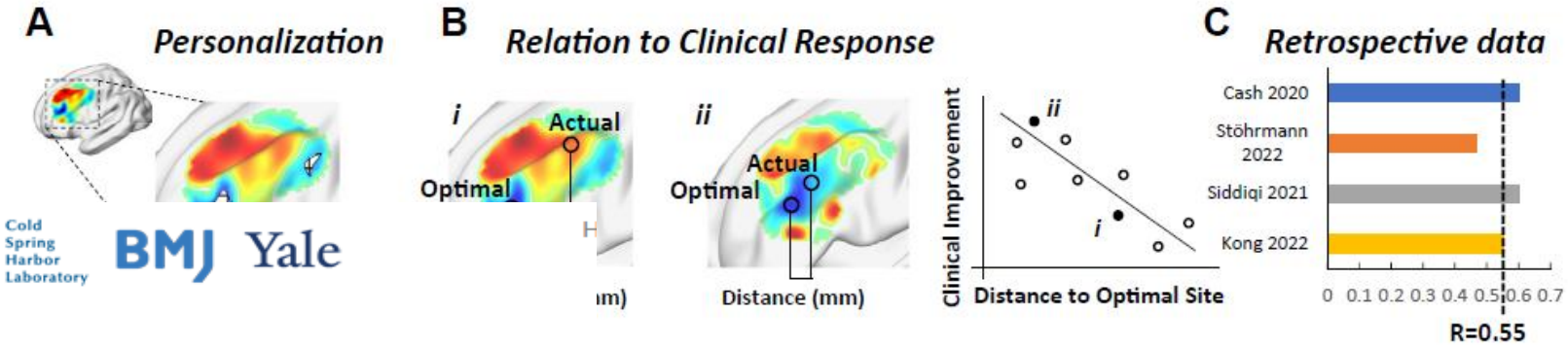
TMS: Progressions

- Sequential dual targeting (Donse et al., 2017; Stubberman 2024)
- Combination therapy with SSRIs (Badaway et al., 2010)
- Accelerated protocols (theta burst stimulation)
- Personalised targeting



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Clinical Response to fMRI-guided Compared to Non-Image Guided rTMS in Depression and PTSD:A Randomized Trial

Desmond J. Oathes, Almaris Figueroa Gonzalez, Julie Grier, Camille Blaine, Sarai D. Garcia, Kristin A. Linn

doi: https://doi.org/10.1101/2024.07.29.24311191

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DBS: Current evidence

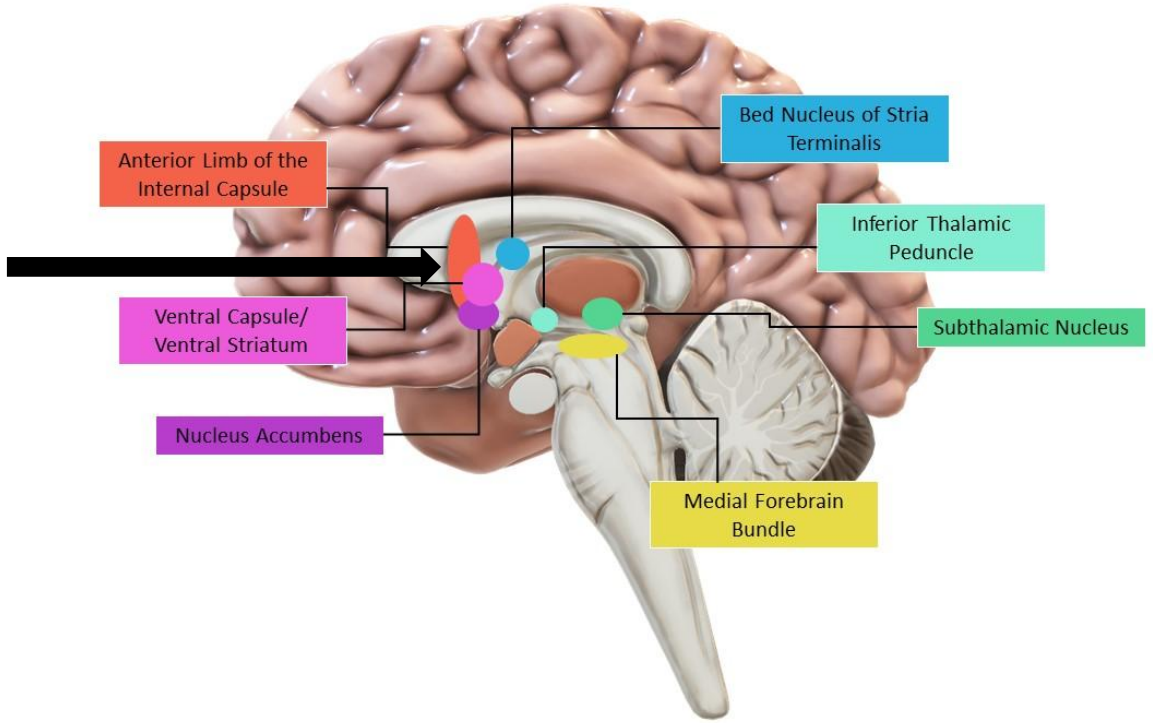
- 7 RCTs: 5 demonstrating clinically significant outcomes
- Response rate- 60% (long term response of 70%)
- Average symptom reduction of 45%
- Optimal target: Ventral Anterior Limb of the Internal Capsule (ALIC)

Naturalistic clinical evidence

- 19 open label studies- robust and long-term treatment effects (up to 9 year follow up)

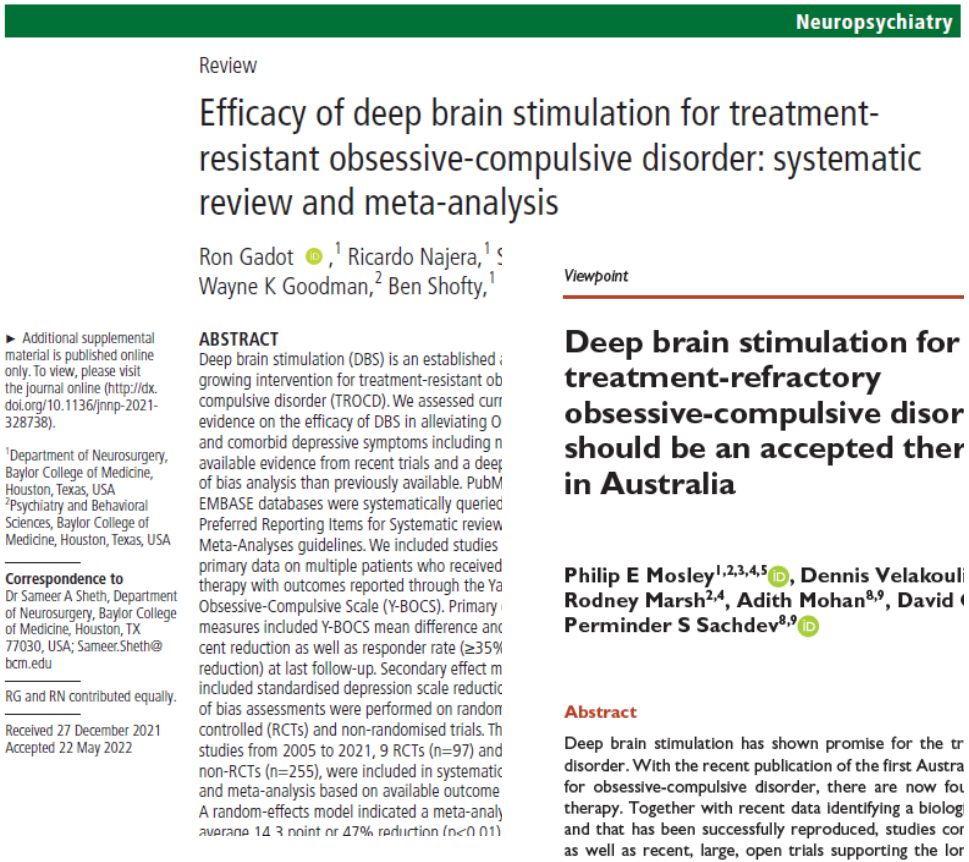
Clinical characteristics associated with clinical response

- Good insight
- Later age of onset
- Hoarding, perfectionism, symmetry symptoms and personality disorder- poor response



DBS: Crisis in access to care

- Global barriers in accessing treatment- a crisis in access to care is proposed, DBS should not be offered as a last resort but as a synergistic approach with conventional therapies[24]
- Insurance denial- violation of mental health acts thus discrimination for mental health patients, placing increased burden on patients, families and health care systems[30]
- DBS therapy for refractory OCD is an established therapy[25-29]
- Resistance from the psychiatric community



Neuropsychiatry

Review

Efficacy of deep brain stimulation for treatment-resistant obsessive-compulsive disorder: systematic review and meta-analysis

Ron Gadot ,[1] Ricardo Najera,[1] Wayne K Goodman,[2] Ben Shofty,[1]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jnnp-2021-328738).

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RG and RN contributed equally.

Received 27 December 2021
Accepted 22 May 2022

ABSTRACT
Deep brain stimulation (DBS) is an established
growing intervention for treatment-resistant ob
compulsive disorder (TROCD). We assessed curr
evidence on the efficacy of DBS in alleviating O
and comorbid depressive symptoms including n
available evidence from recent trials and a deep
of bias analysis than previously available. PubM
EMBASE databases were systematically queried
Preferred Reporting Items for Systematic review
Meta-Analyses guidelines. We included studies
primary data on multiple patients who received
therapy with outcomes reported through the Ya
Obsessive-Compulsive Scale (Y-BOCS). Primary
measures included Y-BOCS mean difference and
cent reduction as well as responder rate (≥35%
reduction) at last follow-up. Secondary effect m
included standardised depression scale reductio
of bias assessments were performed on random
controlled (RCTs) and non-randomised trials. Th
studies from 2005 to 2021, 9 RCTs (n=97) and
non-RCTs (n=255), were included in systematic
and meta-analysis based on available outcome
A random-effects model indicated a meta-analy
average 14.3 point or 47% reduction (p<0.01)

Viewpoint

Deep brain stimulation for treatment-refractory obsessive-compulsive disor should be an accepted ther in Australia

Philip E Mosley[1,2,3,4,5], Dennis Velakoul
Rodney Marsh[2,4], Adith Mohan[8,9], David
Perminder S Sachdev[8,9]

Abstract

Deep brain stimulation has shown promise for the tr
disorder. With the recent publication of the first Austra
for obsessive-compulsive disorder, there are now fou
therapy. Together with recent data identifying a biolog
and that has been successfully reproduced, studies cor
as well as recent, large, open trials supporting the lor

Commentary

Commentary

Deep brain stimulation for treatment-refractory obsessive-compulsive disorder should be an accepted therapy in Australia

Nicola Acevedo[1] and Susan Rossell[1,2]

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DOI: 10.1177/00048674211049344

Mosley and colleagues (2021) recently

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Acevedo et al. syster
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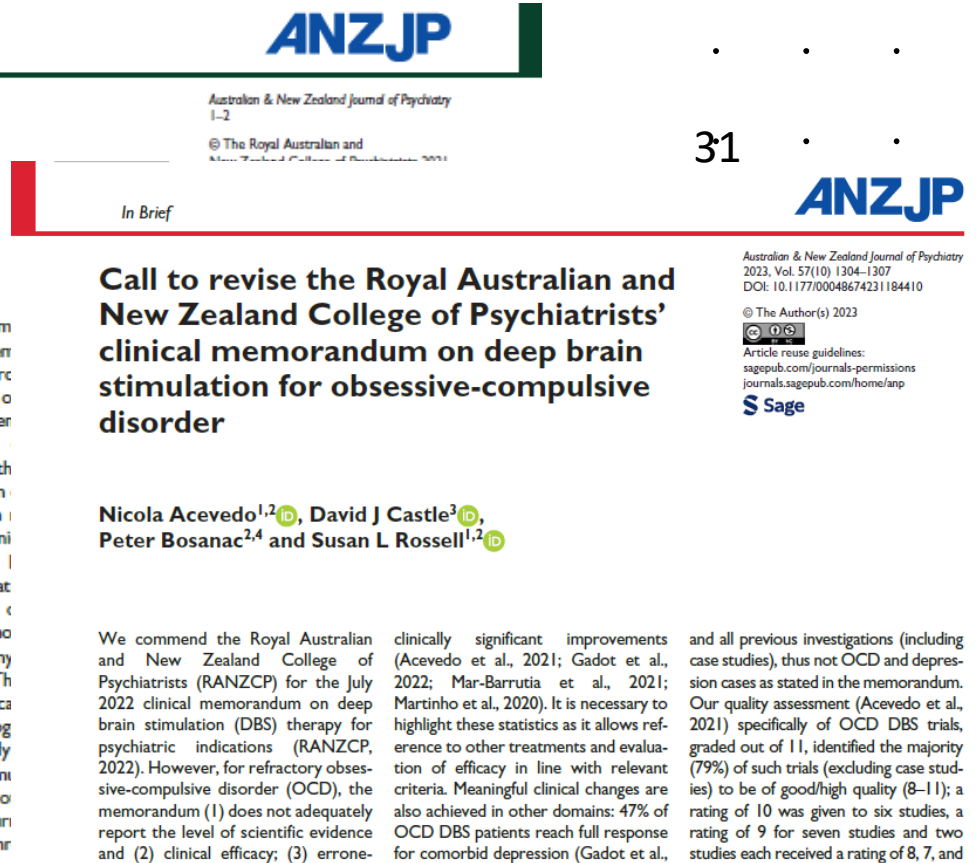

ANZJP

Australian & New Zealand Journal of Psychiatry
1–2
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In Brief

ANZJP

Call to revise the Royal Australian and New Zealand College of Psychiatrists' clinical memorandum on deep brain stimulation for obsessive-compulsive disorder

Nicola Acevedo[1,2], David J Castle[3], Peter Bosanac[2,4] and Susan L Rossell[1,2]

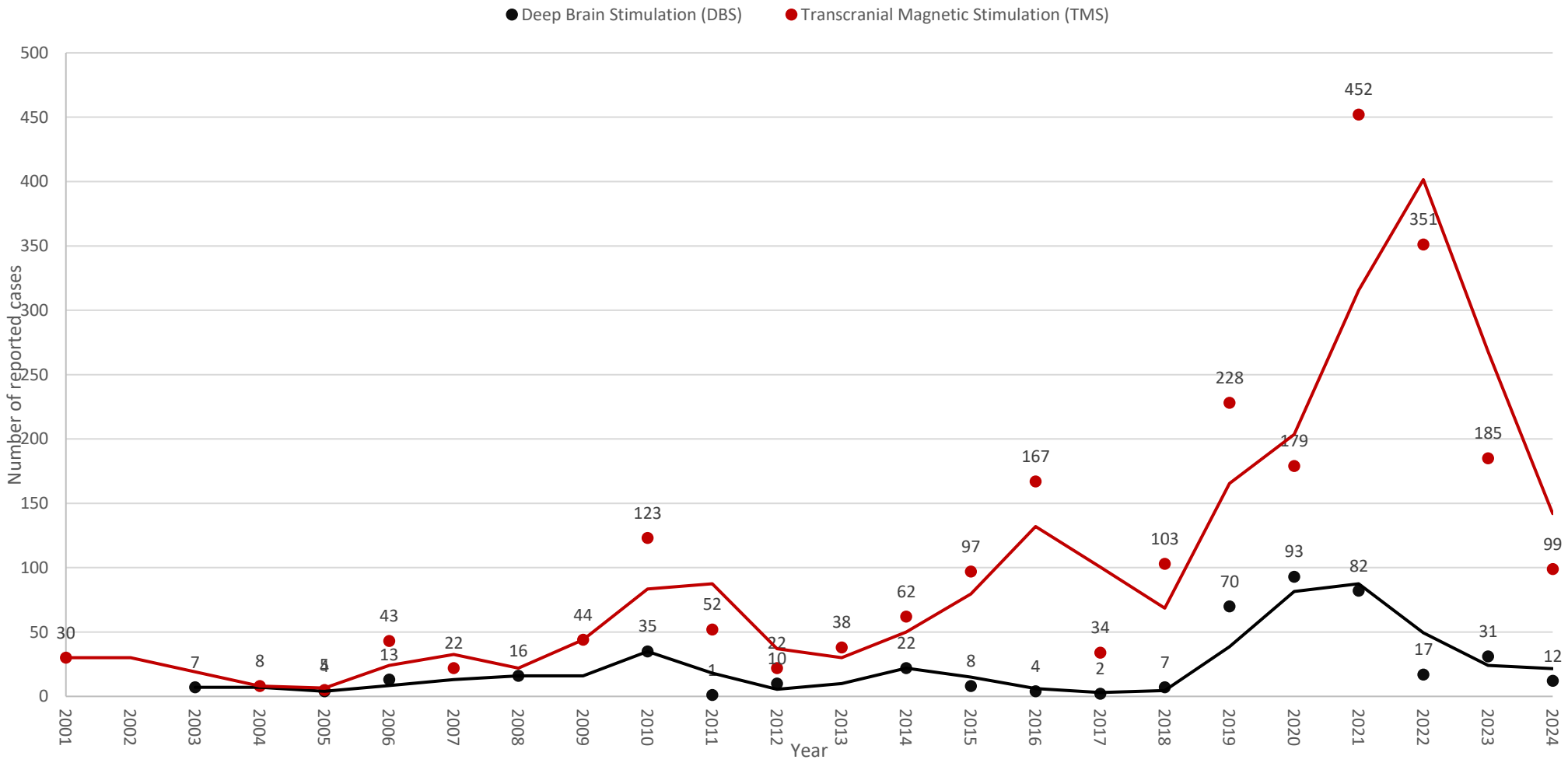
Australian & New Zealand Journal of Psychiatry
2023, Vol. 57(10) 1304–1307
DOI: 10.1177/00048674231184410

We commend the Royal Australian and New Zealand College of Psychiatrists (RANZCP) for the July 2022 clinical memorandum on deep brain stimulation (DBS) therapy for psychiatric indications (RANZCP, 2022). However, for refractory obsessive-compulsive disorder (OCD), the memorandum (1) does not adequately report the level of scientific evidence and (2) clinical efficacy; (3) errone-

clinically significant improvements (Acevedo et al., 2021; Gadot et al., 2022; Mar-Barrutia et al., 2021; Martinho et al., 2020). It is necessary to highlight these statistics as it allows reference to other treatments and evaluation of efficacy in line with relevant criteria. Meaningful clinical changes are also achieved in other domains: 47% of OCD DBS patients reach full response for comorbid depression (Gadot et al.,

and all previous investigations (including case studies), thus not OCD and depression cases as stated in the memorandum. Our quality assessment (Acevedo et al., 2021) specifically of OCD DBS trials, graded out of 11, identified the majority (79%) of such trials (excluding case studies) to be of good/high quality (8–11); a rating of 10 was given to six studies, a rating of 9 for seven studies and two studies each received a rating of 8, 7, and

OCD DBS cases reported each year



DBS for Parkinson's= ~160,000 cases
DBS for OCD= ~450

~47% symptom improvement
~45% symptom improvement

~22% quality of life improvement
~85% quality of life improvement

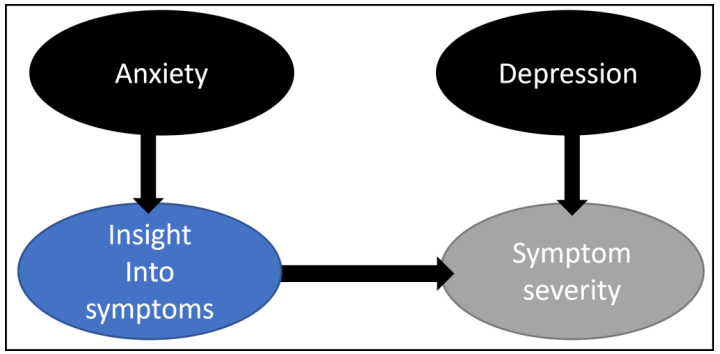
DBS trial: Clinical trial outcomes

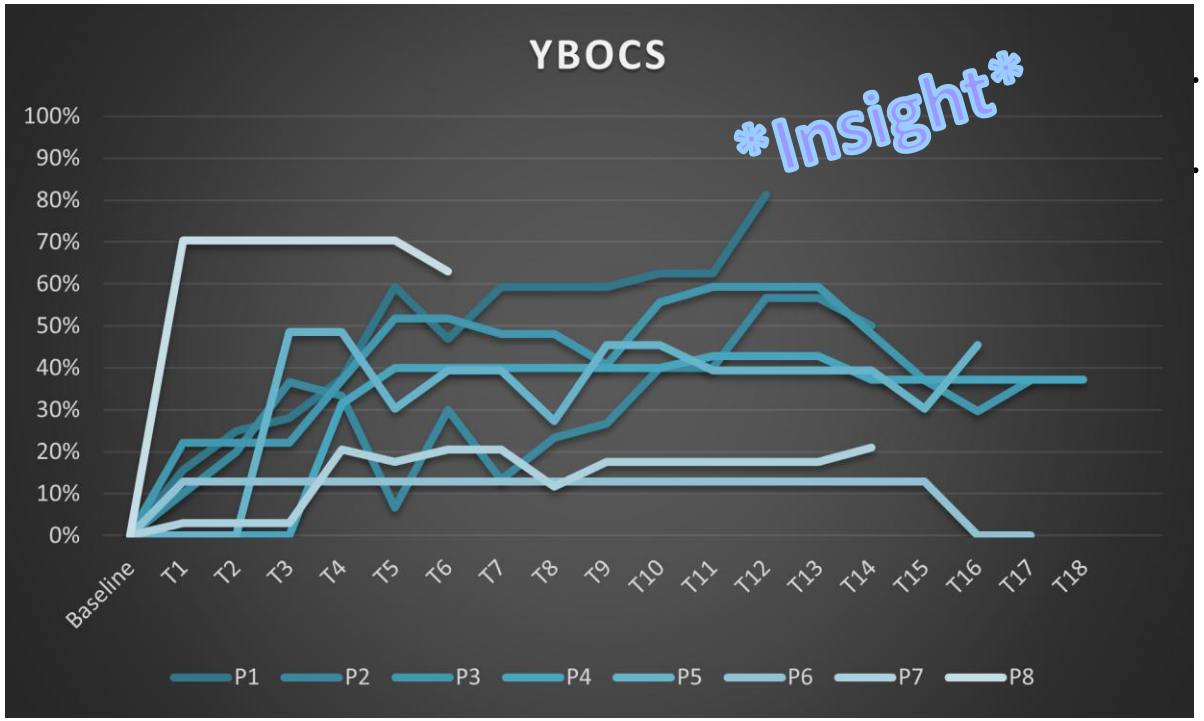
Open label trial (n=8) of DBS of the Nucleus Accumbens

Responders: 75% (6-9 weeks) – disease duration of 23 years

Symptomatic changes
Obsessions and compulsions (10 months- 7 years): 45%
Depression: 42%
Anxiety: 41%

Mixed linear modelling:
Initial changes in anxiety and depression
Insight into symptoms predicted changes in symptom severity (p=.008)





Acevedo et al., (2023) Psychiatry and Clinical Neurosciences

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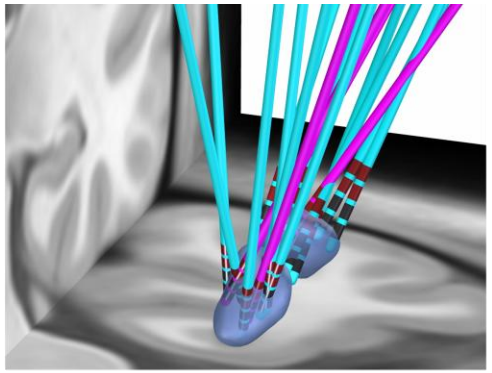
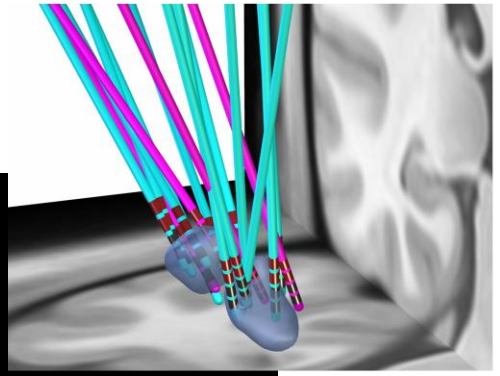
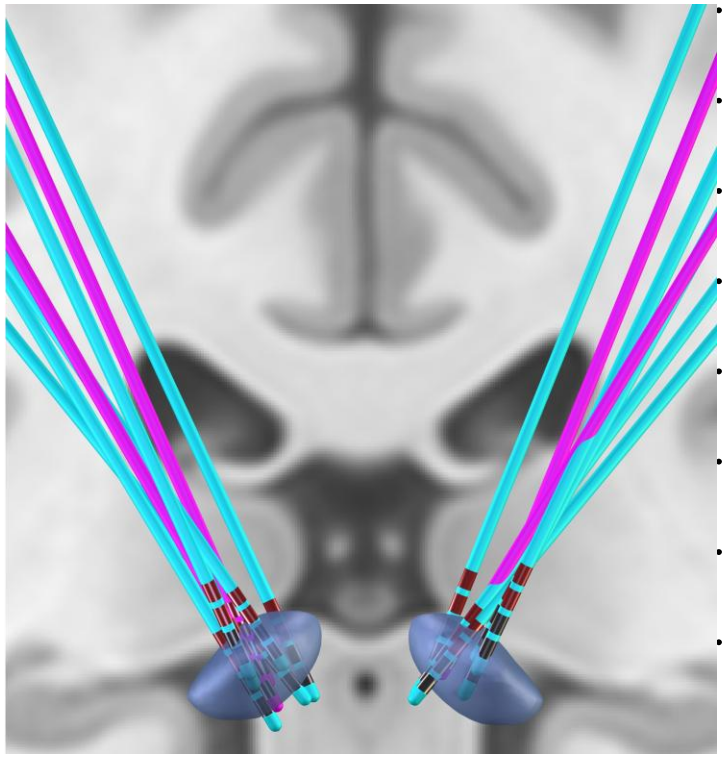
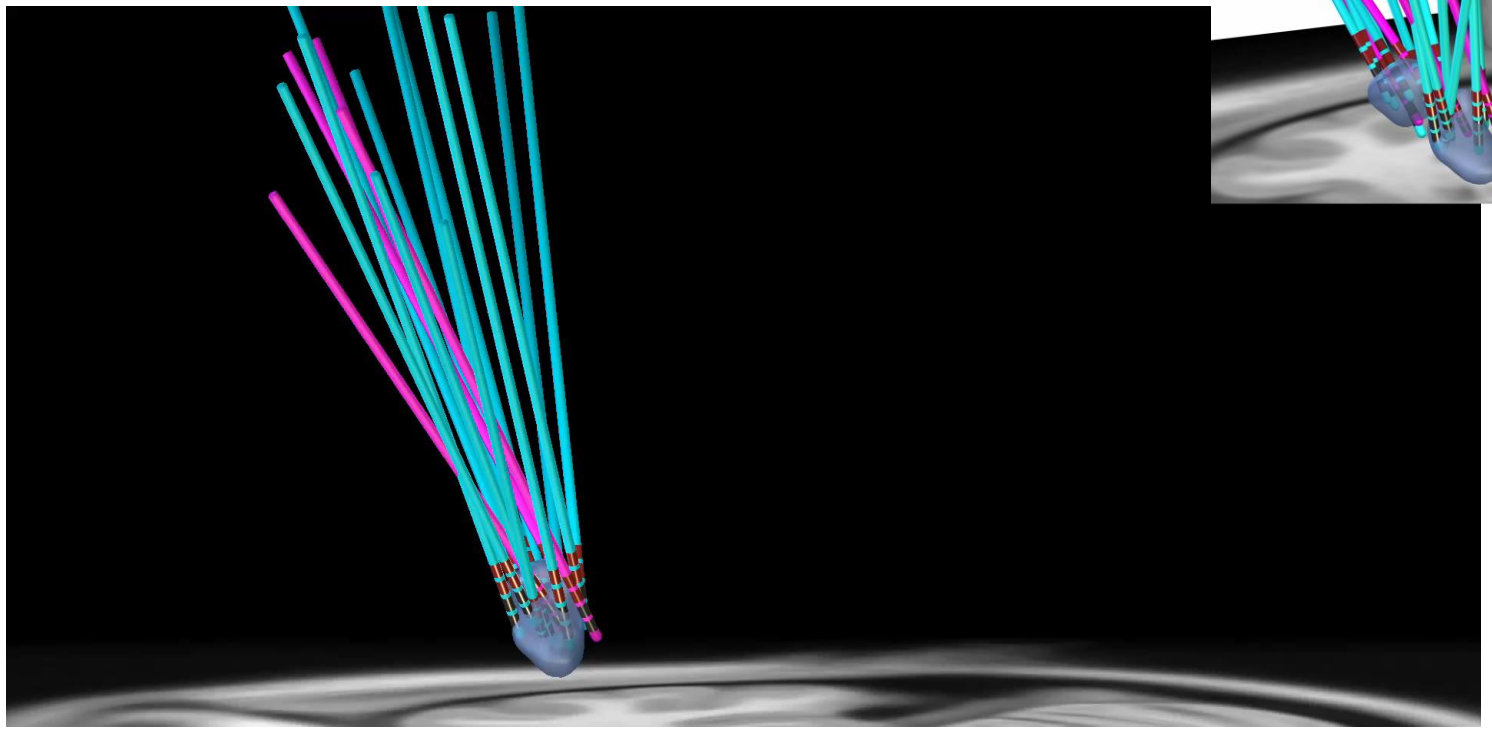
DBS trial: Lead localisation









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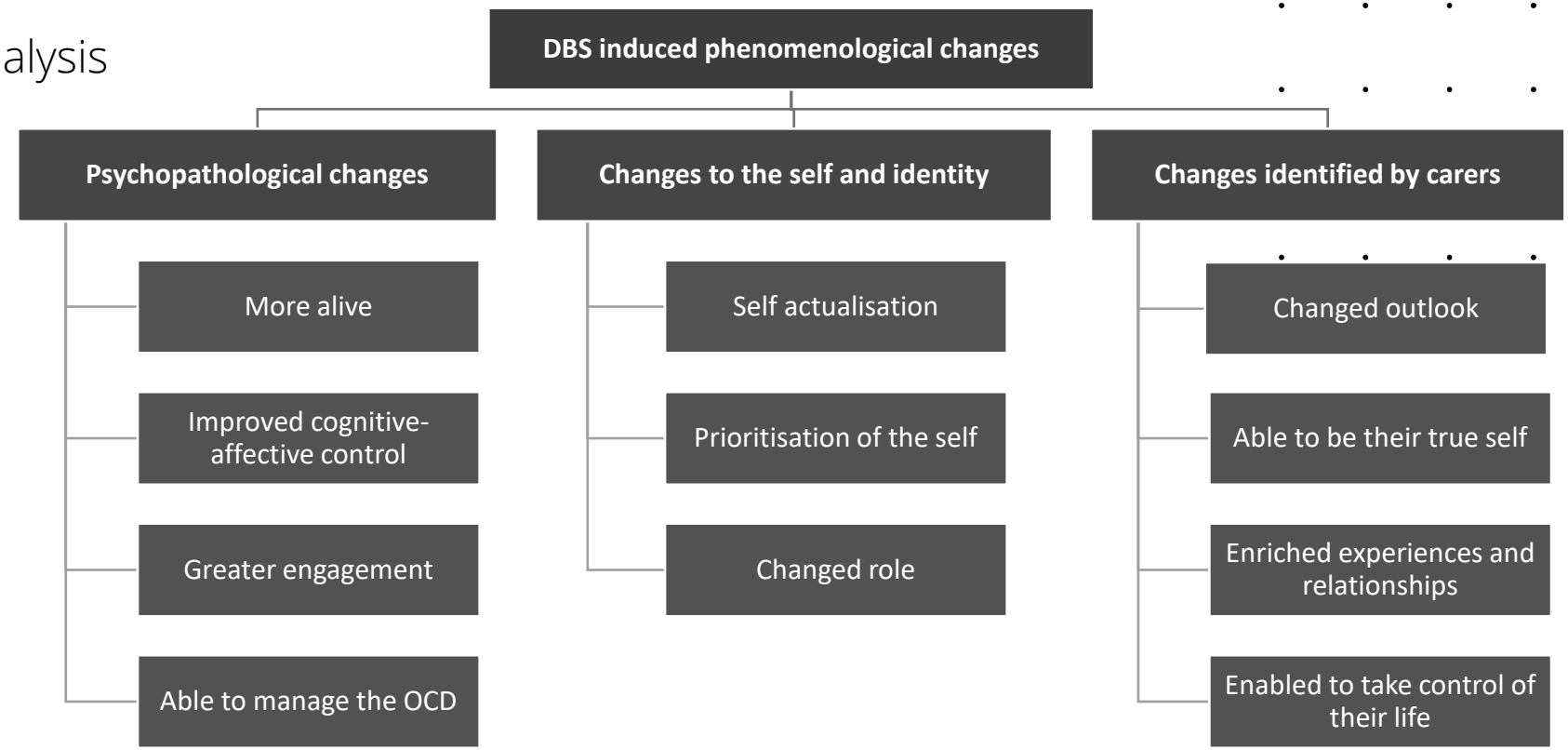
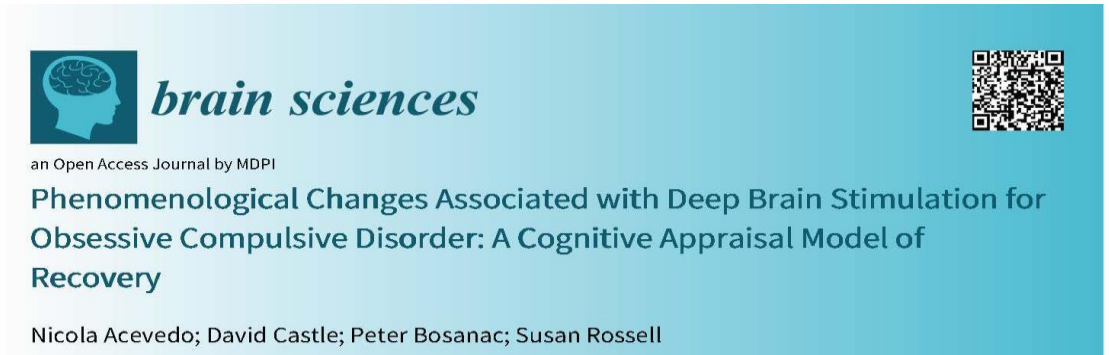
DBS: Lived experiences

- Open ended interviews with OCD DBS patients and carers
- Interpretive phenomenological analysis (IPA)
- Inductive and latent approach





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Framework of phenomenological changes

"Anything is possible, if I put my mind to it anything is possible, I could try and do anything if I wanted to, nothing is out of my reach"

"It's just been joyous, to feel as if life can be wonderful and exciting and interesting and doable"

"I wouldn't be here without the DBS, that's for sure"

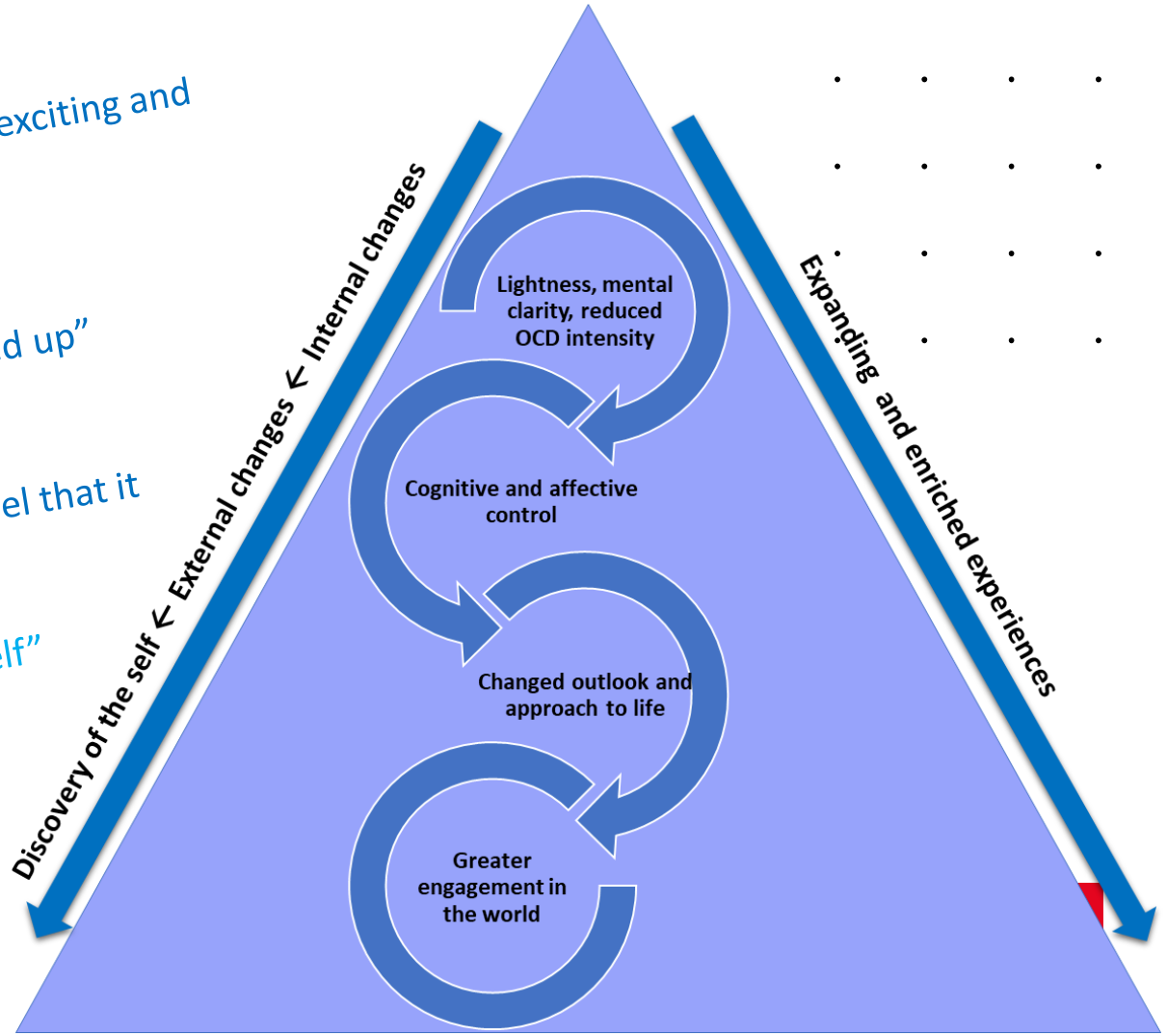
"An expanding horizon opened up"

"All the clouds had been lifted"

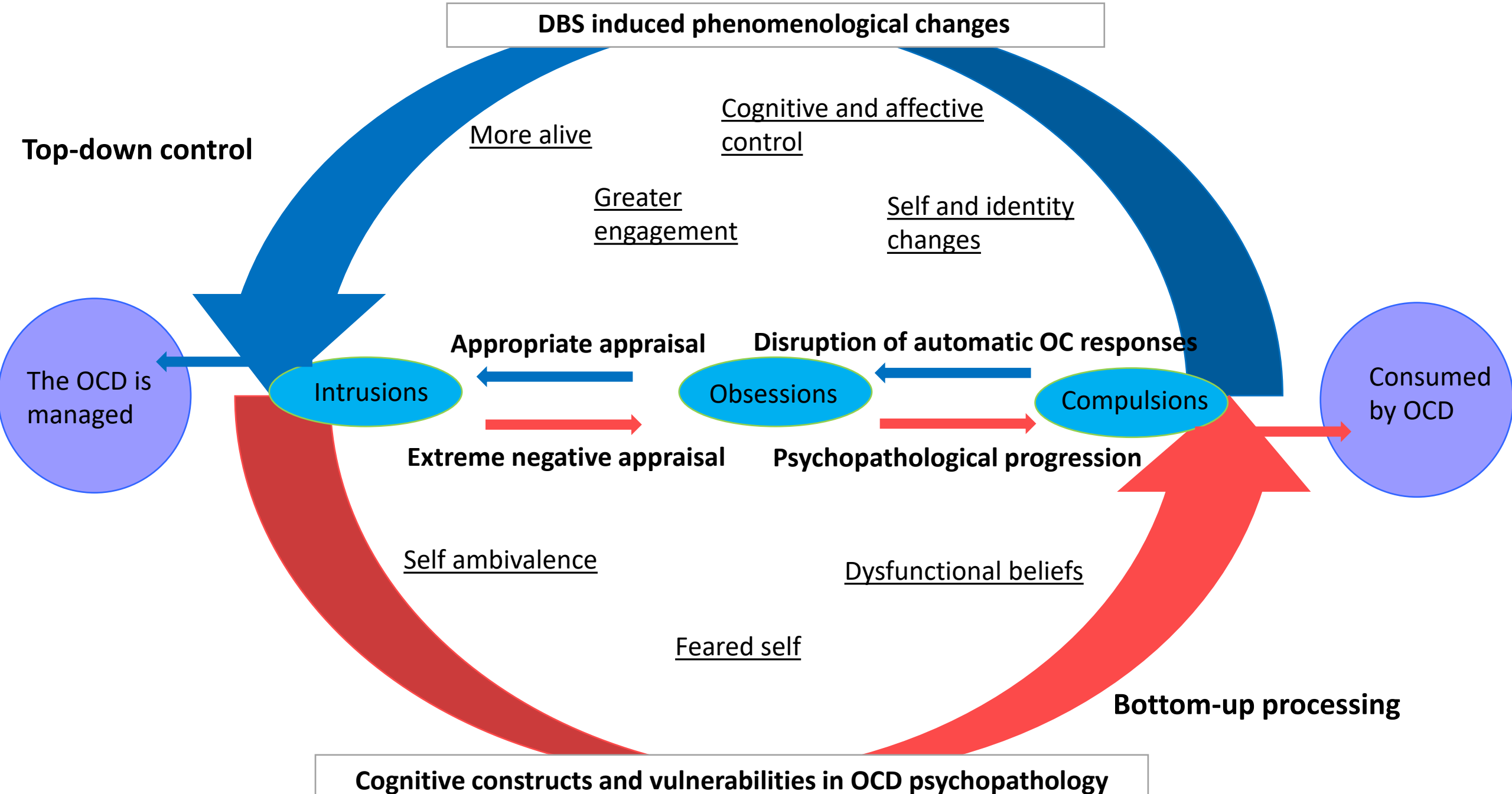
"It's beauty that I saw before, and I knew that it was beautiful, but I didn't feel that it was beautiful, and now I actually feel the beauty of it"

"It's actually a discovery of identity… it's a discovery of the self"

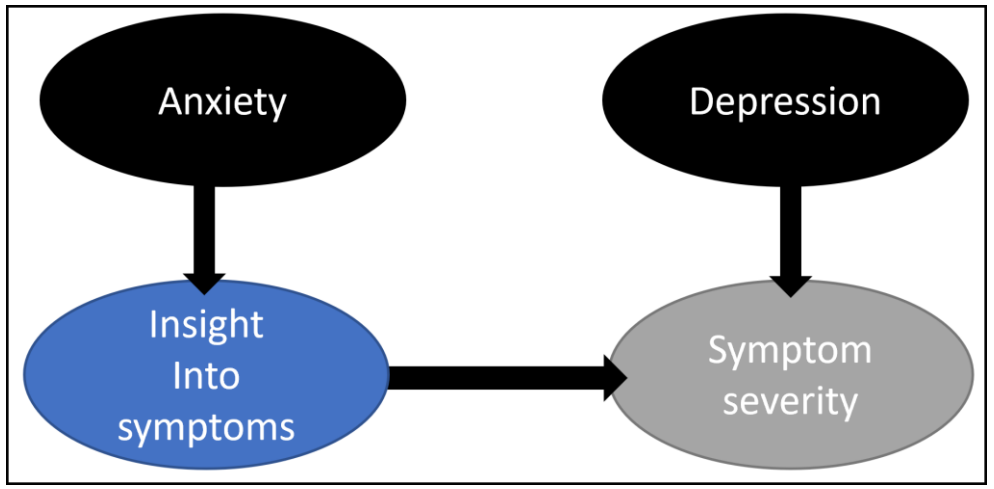
'I feel like I am growing into who I am supposed to be, well not who I am supposed to be but who I am.'

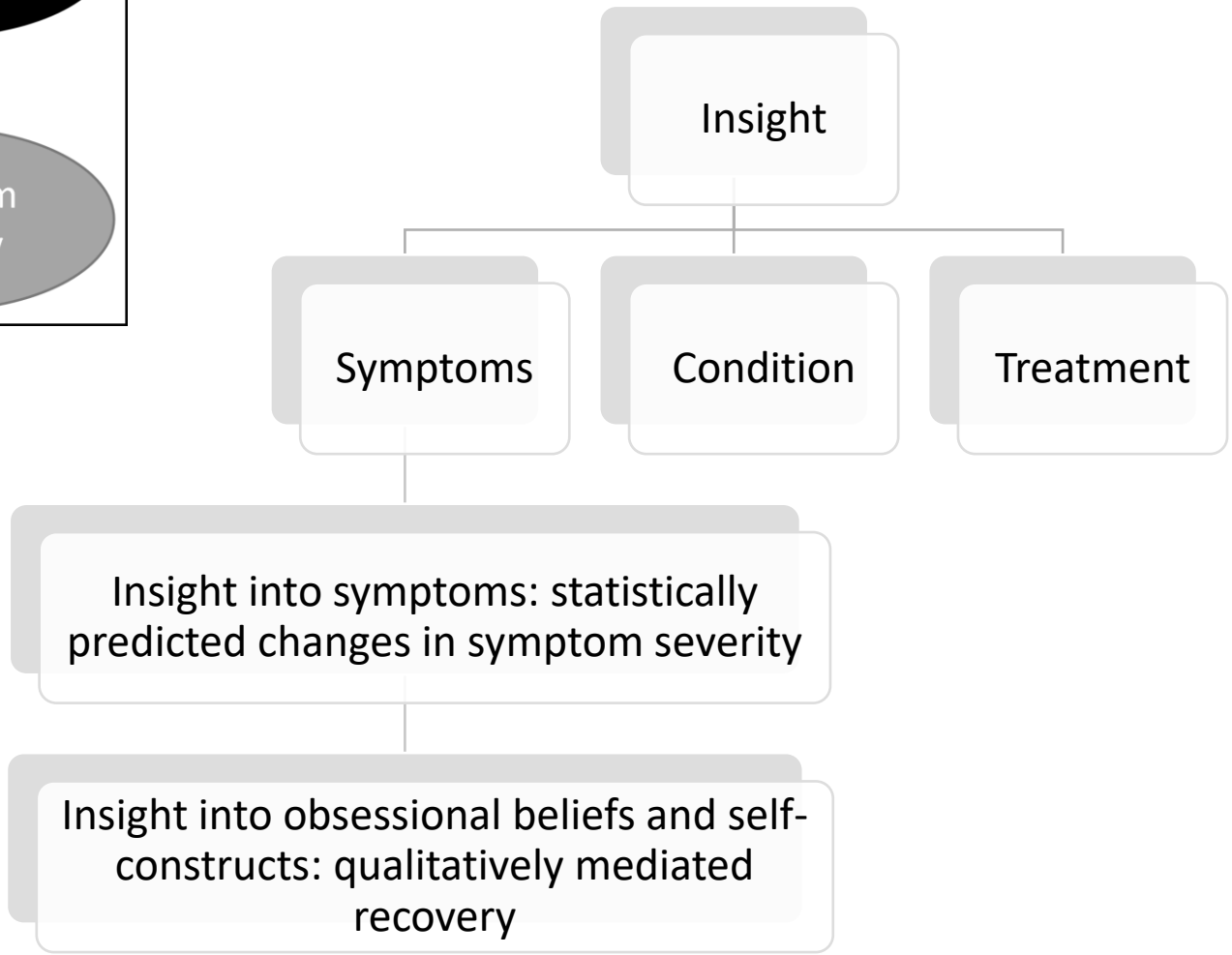


Theoretical model of recovery, on the cognitive appraisal of intrusions



DBS: mechanisms





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DBS: Clinical guideline

- Adjunct cognitive therapy augments and consolidates DBS effects
- Multidisciplinary and specialised support for symptomatic and psychosocial recovery
- Improved psychoeducation and peer support services

Viewpoint

ANZJP

Australian & New Zealand Journal of Psychiatry
1–7
DOI: 10.1177/00048674221100947

Clinical recommendations for the care of people with treatment-refractory obsessive-compulsive disorder when undergoing deep brain stimulation

Nicola Acevedo[1], David Castle[2,3], Clare Groves[4], Peter Bosanac[2,5], Philip E Mosley[6,7,8] and Susan Rossell[1,5]

Abstract

Deep brain stimulation is an emerging therapy for treatment-refractory obsessive-compulsive disorder patients. Yet, accessibility is limited, treatment protocols are heterogeneous and there is no guideline or consensus on the best practices. Here, we combine evidence from scientific investigations, expert opinions and our clinical expertise to propose several clinical recommendations from the pre-operative, surgical and post-operative phases of deep brain stimulation care for treatment-refractory obsessive-compulsive disorder patients. A person-centered and biopsychosocial approach is adopted. Briefly, we discuss clinical characteristics associated with response, the use of improved educational materials, an evaluative consent process, comprehensive programming by an expert clinician, a more global assessment of treatment efficacy, multi-disciplinary adjunct psychotherapy and the importance of peer support programs. Furthermore, where gaps are identified, future research suggestions are made, including connectome surgical targeting, scientific evaluation

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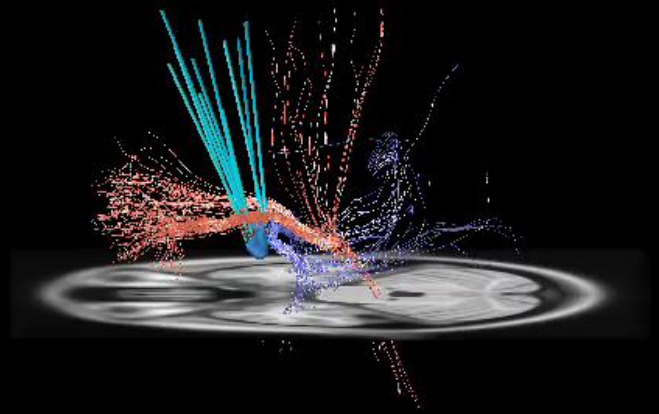
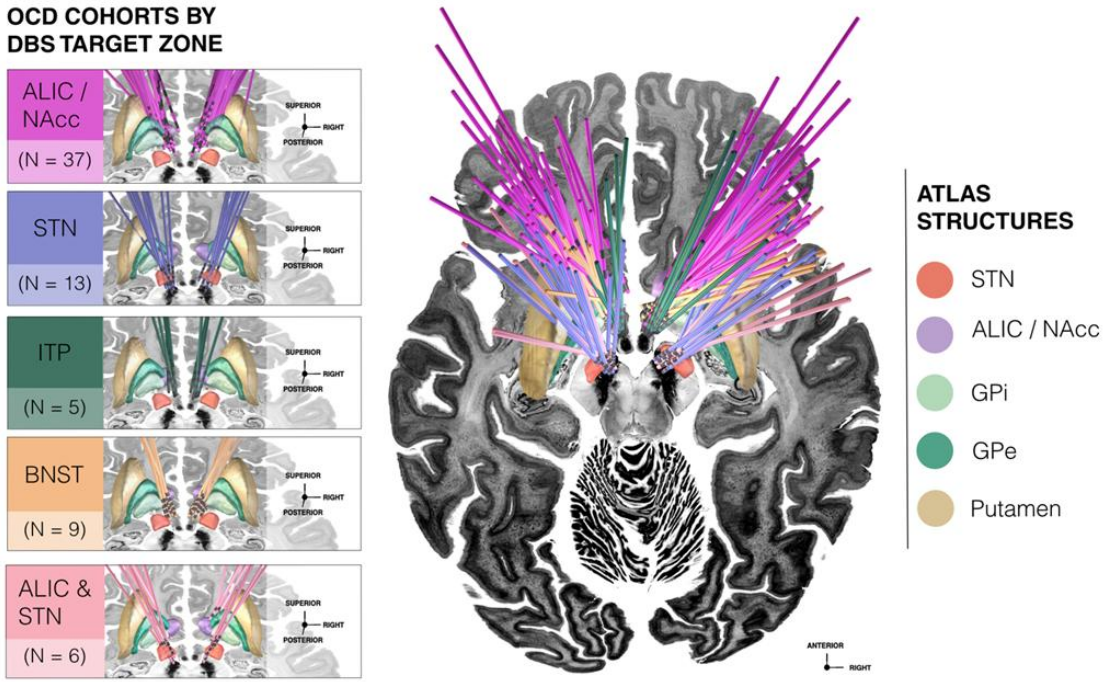
DBS: Progressions

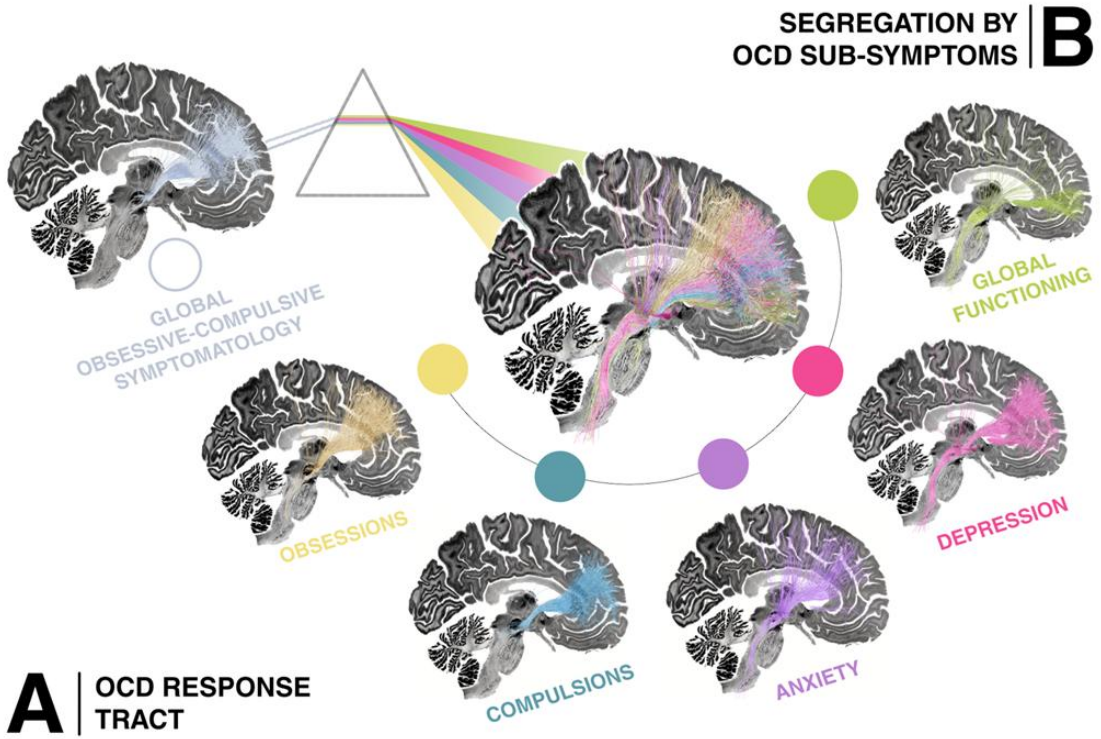
Connectome approach



Li et al., 2020; Baldermann et al., 2021; Smith et al., 2021; Mosley et al., 2021b

DBS: Progressions





Hollunder et al., (unpublished)

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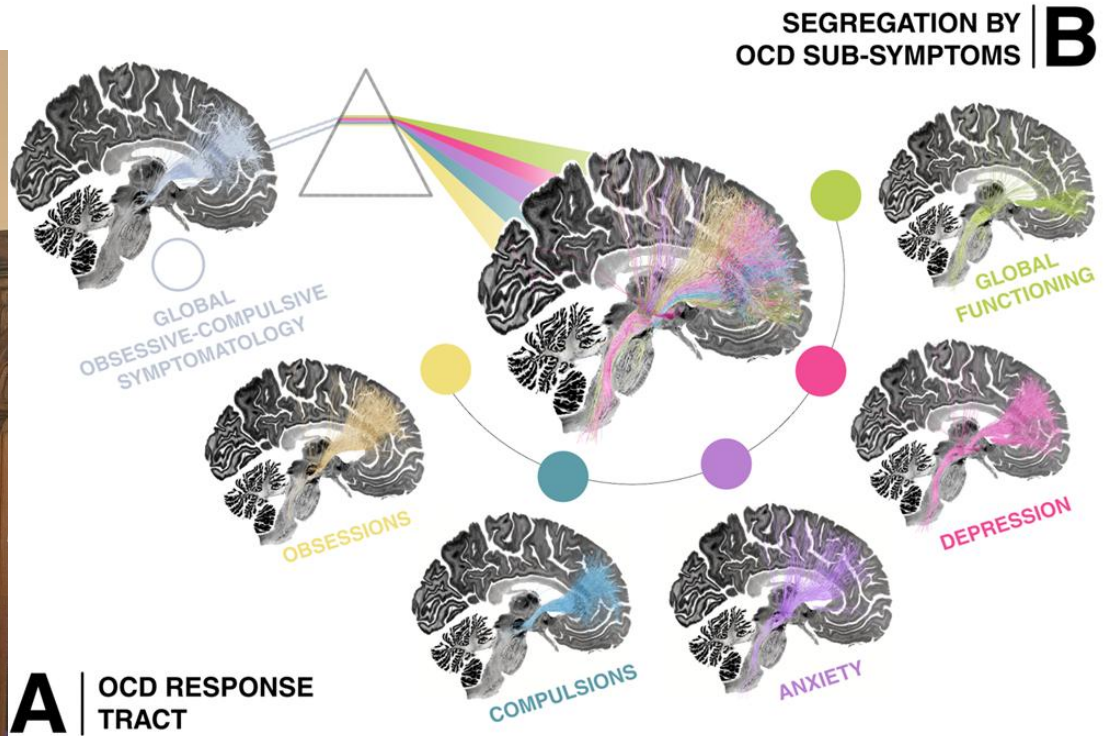
DBS: Connectome approach



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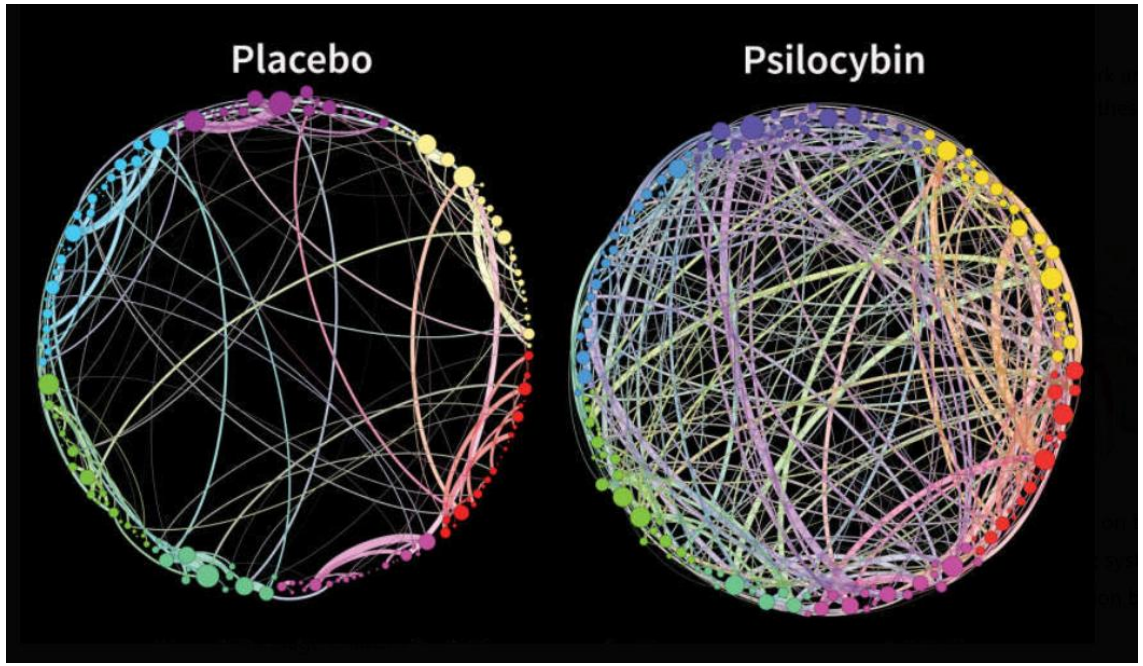
PAP: Empirical and theoretical rationale



Overlapping psychological and neurobiological impairments	Psychedelic effects	Potential therapeutic outcomes
•Neurocognitive dysfunction- cognitive inflexibility •Fear/threat/negative cognitive bias •Compulsive/ ritualistic/ avoidant behaviours •Hypervigilance and hyperarousal •Dysregulated serotonergic and dopaminergic systems •Disengaged in psychotherapy	•Psychological insight •Enhanced mood •Shifts in perceptions of the self and world •Regulated serotonergic and dopaminergic signalling •Network connectivity modulations •Mystical/spiritual experiences •Deep processing and healing	•Increased cognitive flexibility •Improved emotional regulation •Broader perspective •Greater self-love and compassion •Acceptance, appreciation •Somatic insights •Separation/ distance from symptoms •Understanding contributing factors of condition •Reduction of pathological rigidity and compulsive behaviours

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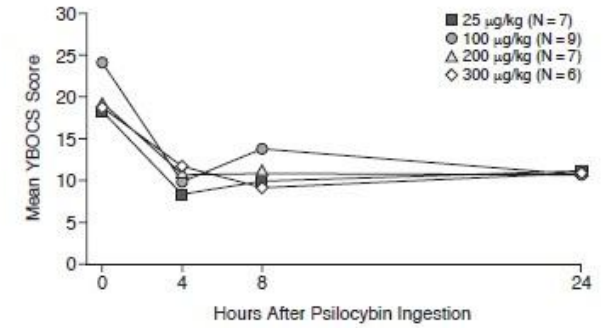
PAP: Current evidence

1 completed open label trial (Moreno et al., 2006; Kelmendi et al., 2022)

- 9 OCD patients: ≥1 treatment failure (average 3.4), moderate- extreme symptom severity (average YBOCS- 24)
- Dose: very low (2.5mg), low dose (10mg), medium dose (20mg), high dose (30mg)- escalating order with randomized very low dose- all well tolerated
- Efficacy: 67% full response (50% improvement), 89% partial response (25% improvement).
- Limitations: minimal rapport building, no structured psychological support (preparatory or integration), only non-directive support during psychedelic experience

Figure 1. Effects of Psilocybin on Obsessive-Compulsive Symptom Severity[a]



[a]Mean YBOCS scores immediately prior to ingesting psilocybin (T-0) and 24 hours after ingesting psilocybin (T-24) for each dose were as follows: 25 µg/kg, T-0 = 18.29, T-24 = 11.14; 100 µg/kg, T-0 = 24.11, T-24 = 10.67; 200 µg/kg, T-0 = 19.57, T-24 = 11.00; 300 µg/kg, T-0 = 18.83, T-24 = 11.33.
Abbreviation: YBOCS = Yale-Brown Obsessive Compulsive Scale.

PAP: Protocol

- Phase II open label basket trial: OCD, BDD, anorexia
- 2 x 25mg doses, 4-weeks apart
- Primary outcomes: clinical response in primary symptoms (objective and subjective)
- Secondary outcomes: depression, anxiety, insight, quality of life, global functioning
- 3-month follow up period

- Preparation: psychoeducation booklet, 1-hour with researcher, 3-hours with therapists
- Non-directive integration: trauma informed approach, shadow work, internal family systems, compassion focused therapy- 6-hours with therapists, and check in calls day prior to dosing

- Registration: ACTRN12624001160527

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PAP: Ongoing trials

Location	Trial phase, Status	Target cohort	Dosage	Methods	Psychotherapy	Registry
US- Yale University	Phase 1, completed	31	25mg	RCT, open label follow-up.	Preparatory and follow up support.	NCT03356483
US- University of Arizona	Phase 1, completed	15	10mg, 30mg	RCT (3-arms), low dose, high dose or placebo, 4 doses	-	NCT03300947
UK- Imperial College London	Phase 1, completed	19	10mg (across 2 doses)	2 doses	-	NCT06258031
US- Yael University	Phase 1, not yet recruiting	30	25mg, 30mg	RCT, waitlist control, 2 doses	2 integration sessions.	NCT05370911
Israel- Beersheva Mental Health Centre	Phase 1, not yet recruiting	15	-	Open label, 3 doses	12 preparation & integration, 3 dosing.	NCT04882839
Toronto- Centre for Addiction and Mental Health	Phase 1,not yet recruiting	10	25mg	Open label, 2 doses	2 integration sessions.	NCT06299319
US- John Hopkins University	Phase 1, Recruiting	30	20mg, 30mg	Open label, waitlist control group, dosage increased if tolerated.	Administered under supportive conditions.	NCT05546658

Conclusions

- Lack of specialised treatment options for severe OCD patients
- Robust evidence to support TMS and DBS therapy for difficult to treat and TR-OCD patients
- Transdiagnostic and theoretical evidence to support PAP for OCD
- Improved treatment approaches- standardised, multi-disciplinary and personalised therapy
- Advocate for greater access to care

Questions?

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NicAcevedo

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Featured work

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DBS: Connectome approach

Tractography surgical targeting [35]

Molecular Psychiatry

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ARTICLE

Check for updates

Tractography-based versus anatomical landmark-based targeting in vALIC deep brain stimulation for refractory obsessive-compulsive disorder

Ilse Graat[1✉], Roel J. T. Mocking[1], Luka C. Liebrand[1,2], Pepijn van den Munckhof[3], Maarten Bot[3], P. Rick Schuurman[3], Isidoor O. Bergfeld[1,4], Guido van Wingen[1,4] and Damiaan Denys[1]

Deep brain stimulation (DBS) of the ventral anterior limb of the internal capsule (vALIC) is effective for refractory obsessive-compulsive disorder (OCD). Retrospective evaluation showed that stimulation closer to the supero-lateral branch of the medial forebrain bundle (slMFB), within the vALIC, was associated with better response to DBS. The present study is the first to compare outcomes of DBS targeted at the vALIC using anatomical landmarks and DBS with connectomic tractography-based targeting of the slMFB. We included 20 OCD-patients with anatomical landmark-based DBS of the vALIC that were propensity score matched to 20 patients with tractography-based targeting of electrodes in the slMFB. After one year, we compared severity of OCD, anxiety and depression symptoms, response rates, time to response, number of parameter adjustments, average current, medication usage and stimulation-related adverse effects. There was no difference in Y-BOCS decrease between patients with anatomical landmark-based and tractography-based DBS. Nine (45%) patients with anatomical landmark-based DBS and 13 (65%) patients with tractography-based DBS were responders ($BF_{10} = 1.24$). The course of depression and anxiety symptoms, time to response, number of stimulation adjustments or medication usage did not differ between groups. Patients with tractography-based DBS experienced fewer stimulation-related adverse effects than patients with anatomical landmark-based DBS (38 vs 58 transient and 1 vs. 17 lasting adverse effects; $BF_{10} = 14.968$). OCD symptoms in patients with anatomical landmark-based DBS of the vALIC and tractography-based DBS of the slMFB decrease equally, but patients with tractography-based DBS experience less adverse effects.

Molecular Psychiatry; https://doi.org/10.1038/s41380-022-01760-y

Tractography targeting:

- 65% responders
- 3 hypomanic AEs

Conventional targeting

- 45% responders
- 11 hypomanic AEs

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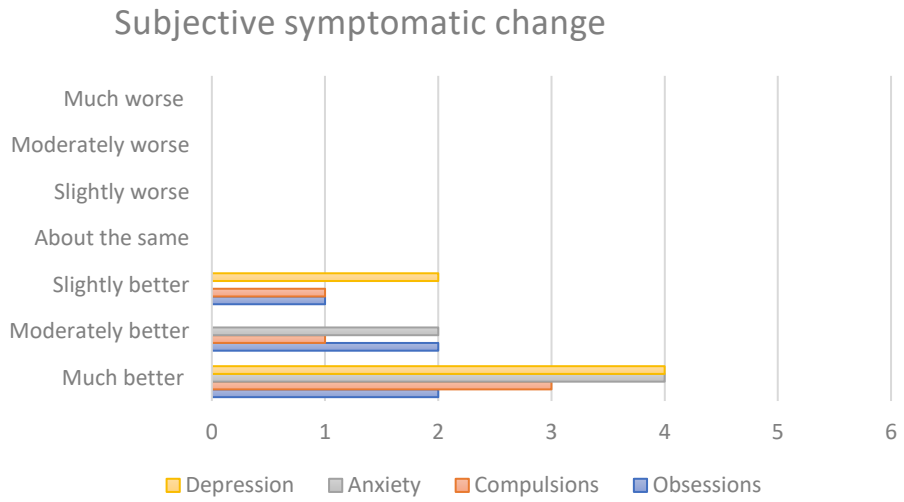
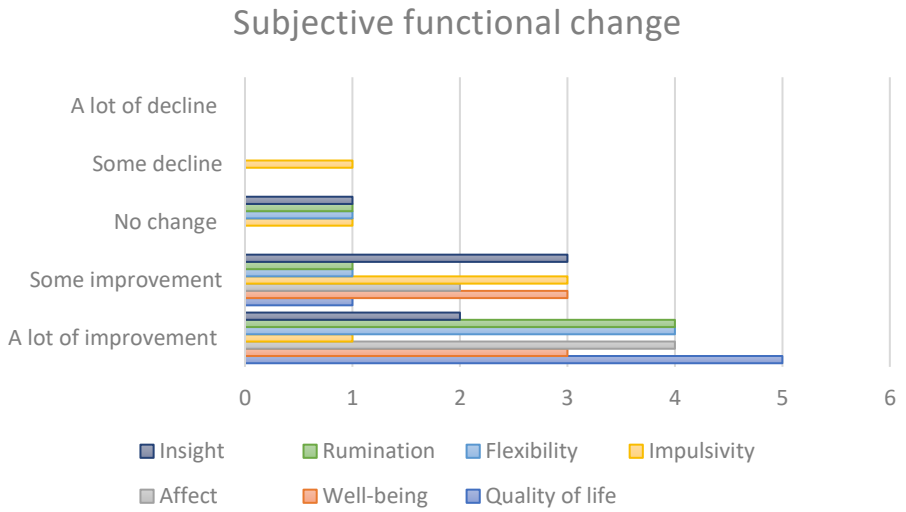
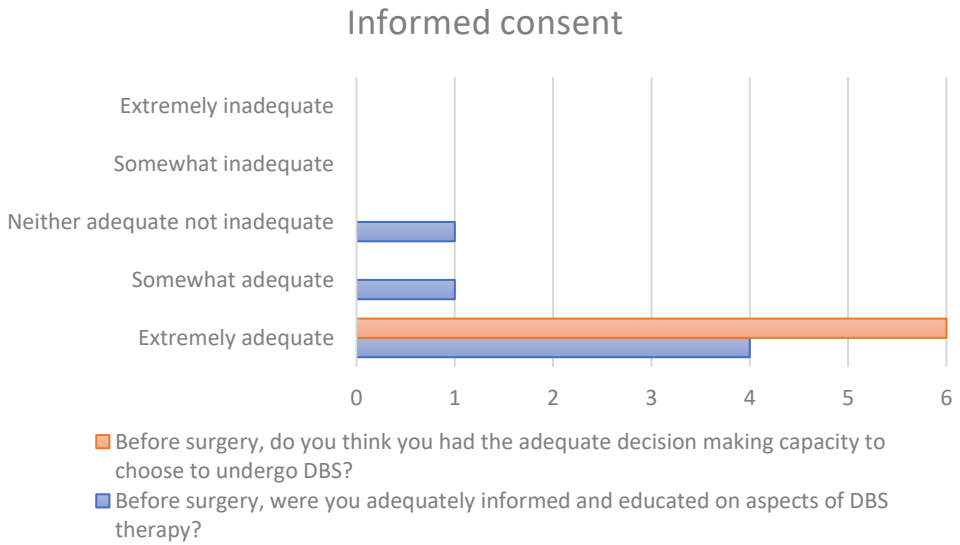
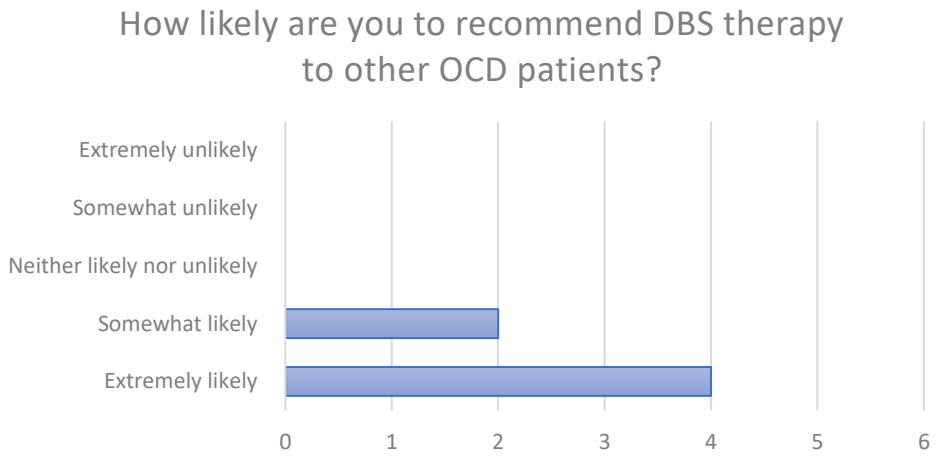
DBS: Lived experiences









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