DEEP BRAIN STIMULATION IN THE TREATMENT OF MAJOR DEPRESSIVE DISORDER & OBSESSIVE-COMPULSIVE DISORDER

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UMEÅ UNIVERSITY

DISCLOSURES

- None

CONTENTS

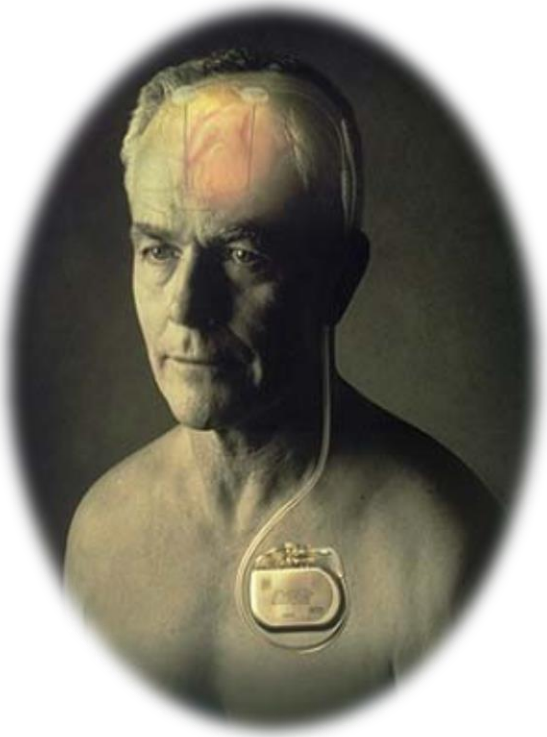
- **What is** deep brain stimulation (**DBS)**?
- **DBS** for **major depressive disorder** (MDD)
- **DBS for MDD** – Umeå experience
- **DBS** for **obsessive compulsive disorder** (OCD)
- **DBS for OCD** – Umeå research & experience
- Conclusion

DEEP BRAIN STIMULATION - DBS

- Neuropacemaker
- First modern DBS Parkinsons disorder 1987[1]
- Established treatment for movement

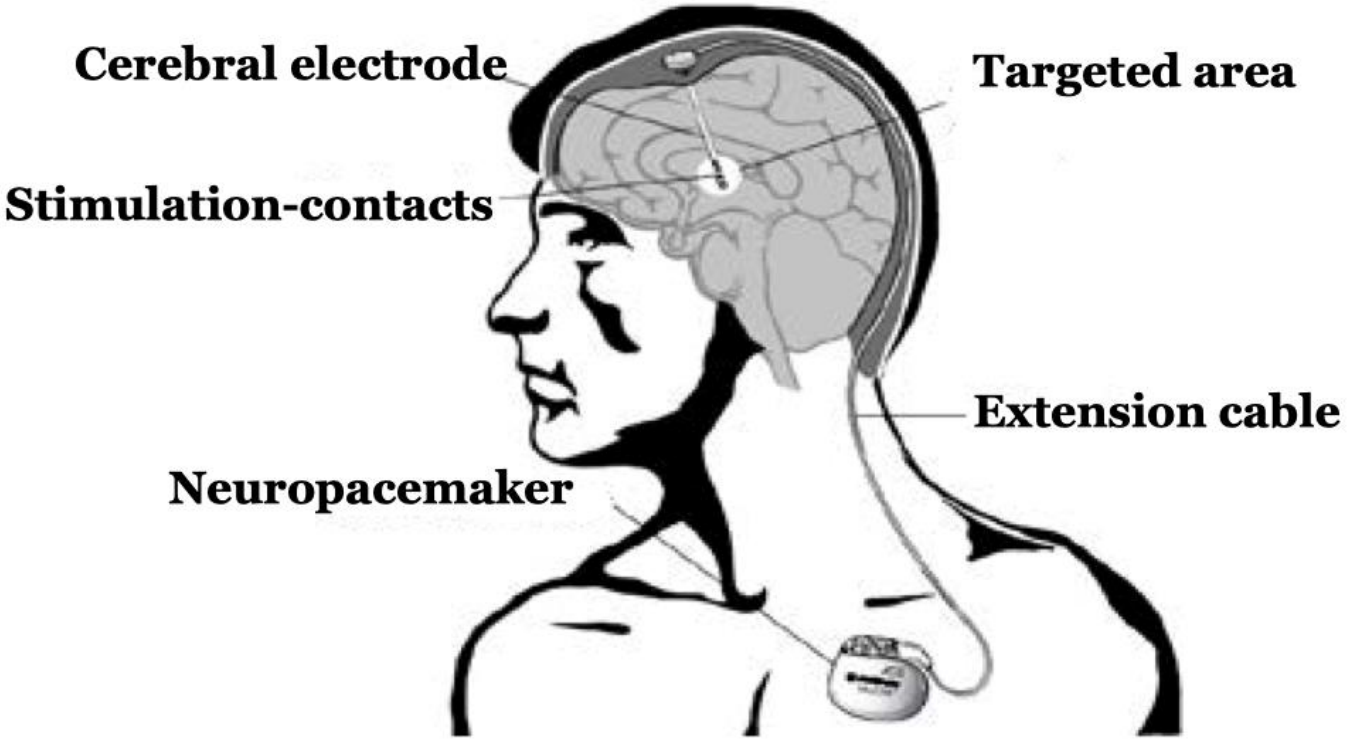
disorders (Parkinsons, essential tremor, dystonia)

- Psychiatric indications for DBS?

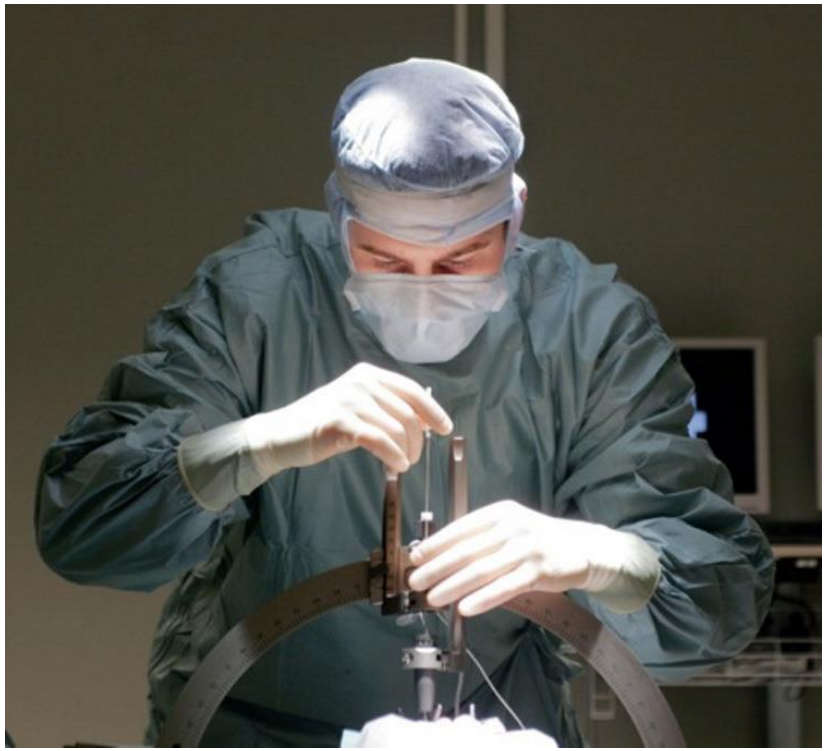


[1]Benabid et al. **Combined (thalamotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson disease**. Appl Neurophysiol. 1987

DBS SYSTEM


Cerebral electrode
Targeted area
Stimulation-contacts
Extension cable
Neuropacemaker

DBS SURGERY



https://youtu.be/JdRCk9U_qYE?t=262

DBS –SIDE EFFECTS

- Surgical related
  - Hemorrhage ~ 2%
  - Infection ~ 3%

- Stimulation induced
  - Varies depending on target
  - Reversible

Koh et al. **Estimating the Risk of Deep Brain Stimulation in the Modern Era: 2008 to 2020**. Oper Neurosurg. 2021

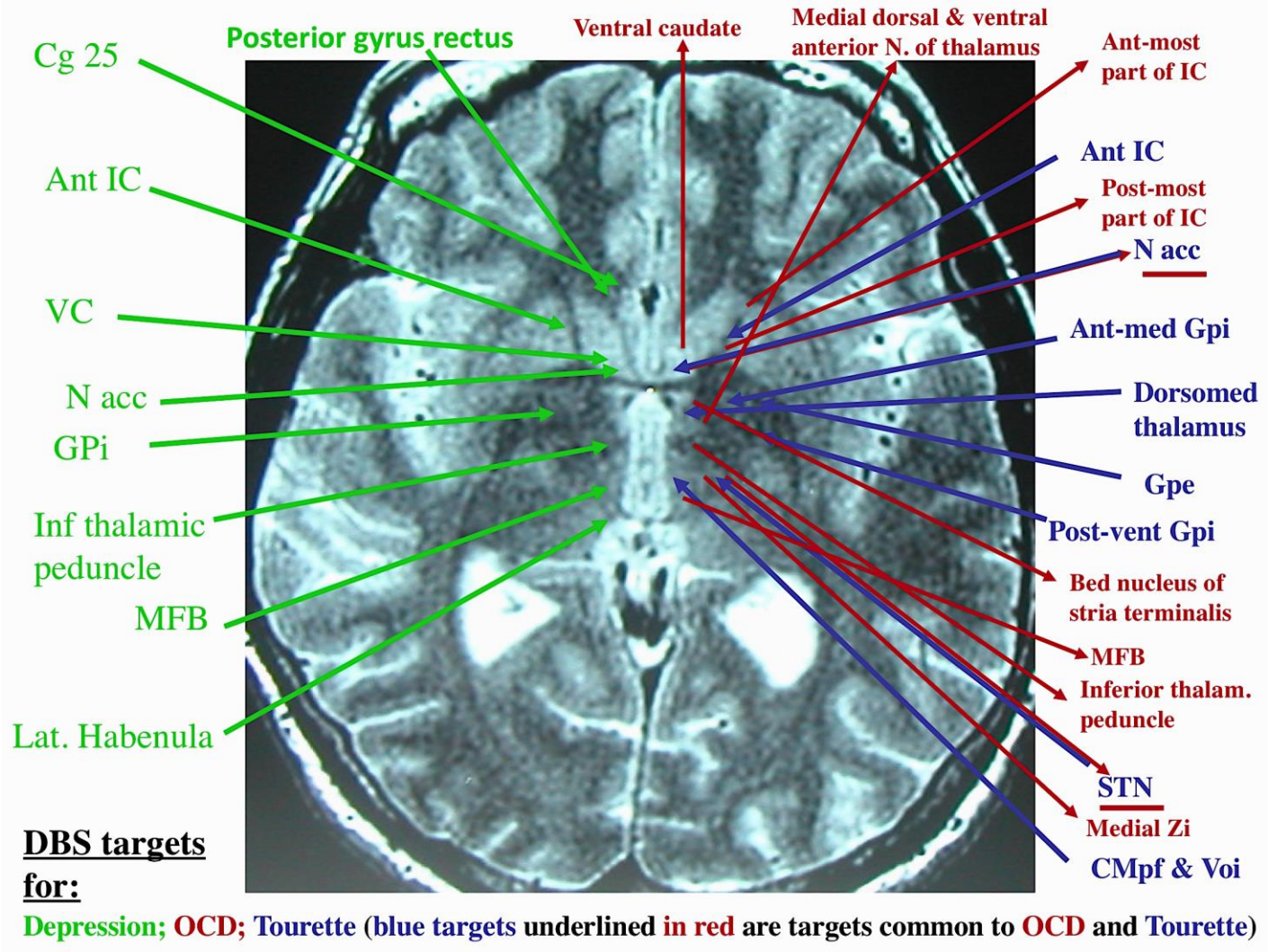


Image courtesy of professor Marwan Hariz

DBS FOR MDD – CURRENT RESEARCH

- First study Mayberg et al. 2005
- Numerous open-label & smaller studies
- Several different brain targets under investigation

➢ *Ventral capsule/ventral striatum (**VC/VS**) (1 positive, 1 negative RCT)*
➢ *Subcallosal cingulate/SC25 (2 positive, 3 negative RCTs)*
➢ *Medial forebrain bundle (**MFB**) (2 positive RCTs)*

Kisely,. **A systematic review and meta-analysis of deep brain stimulation for depression**. *Depress Anxiety*. 2018

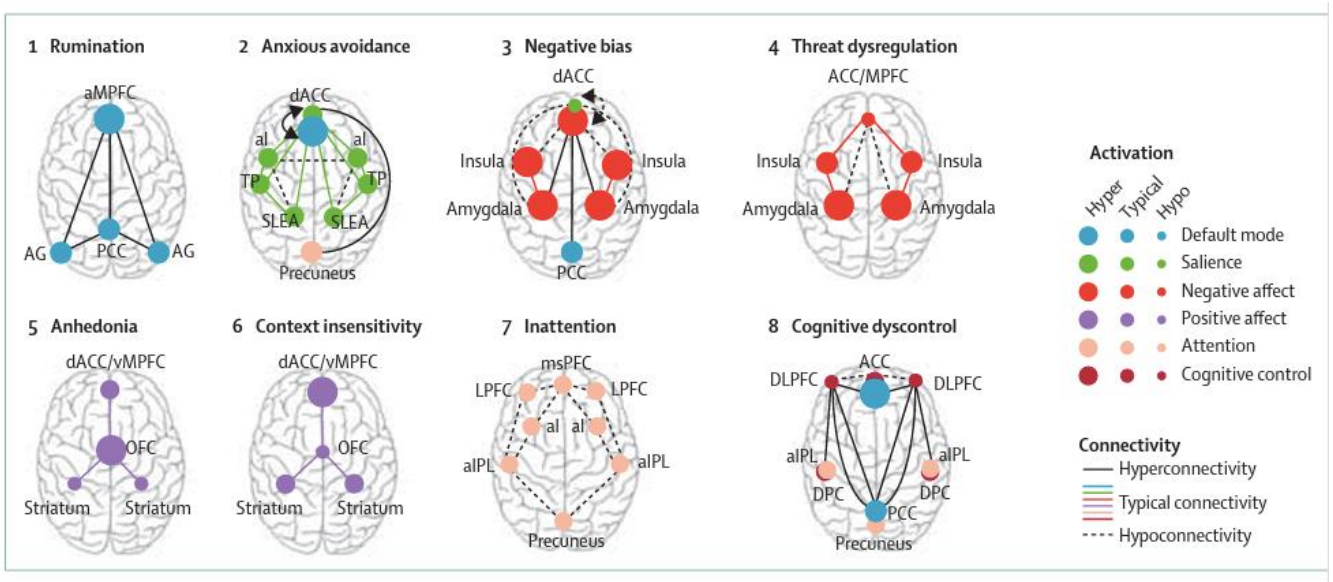
DBS FOR MDD– CURRENT RESEARCH

- Various methodology in the RCTs making them hard to compare
- Longer sham periods favored positive outcome for DBS
- Heterogeneous disorder & patients
- Lack of predictors of response

Kisely,. **A systematic review and meta-analysis of deep brain stimulation for depression**. *Depress Anxiety*. 2018

DBS FOR MDD – FUTURE RESEARCH

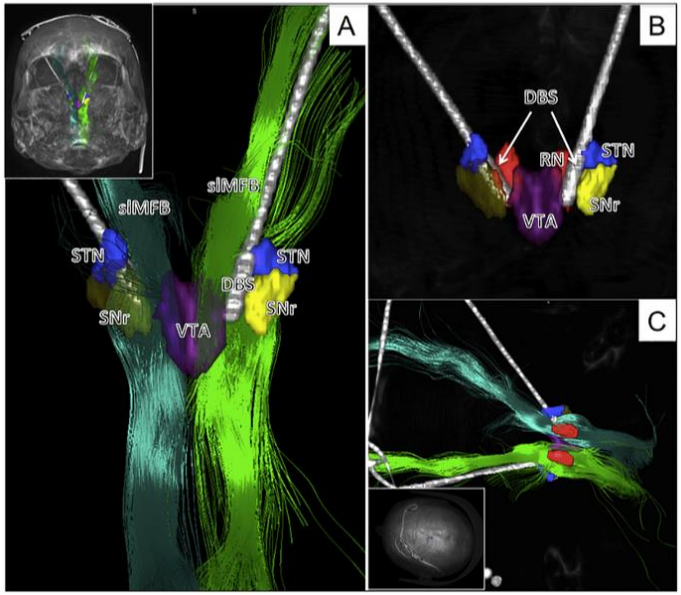
- RCTs with longer sham/active phase
- Network based approach to MDD



Williams **Precision psychiatry: a neural circuit taxonomy for depression and anxiety**. Lancet Psychiatry. 2016

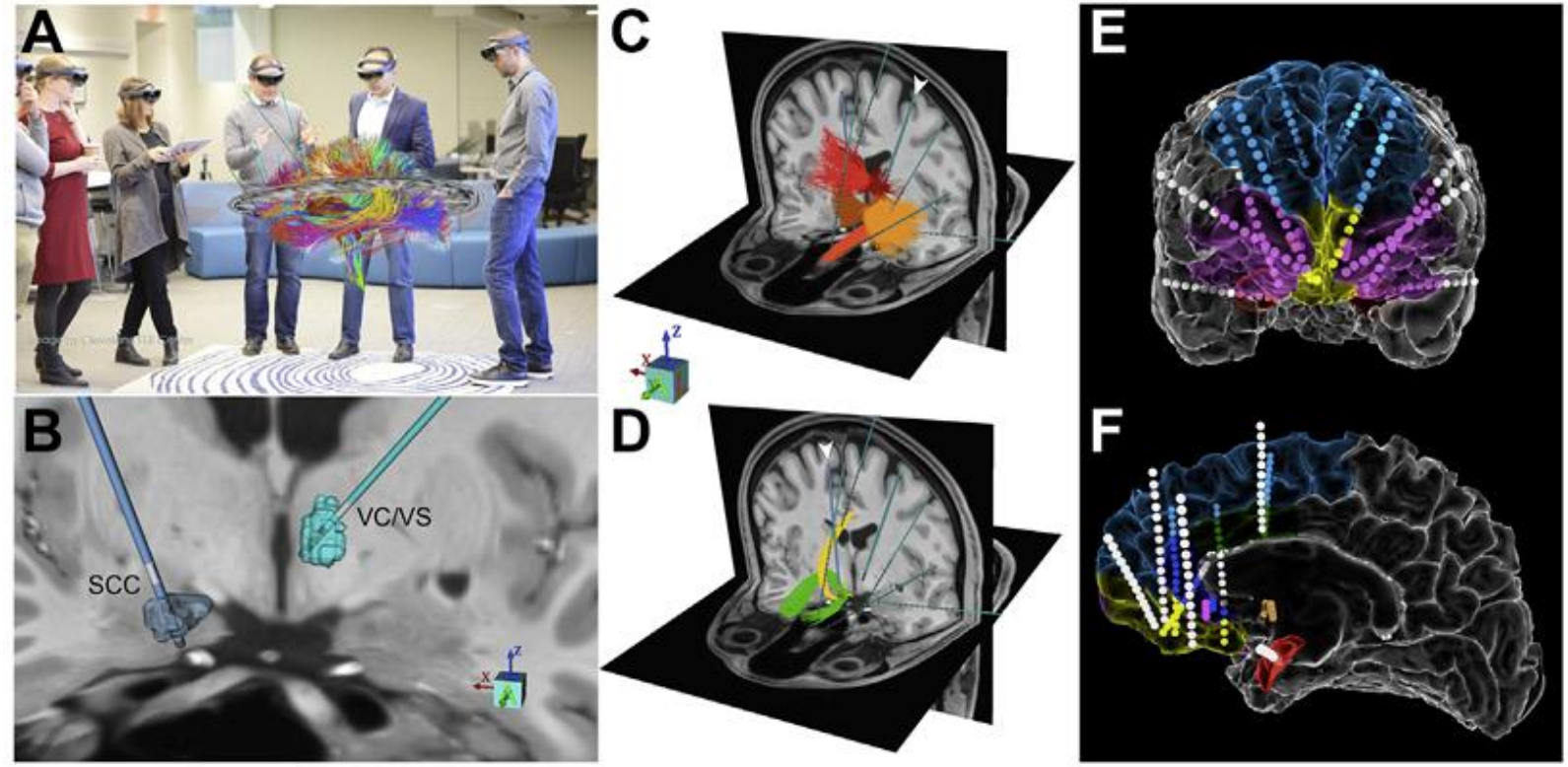
DBS FOR MDD – FUTURE RESEARCH

- Patient selection based on imaging (fMRI, sEEG, tractography, PET)?
- Target selection based on symptoms/imaging?



Coenen et al**. Tractography-assisted deep brain stimulation of the superolateral branch of the medial forebrain bundle (slMFB DBS) in major depression**. Neuroimage Clin. 2018

DBS FOR MDD – FUTURE RESEARCH



Sheth et al. **Deep Brain Stimulation for Depression Informed by Intracranial Recordings**. Biol Psychiatry. 2021

DBS FOR MDD – UMEÅ EXPERIENCE

- Pilot-study start **2013**
- Department of Psychiatry & Unit for DBS, Umeå University Hospital
- National intake

DBS FOR MDD – UMEÅ EXPERIENCE

- Age: 18-65
- Severe and **therapy-ressistant MDD** diagnosed according to the criteria in DSM-IV
- Symptom >1 years
- The patient suffering from substantial **incapacity** because of his/hers symptoms
- **HDRS-17 ≥ 20**
- No significant improvemet of MDD symptoms from **> 4** established **treatments**:
  - Pharmacotherapy
  - Psychotherapy
  - ECT
- No co-comittant substance abuse or severe psychiatric disorder that can impact the evaluation
- No contraindications for surgery

DBS FOR MDD – UMEÅ EXPERIENCE

- **Target of ≥10 patients**
- **Operated 2013-2018:**

➢ 5 patients

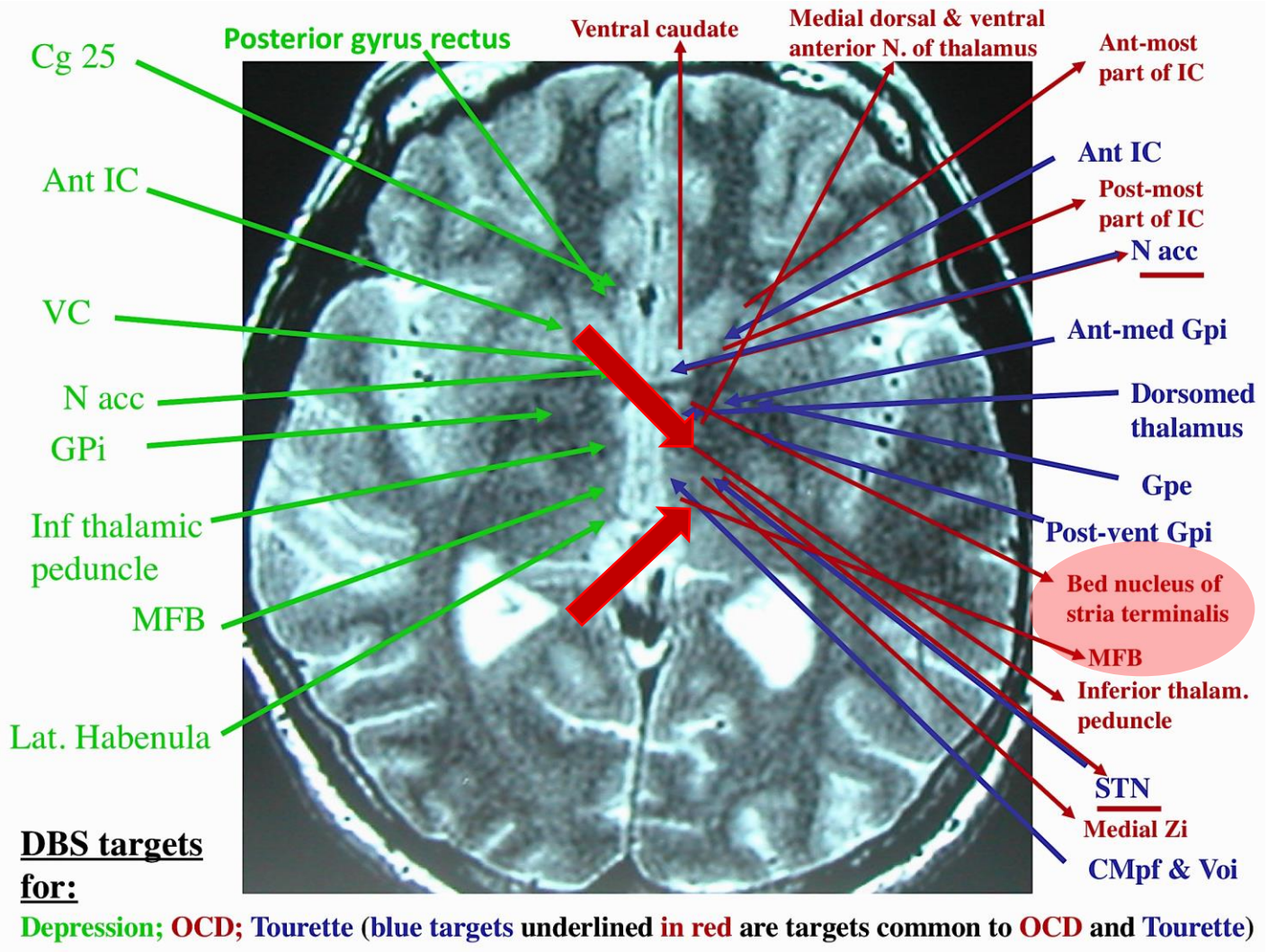
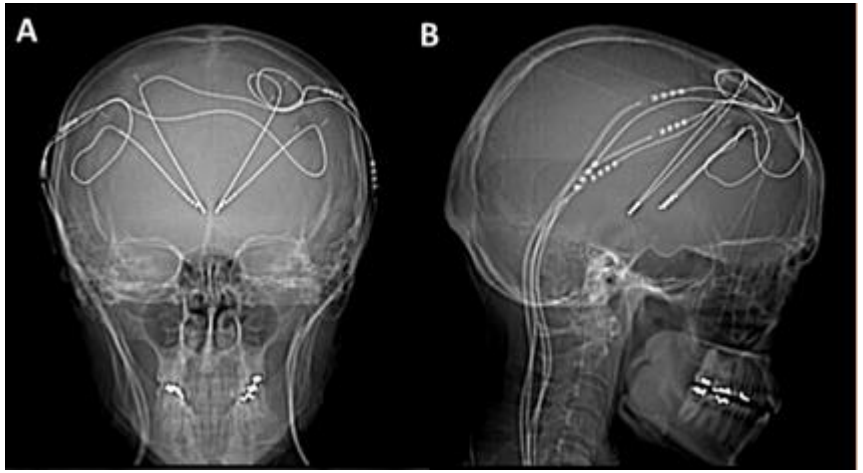


Image courtesy of professor Marwan Hariz

DBS FOR MDD – UMEÅ EXPERIENCE

- **1** patient only **MFB** target (+ bed nucleus of stria terminalis (**BNST**) 2015)
- **2** patients **MFB & BNST** target
- **2** patients **BNST** only



DBS FOR MDD – UMEÅ EXPERIENCE

Patient no.	MADRS PRE	MADRS 1 YR DBS	MADRS % reduction	Comorbidity
1 MFB (+BNST)	43	33	23%	Anorexia nervosa
2 MFB/BNST	44	27	39%**	GAD
3 MFB/BNST	49	34	31%*	GAD
4 BNST	33	16	52%**	GAD
5 BNST	35	35	0%	Anorexia nervosa

MADRS: Montgomery Asberg depression rating scale, **responder decrease

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DBS FOR MDD – UMEÅ EXPERIENCE

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BNST	35	35	0%	nervosa

MADRS: Montgomery Asberg depression rating scale

Clin Case Rep. 2017 Mar 31;5(5):679-684. doi: 10.1002/ccr3.856. eCollection 2017 May.

Deep brain stimulation in the bed nucleus of the stria terminalis and medial forebrain bundle in a patient with major depressive disorder and anorexia nervosa.

Blomstedt P[1], Naesström M[2], Bodlund O[2].

DBS FOR OCD – CURRENT RESEARCH

- First study Nuttin et al. 1999
- Numerous uncontrolled & smaller studies
- Several different brain targets under investigation
  - ➢ *Nucleus accumbens/anterior limb of internal capsule (1 positive blinded-RCT)*
  - ➢ *BNST (2 positive blinded-RCT)*

Wu et al. **Deep brain stimulation for refractory obsessive-compulsive disorder (OCD): emerging or established therapy**? Mol Psychiatry. 2021

Visser-Vandewalle et al. **Deep brain stimulation for obsessive-compulsive disorder: a crisis of access.** Nature 2022

Bed nucleus of the stria terminalis

Compensative study of the effects of electrical stimulation in the nucleus accumbens, the mediodorsal thalamic nucleus and the bed nucleus of the stria terminalis in rats with schedule-induced polydipsia

Targeting Bed Nucleus of the Stria Terminalis for Severe Obsessive-Compulsive Disorder: More Unexpected Lead Placement in Obsessive-Compulsive Disorder than in Surgery for Movement Disorders

Molecular Psychiatry (2016) 21, 1272–1280
www.nature.com/mp

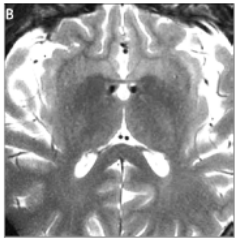
OPEN

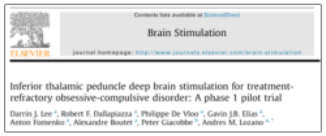
ORIGINAL ARTICLE

Electrical stimulation in the bed nucleus of the stria terminalis alleviates severe obsessive-compulsive disorder

L Luyten[1,2], S Hendrickx[1], S Raymaekers[3], L Gabriëls[4,5] and B Nuttin[1,5,6]

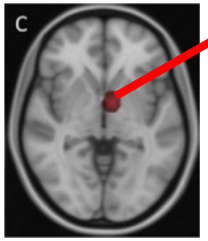
More anterior ITP



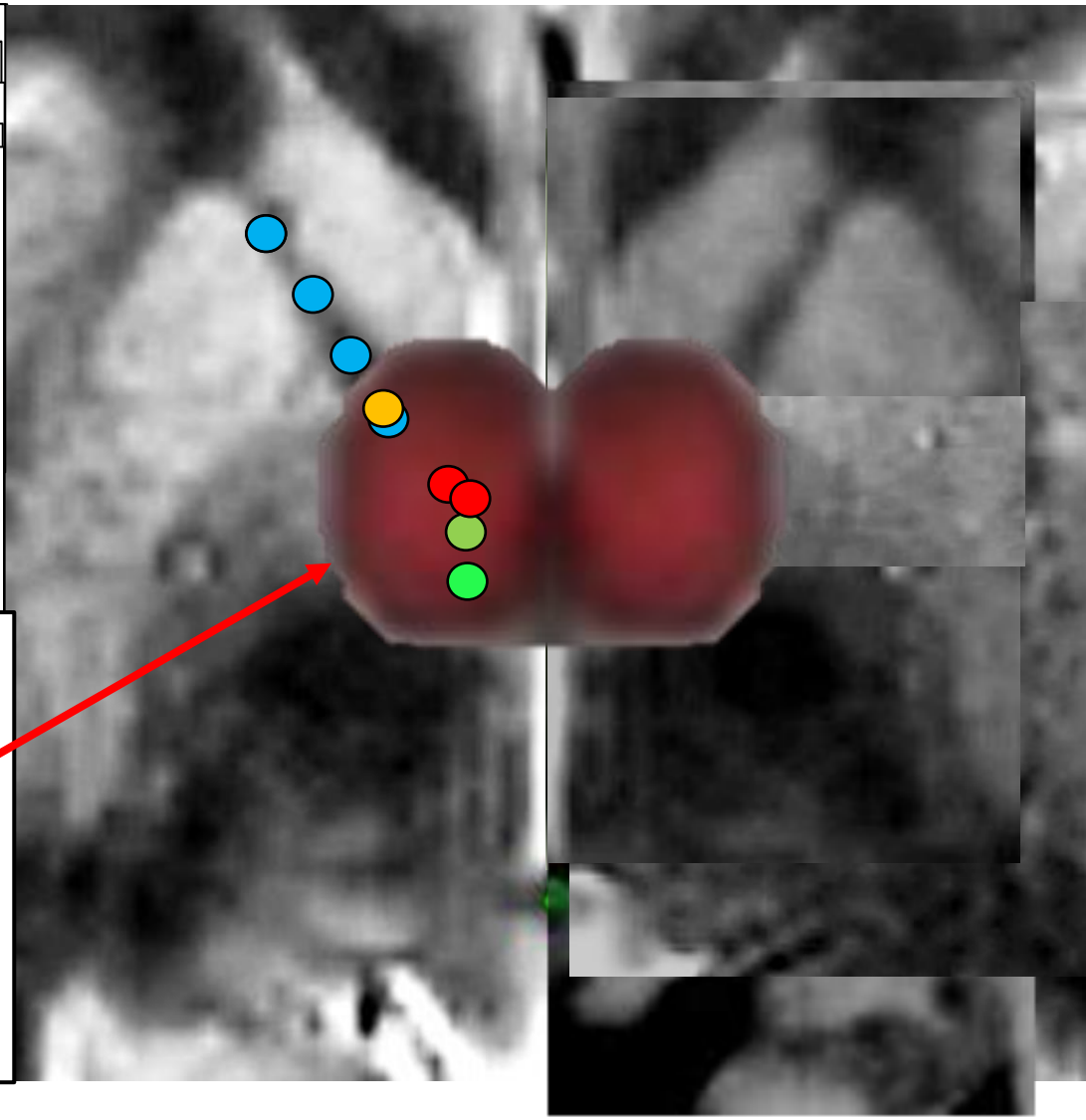


Brain Stimulation

Inferior thalamic peduncle deep brain stimulation for treatment-refractory obsessive-compulsive disorder: A phase 1 pilot trial



52% improvement in 5 patients with ITP DBS
Target 2 mm more anterior than Velasco



LIMBIC STN & MFB

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Subthalamic Nucleus Stimulation in Severe Obsessive–Compulsive Disorder

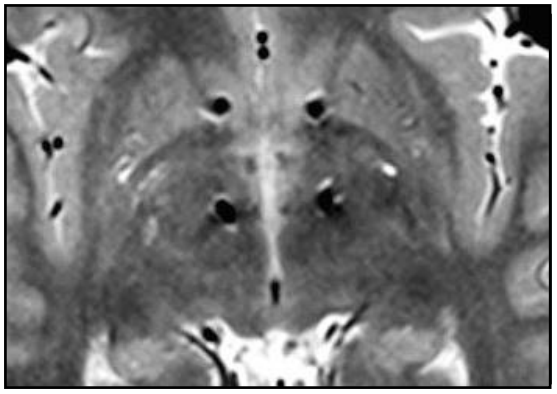
41 % improvement in 17 patients with STN DBS, but only 3 months of active stimulation

Archival Report

Biological Psychiatry

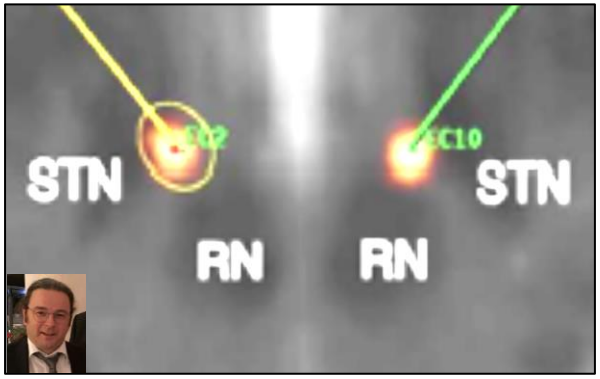
A Randomized Trial Directly Comparing Ventral Capsule and Anteromedial Subthalamic Nucleus Stimulation in Obsessive-Compulsive Disorder: Clinical and Imaging Evidence for Dissociable Effects

Himanshu Tyagi, Annemieke M. Apergis-Schoute, Harith Akram, Tom Foltynie, Patricia Limousin, Lynne M. Drummond, Naomi A. Fineberg, Keith Matthews, Marjan Jahanshahi, Trevor W. Robbins, Barbara J. Sahakian, Ludvic Zrinzo, Marwan Hariz, and Eileen M. Joyce



The medial forebrain bundle as a target for deep brain stimulation for obsessive-compulsive disorder

Volker A. Coenen,[1] Thomas E. Schlaepfer,[2] Peter Goll,[3] Peter C. Reinacher,[1] Ulrich Voderholzer,[4] Ludger Tebartz van Elst,[3] Horst Urbach,[5] and Tobias Freyer[3]*



Is there any real diference in the actual location of these electrodes in the ”limic STN” and ”MFB”, respectively ???

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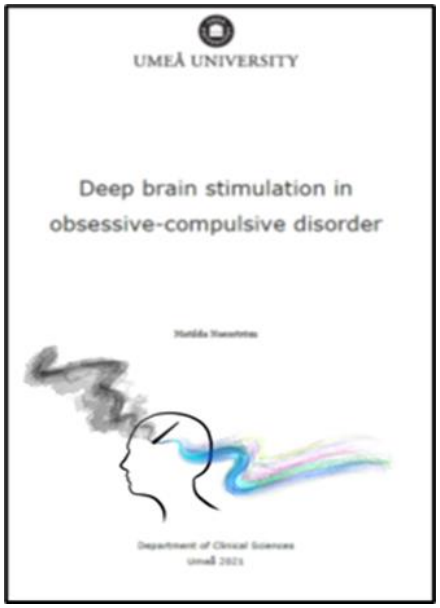
DBS FOR OCD – FUTURE RESEARCH

- Patient selection based on imaging?
- Larger RCT studies
- Long-term follow-up results
- Other outcome measures than Y-BOCS (e.g. quality of life)
- Qualitative studies

DBS FOR OCD – UMEÅ EXPERIENCE

- What is the **effect** of DBS in the BNST on OCD symptoms?
- What are the potential **side-effects** of DBS in the BNST?
- Which areas of the brain are affected by stimulation in the BNST?
- What is the mechanism of action of BNST DBS in OCD?
- What is the knowledge and attitudes towards DBS in OCD among psychiatrists, CBT psychotherapists and patients with OCD?



DBS FOR OCD – PILOT STUDY UMEÅ

Inclusion criteria

- Diagnosis of OCD DSM-IV
- YBOCS ≥ 25
- Disease duration ≥ 5 years
- ≥ 3 different serotonergic antidepressants + antipsychotic
- CBT


ORIGINAL ARTICLE

Check for updates

Deep Brain Stimulation in the Bed Nucleus of Stria Terminalis in Obsessive-Compulsive Disorder—1-Year Follow-up

Matilda Naesström[1], Marwan Hariz[2,3], Lotta Strömsten[1], Owe Bodlund[1], Patric Blomstedt[2]

Exclusion criteria

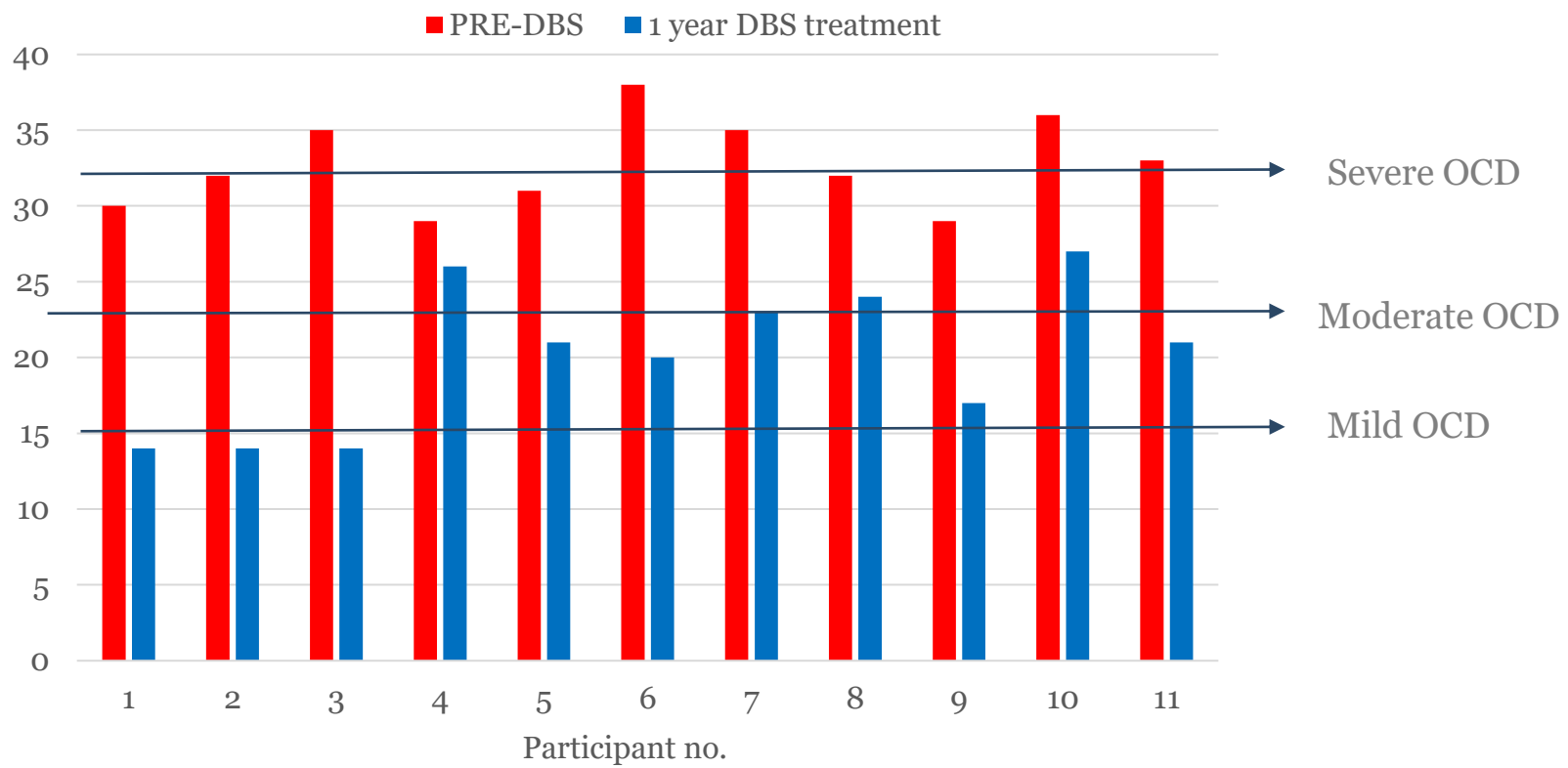
- Severe psychiatric comorbidity affecting consent or follow-up
- Contraindications to surgery or anesthesia

DBS FOR OCD – PILOT STUDY UMEÅ

Participants

- 11 participants completed 1-year follow-up
- 7 females, 4 males
- Mean age of onset OCD 17 ±14
- Mean age at surgery 38±14
- Mean YBOCS score 33±3.0 (range 29-38)
- Asperger syndrome, atypical autism, ADHD, Bipolar II

DBS FOR OCD – PILOT STUDY UMEÅ



- Mean YBOCS score reduced from **33**±3.0 (range 29-38) to **20**±4.8 (range 14-27)
- Mean reduction of YBOCS **38%** (range 10-60%)
- 6/11 responders, 4/11 partial responders, 1/11 non-responder

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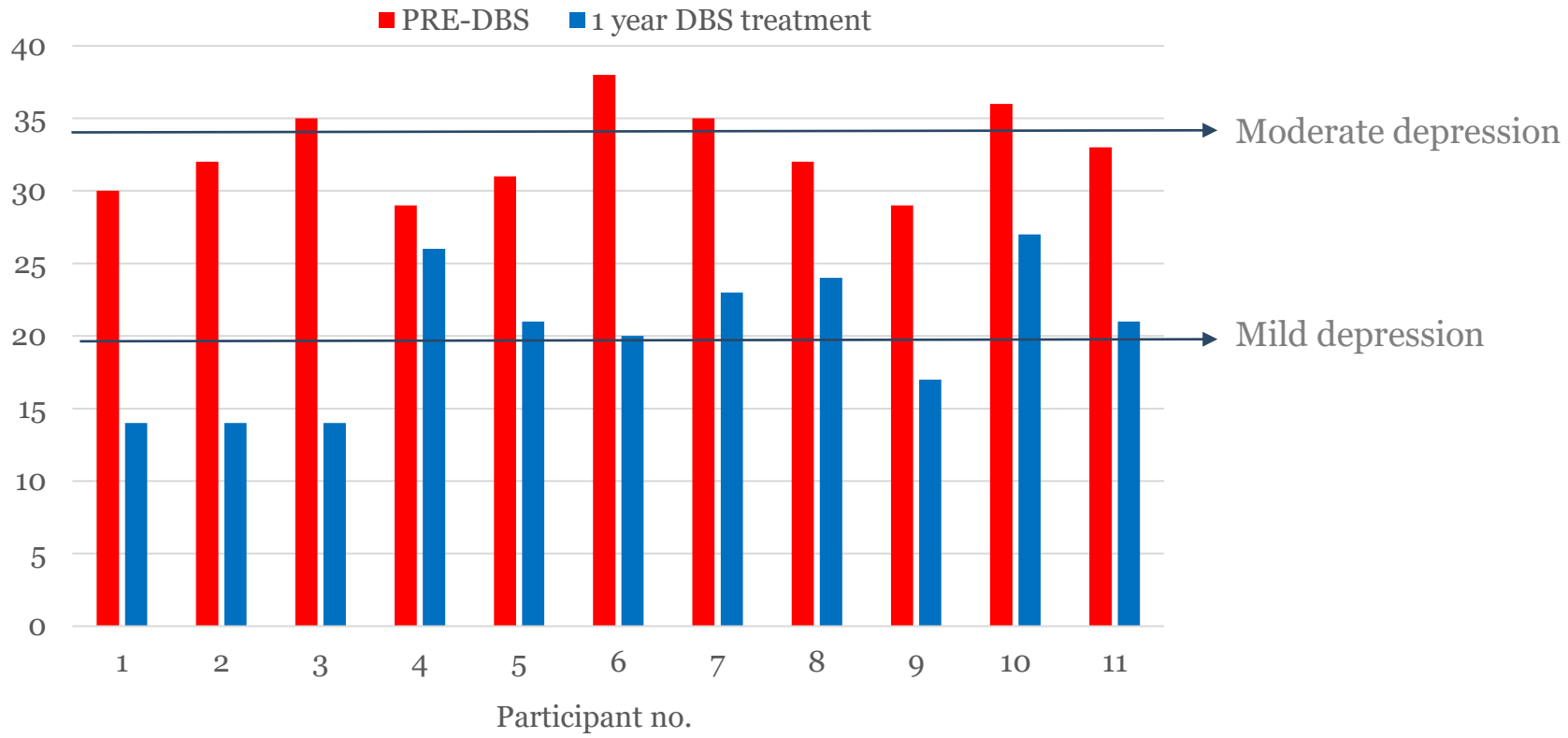
DBS FOR OCD – PILOT STUDY UMEÅ



- Mean MADRS score reduced from **29**±4.5 (range 22-37) to **21**±5.8 (range 9-32)
- Mean reduction of MADRS **27%** (range 4-74%)

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DBS FOR OCD – PILOT STUDY UMEÅ

Adverse events:

- 1 case unrelated trauma: skin infection & re-implantation

- Anxiety & insomnia most common stimulation-induced side-effect during programming sessions

- 2 cases of transient symptoms of hypomania

Deep Brain Stimulation in the Bed Nucleus of Stria Terminalis in Obsessive-Compulsive Disorder—1-Year Follow-up

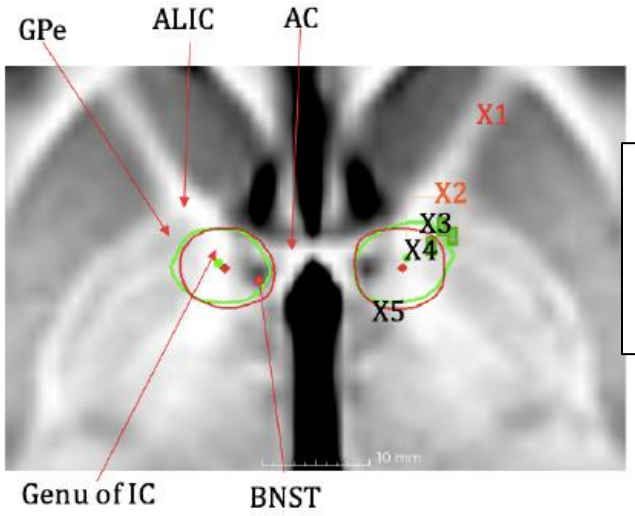
Matilda Naesström[1], Marwan Hariz[2,3], Lotta Strömsten[1], Owe Bodlund[1], Patric Blomstedt[2]

- Mean YBOCS score reduced from **33**±3.0 (range 29-38) to **20**±4.8 (range 14-27)
- Mean reduction of YBOCS **38%** (range 10-60%)
- 6/11 responders, 4/11 partial responders, 1/11 non-responder

Author	No. partic-pants	Target	Response rate	Mean YBOCS reduction	Stimulation related mostly transient adverse events
Greenberg et al. 2006	10	VC/VS	40%	36%	Transient hypomanic symptoms, anxiety, recurring brief memory experiences (flashbacks)
Mallet et al. 2008	16	STN	75%	32%	Transient hypomania, anxiety, dyskinesia with impulsivity, facial asymmetry, dysarthria, dysphagia and walking difficulties
Greenberg et al 2010	26	VC/VS	62%	39%	Transiently increased depression/suicidal ideation, hypomania, recurring brief memory experiences (flashbacks)
Huff et al. 2010	10	NA	10%	21%	Transient hypomania, anxiety, agitation, concentration/memory difficulties, suicidal ideation, headaches, reduced sleep duration, weight gain <5 kg
Luyten et al. 2016	24	ALIC/ BNST	71%	45%	Problems with memory, disinhibition, increased assertiveness, logorrhea, hyperactivity, hypomania, confusion, paresthesia/pain/twitches in the lower facial area, decreased libido, increased libido, ejaculation & erection problems, diarrhoea, slow gastric emptying, fatigue, cough
Menchon et al 2019	30	ALIC	60%	42%	Anxiety, worsening of affective symptoms, seizures, dissociation, dyskinesia, abnormal behaviour, urinary incontinence, nausea, delirium, irritability, weight decrease, headache, sensory disturbances, insomnia, asthenia, muscular pain
Denys et al. 2020	70	ALIC	52%	40%	Hypomania, restlessness, confusion, agitation, impulsivity, disinhibition, sleep disorder, fatigue, panic attacks, subjective concentration and memory problems, dizziness, balance problems, weight gain or weight loss, worsening of affective symptoms

Image courtesy of prof. Patric Blomstedt

WHAT ARE WE STIMULATING?



Acta Neurochirurgica
https://doi.org/10.1007/s00701-021-04991-0

ORIGINAL ARTICLE - FUNCTIONAL NEUROSURGERY - OTHER

Distribution of electric field in patients with obsessive compulsive disorder treated with deep brain stimulation of the bed nucleus of stria terminalis

Matilda Naesström[1] · Johannes Johansson[2] · Marwan Hariz[3,4] · Owe Bodlund[1] · Karin Wårdell[2] · Patric Blomstedt[3]

Fig 10. Anatomical target overview.

Light green circle: mean volume of tissue activated with mean voltage in responders

Dark red circle: mean volume of tissue activated with mean voltage in non-responders

Green dot: the mean electrode localisation for responders

Red diamond: the mean electrode localisation for non-responders

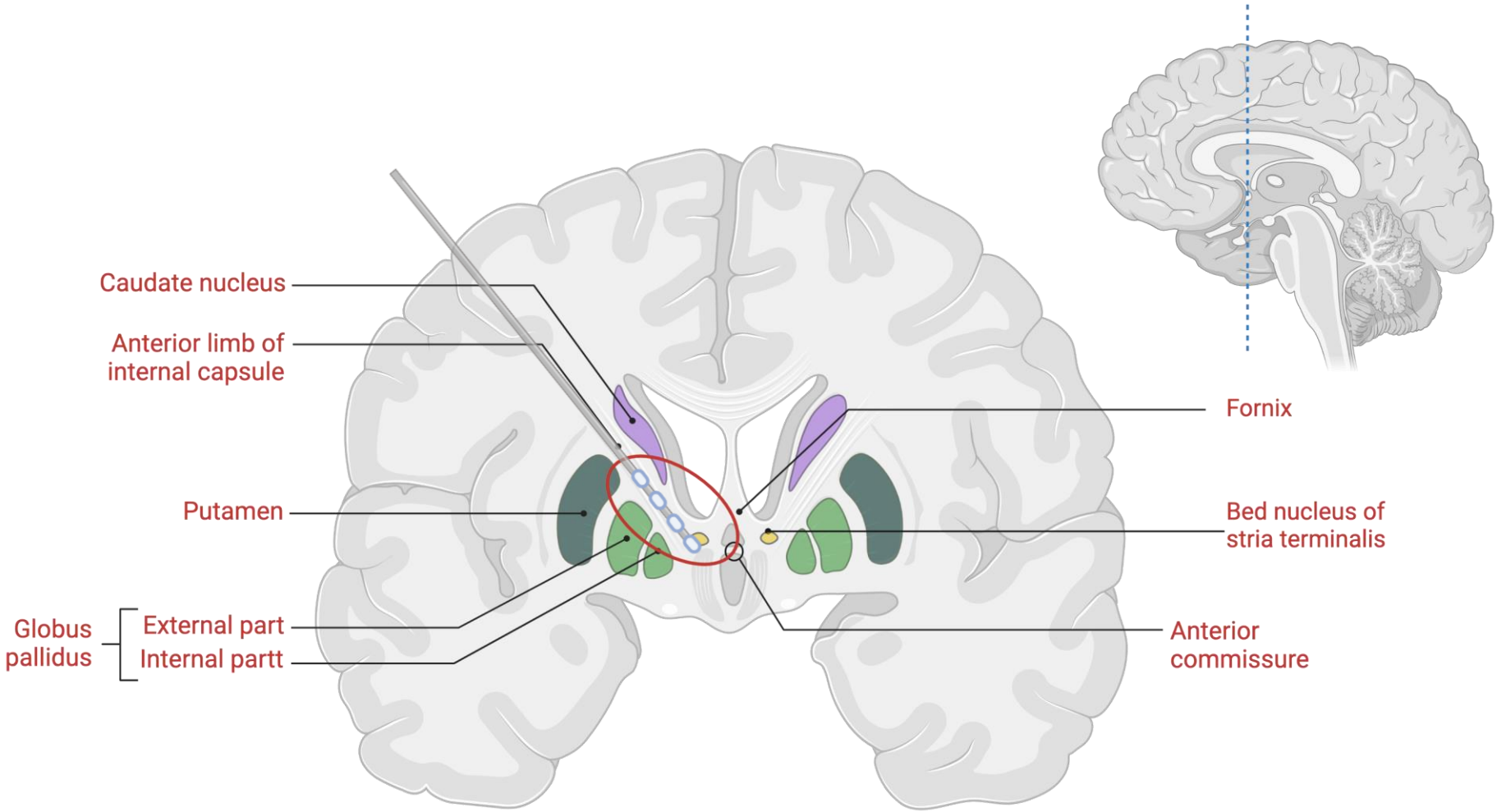
Dark green voxels: linear regression analysis between the electrical field over 0.2 V/mm and clinical effect of YBOCS ($p < 0.05$).

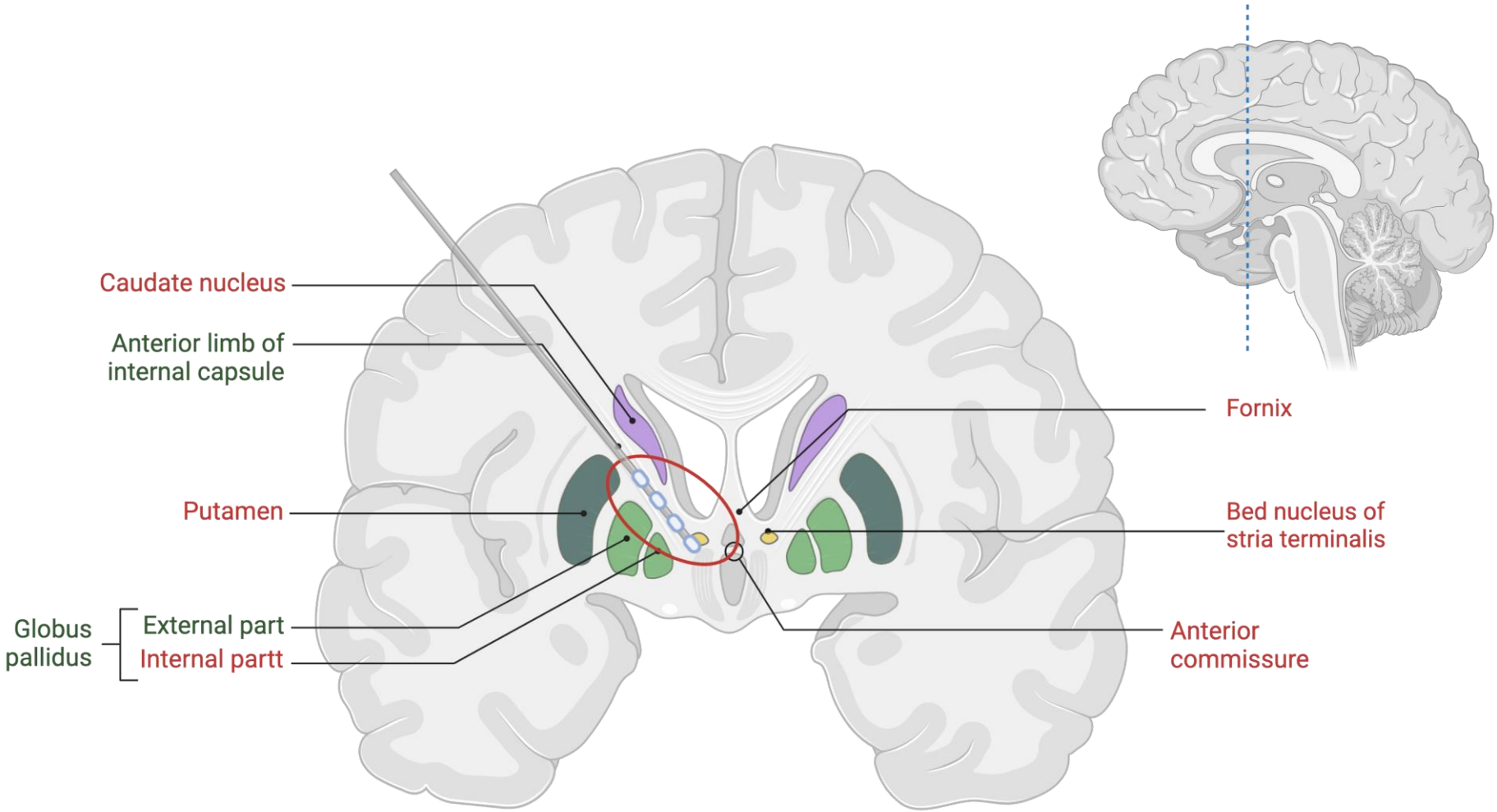
X1 and X2: estimation of the anterior targets described by Greenberg et al. 2010.[84]

X3 and X4: estimation of the more posterior targets with best clinical effect described by Greenberg et al. 2010.[84]

X5: estimation of the ITP target described by Jimenez-Ponce et al. 2009.[91]

AC= anterior commissure, ALIC = anterior limb of internal capsule, BNST = bed nucleus of stria terminalis, GPe= globus pallidus externa, IC= internal capsule


Caudate nucleus
Anterior limb of internal capsule
Putamen
Globus pallidus
External part
Internal partt
Fornix
Bed nucleus of stria terminalis
Anterior commissure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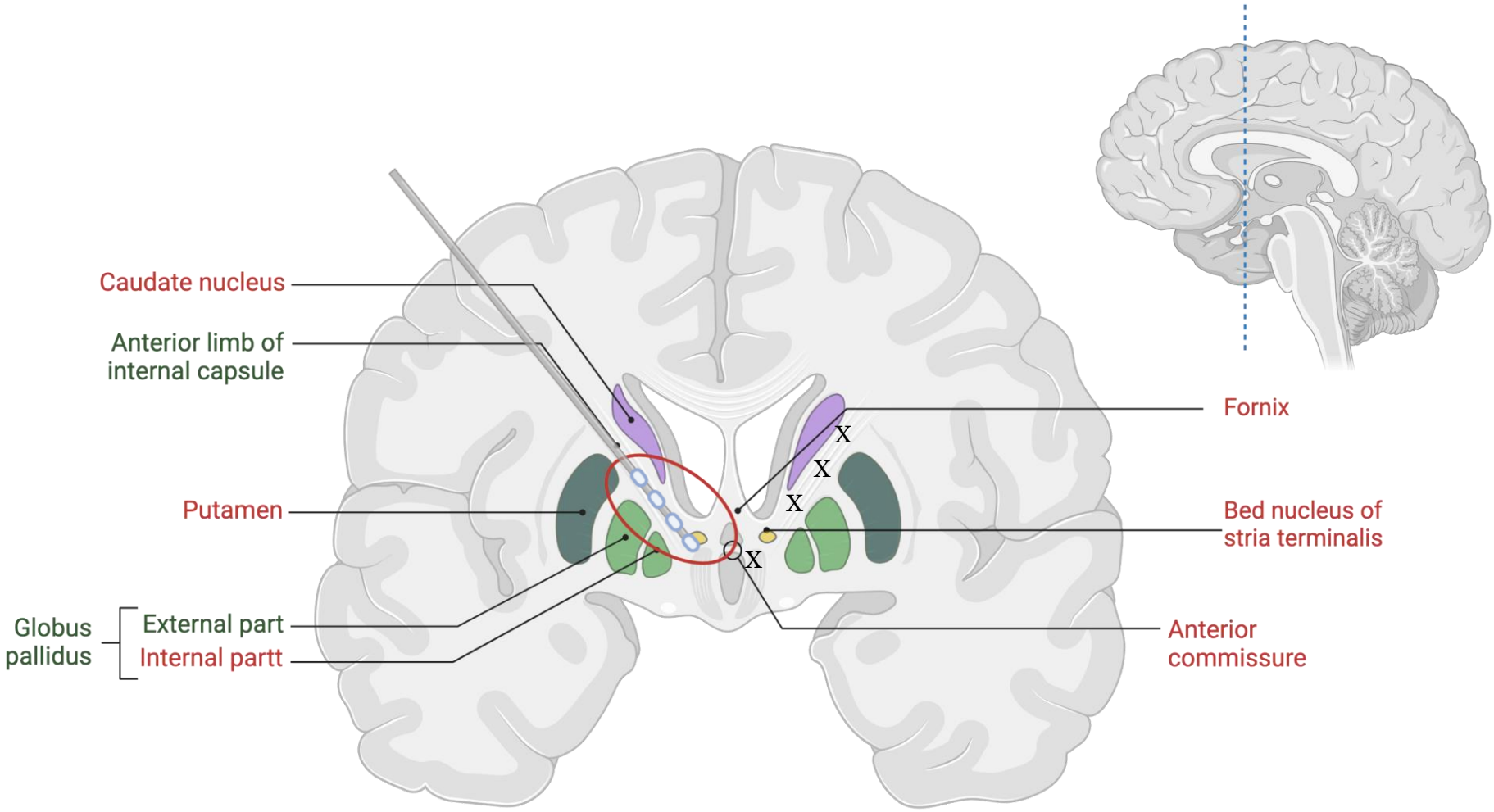

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DBS FOR OCD – PILOT STUDY UMEÅ

- Similar individual fields of stimulation at 12- and 24-months follow-up
- Mainly involving anterior limb and genu of the internal capsule, BNST, fornix, anteromedial globus pallidus externa (GPe) and the anterior commissure
- Correlation between YBOCS reduction at 12-months in the ventral ALIC and anteromedial GPe
- Perhaps DBS in these regions may be considered to be stimulation of same target?

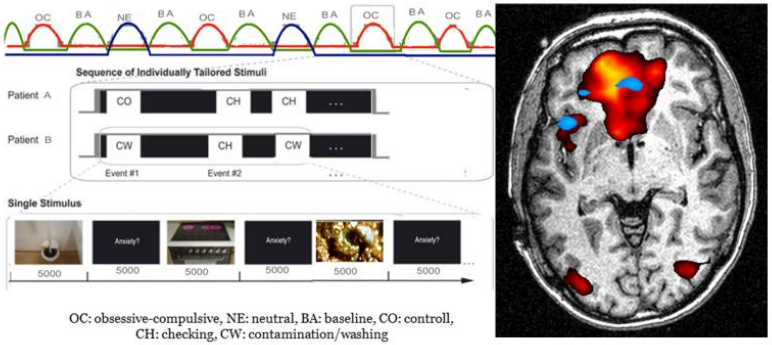
Functional MRI Evaluation of Deep Brain Stimulation of Bed Nucleus of Stria Terminalis in Obsessive-Compulsive Disorder

-

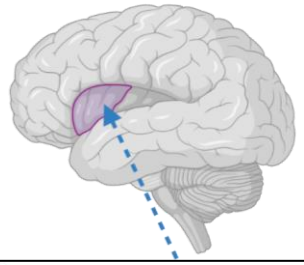
Functional MRI in deep brain stimulation in obsessive-compulsive disorder

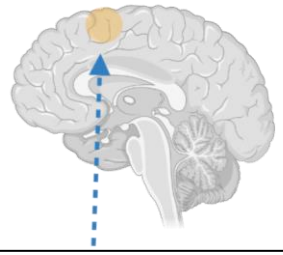
*Matilda Naesström M.D[1], Johan Eriksson Ph.D[2,3], Patric Blomstedt M.D

fMRI



OC: obsessive-compulsive, NE: neutral, BA: baseline, CO: controll, CH: checking, CW: contamination/washing





Neurosurgery

OPEN ACCESS

Review

Defining functional brain networks underlying obsessive–compulsive disorder (OCD) using treatment-induced neuroimaging changes: a systematic review of the literature

Kelly R. Bijanki [1], Yagna J. Pathak,[2] Ricardo A. Najera,[1] Eric A. Storch,[3] Wayne K Goodman,[3] H. Blair Simpson,[4] Sameer A. Sheth[1]

Bijanki KR, *et al*. *J Neurol Neurosurg Psychiatry* 2021;**92**:776–786. doi:10.1136/jnnp-2020-324478

CONCLUSION

Several regions within and outside CSTC circuits have shown consistent patterns of change following effective OCD treatment. Within the CSTC, the caudate, OFC, PFC, ACC and thalamus all demonstrated decreases in metabolism and perfusion after successful treatment with medications, CBT, stereotactic lesions or DBS.

perhaps the best framing of the problem would be as a need to 'tune' the CSTC circuit, rather than to increase or decrease activity en masse.

DEEP BRAIN STIMULATION IN OBSESSIVE-COMPULSIVE DISORDER

Matilda Naesström

UMEÅ UNIVERSITY

UMEÅ UNIVERSITY

DBS FOR OCD – UMEÅ EXPERIENCE UNPUBLISHED

- Effects on cognition
- Effects on personality
- Long-term data on Y-BOCS effects

DBS FOR OCD UMEÅ – EFFECTS ON COGNITION ONE YEAR AFTER SURGERY

- 8/11 participants from the BNST DBS OCD pilot
- 5 females, 3 males
- Neuropsychological assessment verbal & spatial memory, executive function & attention
- Preoperatively & 12 months postoperatively

Johanna Philipson, neuropsychologist & PhD student
Department of Clinical Sciences/Neurosciences

DBS FOR OCD UMEÅ – EFFECTS ON COGNITION ONE YEAR AFTER SURGERY

- Mean **age** at surgery **36**±15 years
- Average **12**±2 years of **education**
- Assessment of intelligence Wechscler Adult Intelligence Scale were in normal range at baseline

DBS FOR OCD UMEÅ – EFFECTS ON COGNITION ONE YEAR AFTER SURGERY

- Claeson-Dahls test – *Verbal learning & memory*
- Brief visospatial memory test – *Visual memory*
- Digit forward and backward – *Attention*
- Delis-Kaplan Executive Function - *Executive function*
- Trail Making Test - *visual attention, behavioral regulation, task switching/cognitive flexibility*
- Verbal fluency - *Verbal fluency*
- Stroop Color Word Interference test – *inhibition/switching*
- Dichotic listening task – *auditory attention*

DBS FOR OCD UMEÅ – EFFECTS ON COGNITION ONE YEAR AFTER SURGERY

- Claeson-Dahls test – *Verbal learning & memory*
- Brief visospatial memory test – *Visual memory* *(T-score baseline* 58.13±9.51, 12-months 46.75±3.85 p=0,027)
- Digit forward and backward – *Attention*
- Delis-Kaplan Executive Function - *Executive function*
- Trail Making Test - *visual attention, behavioral regulation, task switching/cognitive flexibility*
- Verbal fluency - *Verbal fluency*
- Stroop Color Word Interference test – *inhibition/switching* *(scaled score baseline* 8.00±3.30, 12-months 10.00±2.45)
- Dichotic listening task – *auditory attention*

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DBS FOR OCD UMEÅ – EFFECTS ON COGNITION ONE YEAR AFTER SURGERY

Limitations

- Small sample size
- Open-label study

Conclusions

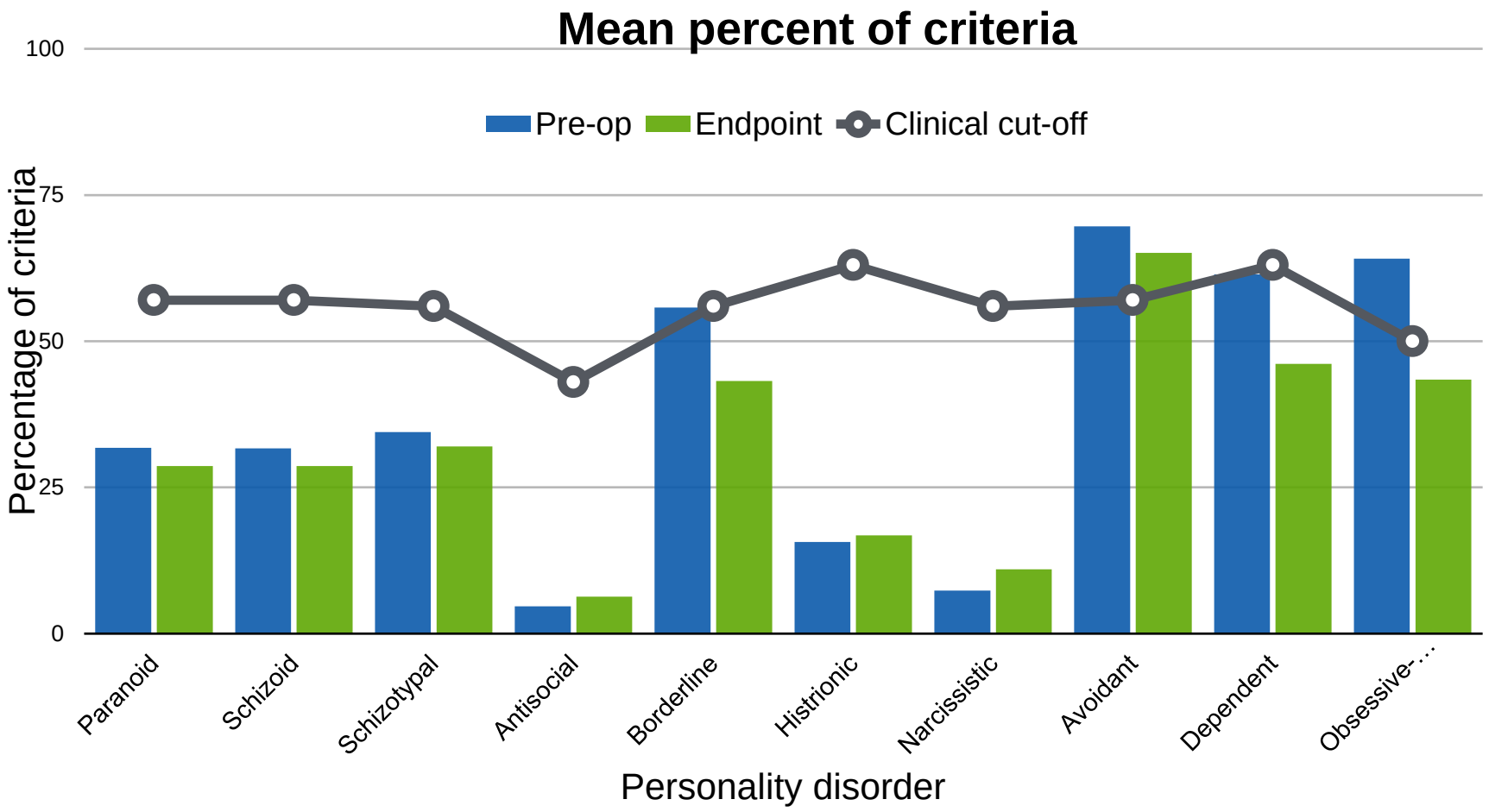
- BNST DBS generated few significant cognitive effects

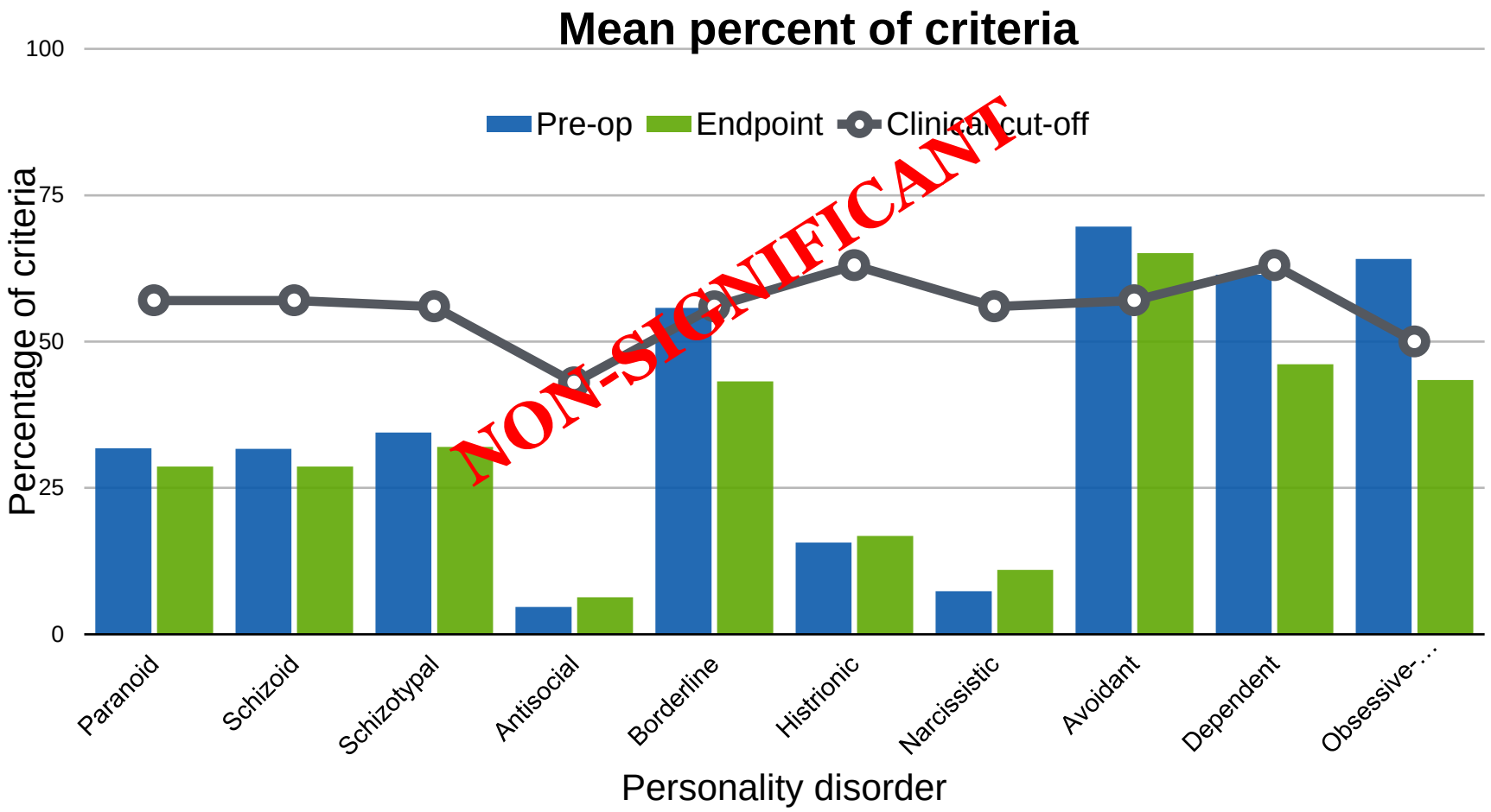
DBS FOR OCD UMEÅ – EFFECTS ON PERSONALITY

- **9/11** participants from the OCD BNST DBS pilot
- Self-assessment questionnaire (DIP-Q) **pre-operatively** & at **12-months post-operatively**
- **DIP-Q** = DSM-IV & ICD-10 Personality Questionnaire
- 140 yes/no statements
- Divided into 10 personality traits (cluster A, B & C)

Oscar Carlberg, medical student
Umeå University

RESULTS GROUP LEVEL




Mean percent of criteria
100
75
50
25
0
Pre-op
Endpoint
Clinical cut-off
NON-SIGNIFICANT
Percentage of criteria
Paranoid
Schizoid
Schizotypal
Antisocial
Borderline
Histrionic
Narcissistic
Avoidant
Dependent
Obsessive-…
Personality disorder

DBS FOR OCD UMEÅ – EFFECTS ON PERSONALITY

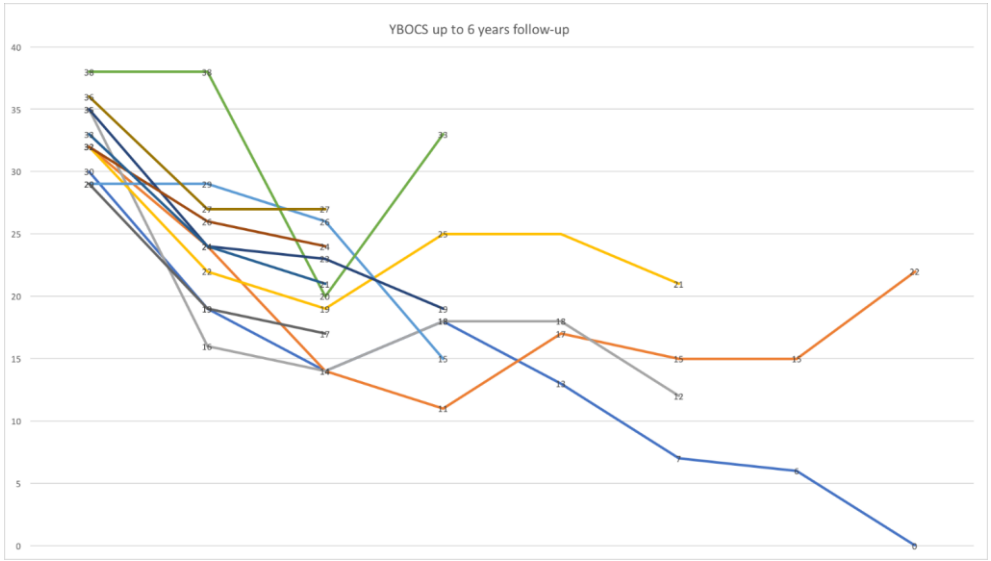
Limitations

- Small sample size
- Missing/ambiguous data

Results

- No significant effect on personality traits

DBS for OCD Umeå – LONGTERM EFFECTS



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ISSN 2220-3206 (online)

SYSTEMATIC REVIEWS

Deep brain stimulation for obsessive-compulsive disorder: A systematic review of worldwide experience after 20 years

Lorea Mar-Barrutia, Eva Real, Cinto Segalás, Sara Bertolín, José Manuel Menchón, Pino Alonso

- 11 studies with 155 patients
- 47% improvement after ≥ 36 months
- ½ responders, ¼ partial responders, ¼ non responders
- Most of the improvemnt is reached within 12-14 months

DBS FOR OCD UMEÅ – FUTURE PLANS

- Statistical data on long-term (5-year) effects & side-effects from the DBS OCD-pilot study
- **Qualiative study from the pilot-study**
- **Genetic study with participants from the pilot-study**
- *Mixed methodology study comparing participants in the DBS-pilot with uncompleted referrals*
- DBS RCT with 6 months sham-stimulation
- *fMRI of the DBS RCT*

DBS FOR OCD UMEÅ – CONCLUSIONS FROM 12 YEARS EXPERIENCE

- BNST DBS is a promising therapy in severe therapy-refractory OCD
- Our results are in line with previous publications regarding effect and safety profile
- Filed of stimulation includes several of the ”striatal” targets used in OCD – perhaps DBS in these regions might be considered stimulation of the same target?
- Lack of predictors for response for participant selection a critical issue
- DBS for psychiatric indications is a longterm commitment for both the patient and psychiatrist
- Psychiatric DBS is very dependent on multidisciplinary collaboration and team-work

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- Psychiatric DBS is very dependent on multidisciplinary collaboration and team-work!

THANK YOU!

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The Unit for Deep Brain Stimulation in Umeå

UMEÅ UNIVERSITY

CHALLENGES FOR DBS FOR PSYCHIATRIC DISORDERS IN SWEDEN?

- Lack of access to optimal standard care for psychiatric patients?
- Lack of larger psychiatric DBS RCTs
- Issues with financing for DBS for patients outside our regional uptake
- DBS is seen as ‘’too expensive”
- Lack of predictive factors for response to DBS
- Over-estimate how many patients qualify for DBS?