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ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

The human bed nucleus of the stria terminalis as a deep brain stimulation target. A systematic scoping review.

ANTONIADES ELIAS

ΑΘΗΝΑ 2025

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Ευχαριστίες

Με την παρούσα διπλωματική εργασία ολοκληρώνεται ο κύκλος παρακολούθησης μου στο Πρόγραμμα Μεταπτυχιακών Σπουδών της Ιατρικής Σχολής του Εθνικού Καποδιστριακού Πανεπιστημίου Αθηνών «Κλινική και Πειραματική Νευροχειρουργική».
Ευχαριστώ θερμά τον επιβλέποντα επίκουρο καθηγητή του Πανεπιστημίου Δυτικής Αττικής κύριο Καλαματιανό για την εμπιστοσύνη του και τις συνεχείς συμβουλές του. Εκφράζω τις ευχαριστίες μου στον καθηγητή Νευροχειρουργικής κύριο Στράντζαλη Γεώργιο και Νευρολογίας κύριο Τσάμη για το γεγονός, ότι δέχτηκαν να συμμετάσχουν ως μέλη της Τριμελούς Συμβουλευτικής και Αξιολογικής Επιτροπής.

Επιθυμώ να ευχαριστήσω τη γυναίκα μου Ευαγγελία, τα παιδιά μου Κωνσταντίνο-Ραφαήλ, Χρυσοθέα και τη νεήλυδα κόρη μας, όπως και τους γονείς μου Κωνσταντίνο και Μαρία για την υπομονή και τη συμπαράσταση τους προκειμένου να ολοκληρωθεί η παρούσα εργασία.

Περιεχόμενα

List of abbreviations

AC: Anterior commissure
ACC: Anterior cingulate cortex
AI: Anterior insula
BDI: Beck Depression Inventory
BLA: Basolateral nucleus of amygdala
BMA: Basomedial nucleus of amygdala
BNST: Bed nucleus of stria terminalis
avBNST: Anteroventral subnucleus of BNST
alBNST: Anterolateral subnucleus of BNST
amBNST: Anteromedial subnucleus of BNST
dmBNST: Dorsomedial subnucleus of BNST
fuBNST: Fusiform subnucleus of BNST
ovBNST: Ovoid subnucleus of BNST
prBNST: Principal subnucleus of BNST
trBNST: Transverse subnucleus of BNST
CCK: Cholocystokinin
CeA: Central group of nucleus of amygdala
CRF: Corticotropin releasing factor
CRH: Corticotropin releasing hormone
CN: Caudate Nucleus
CSTC: Corticostriatothalamocortical (network)
DA: Dopamine
DASS: Depression, Anxiety and Stress Scales
DBS: Deep Brain Stimulation
EEG: Electroencephalogram
EcoG: Electrocorticography
FPC: Frontopolar Cortex
Fx: Fornix
GABA: Gamma aminobutyric acid
GAF: Global assessment functioning Scale
Gpe: Globus Pallidus externa
GPi: Globus pallidus interna
HAMD: Hamilton Deprression Rating Scale
HPA: Hypothalamus pituitary axis
IC: Internal capsule
ALIC: Anterior limb of internal capsule
ICH: Intracerebral hemorrhage
LC: Locus coeruleus
LH: Lateral hypothalamus
LV: Lateral ventricle
MADRS: Montgomery-Asberg Depression Rating Scale
MCC: Midcingulate cortex
MeA: Medial nucleus of amygdala
MeS: Medical Subject Headings

MPOA: Medial preoptic area
slMFB: Superolateral medial forebrain bundle
NA: Noradrenaline
NAcc: Nucleus accumbens
NE: Norepinephrine
NMDA: N-methyl-D-aspartate
OCD: Obsessive-Compulsive Disorder
OFC: Orbitofrontal cortex
MDD: Major Depressive Disorder
PAG: Periaqueductal gray
PD: Parkinson's Disease
PET: Positron Emission tomography
PKCd: Protein kinase C delta
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses
PVN: Paraventricular group of neurons of hypothalamus
PVH: Periventricular area or zone of ypotalamus
dlPFC: Dorsolateral prefrontal cortex
dmPFC: Dorsomedial prefrontal cortex
mPFC: Medial prefrontal cortex
vmPFC: Ventromedial prefrontal cortex
Pu: Putamen
VMH: Ventromedial hypothalamus
NPY: Neuropeptide Y
PACAP: Pituitary adenylate cyclase activating polypeptides
PCC: Posterior cingulate cortex
PTSD: Post-traumatic stress disorder
QoL: Quality of Life
SNc: Substantia nigra compacta
SNr: Substantia nigra reticulata
STAI: State-Trait Anxiety Inventory
SSRI: Serotonin Selective Reuptake Inhibitors
SST: Somatostatin
STN: Subthalamic Nucleus
VTA: Ventral tegmental area
VC: Ventral Capsule
VS: Ventral striatum
YBOCS: Yale Brown Obsessive Compulsive Scale

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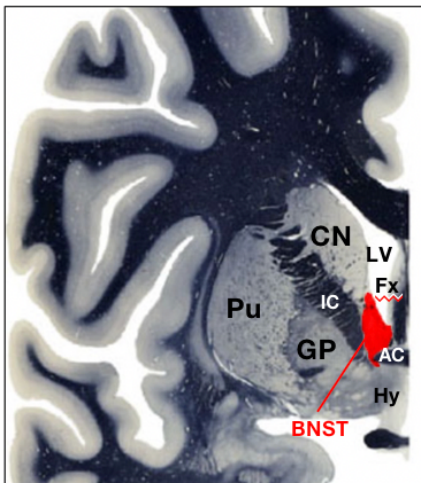

Figure 1., page 20 Coronal section of human brain stained for myelin (dark regions). The location of the human (BNST), at the level of the medial hypothalamus (Hy) is identified using a red mask. CN = Caudate Nucleus. Pu = putamen, LV = lateral ventricle. IC = internal capsule, Fx = fornix, AC =anterior commissure. Adopted from the Atlas of the Human Brain (J.K Mai, T. Voss and G. Paxinos, www.thehumanbrain.info).

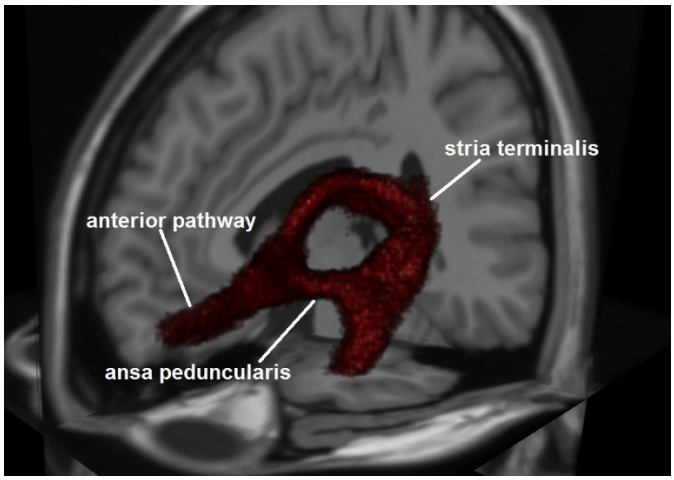

Figure 2., page 21 3D reconstruction of BNST major associative pathways. Stria terminalis, ventral amydalofugal pathway or ansa peduncularis, anterior pathway towards orbitofrontal cortex. **[**Krüger O. Examination of the structural connectivity profile of the Bed nucleus of the Stria terminalis in the human brain using probalistic fiber tracking of diffusion weighted magnetic resonance imaging data. Eberhardt Karls Universität zu Tübingen 2016]

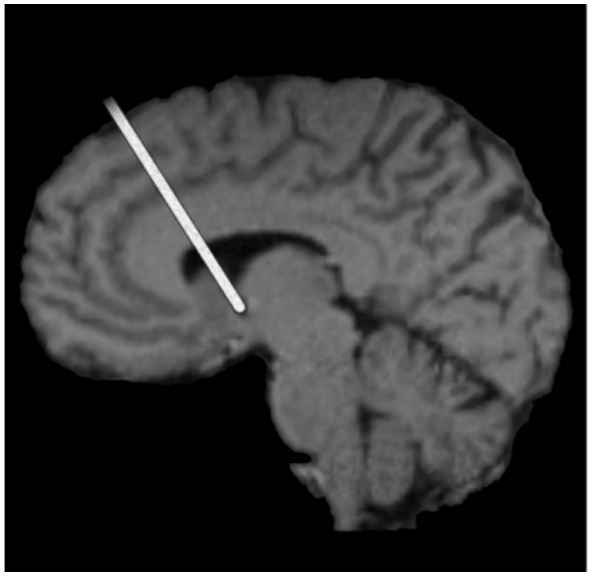

Figure 3.**page 33** Typical trajectory of a BNST and ALIC deep brain stimulation electrode [Luyten et al. 2020]

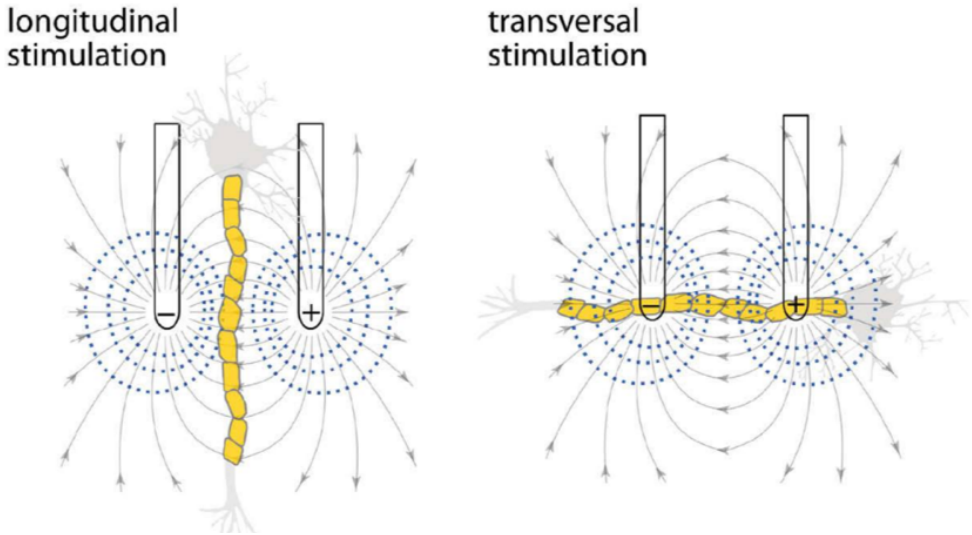

Figure 4.,**page 35** Differences between longitudinal and transverse stimulation. Greater part of neuraxons are involved in longitudinal stimulation [Deep Brain Stimulation. Indications and Applications. Lee KH, Duffy PS, Bieber AJ. Taylor Francis, Singapore: 2017]

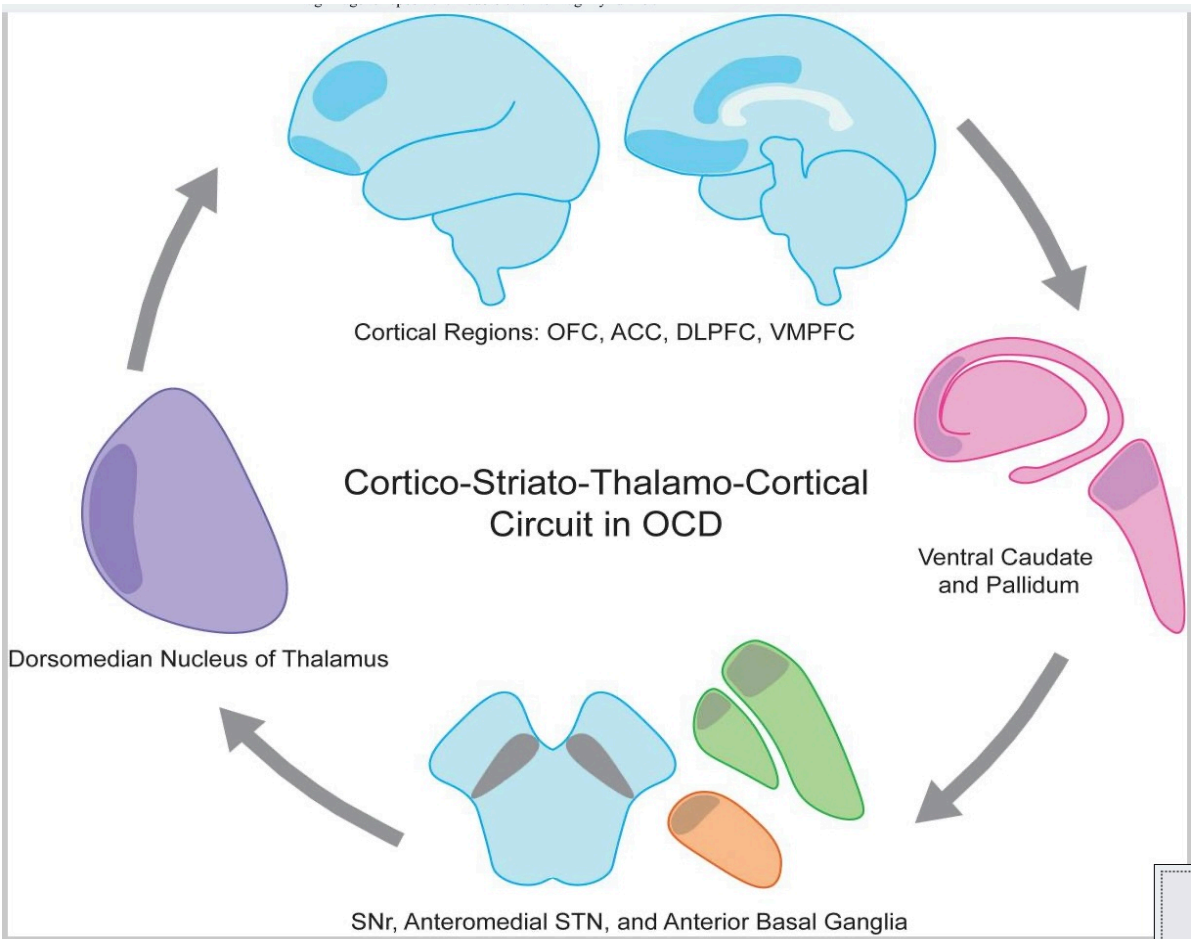

Figure 5.,page 38 OFC, ACC, dlPFC, and vmPFC (colored blue), ventral caudate and pallidum (colored pink), anterior GPi and GPe (colored green), anteriomedial STN (colored orange), SNr, and dorsomedian nucleus of the thalamus (colored purple). ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; OFC, orbitofrontal cortex; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; VMPFC, ventromedial prefrontal cortex. [Karas PJ, et al. 2019]

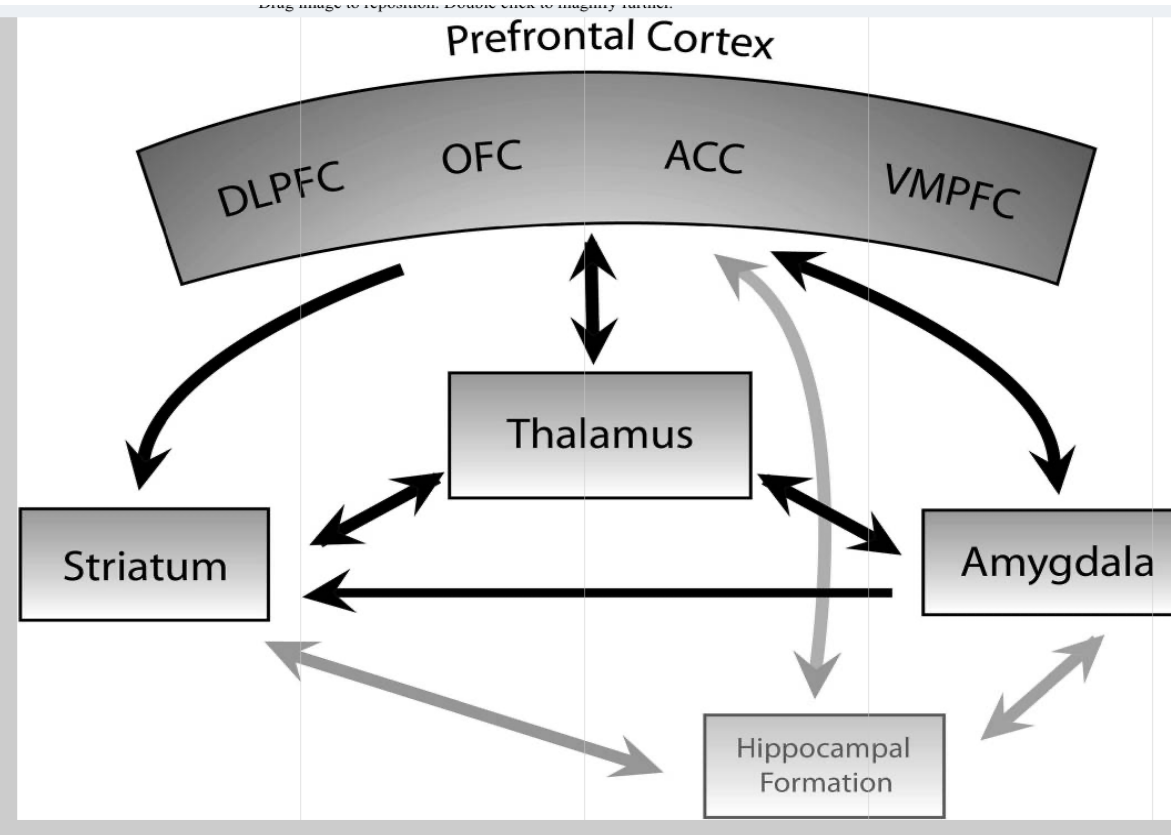

Figure 6.,page 39 Cortico-striato-thalamocortical network. In DBS for OCD, high frequency stimulation modulates the functionality of this network. DLPFC, dorsolateral prefrontal cortex; ACC, anterior cingulate cortex; OFC, orbitofrontal cortex; VMPFC, ventromedial prefrontal cortex. Arrowheads denote the trajectory of neural input. Black vectors respond to major connections. Gray vectors respond to additional connections [Bourne SK, et al. 2012].

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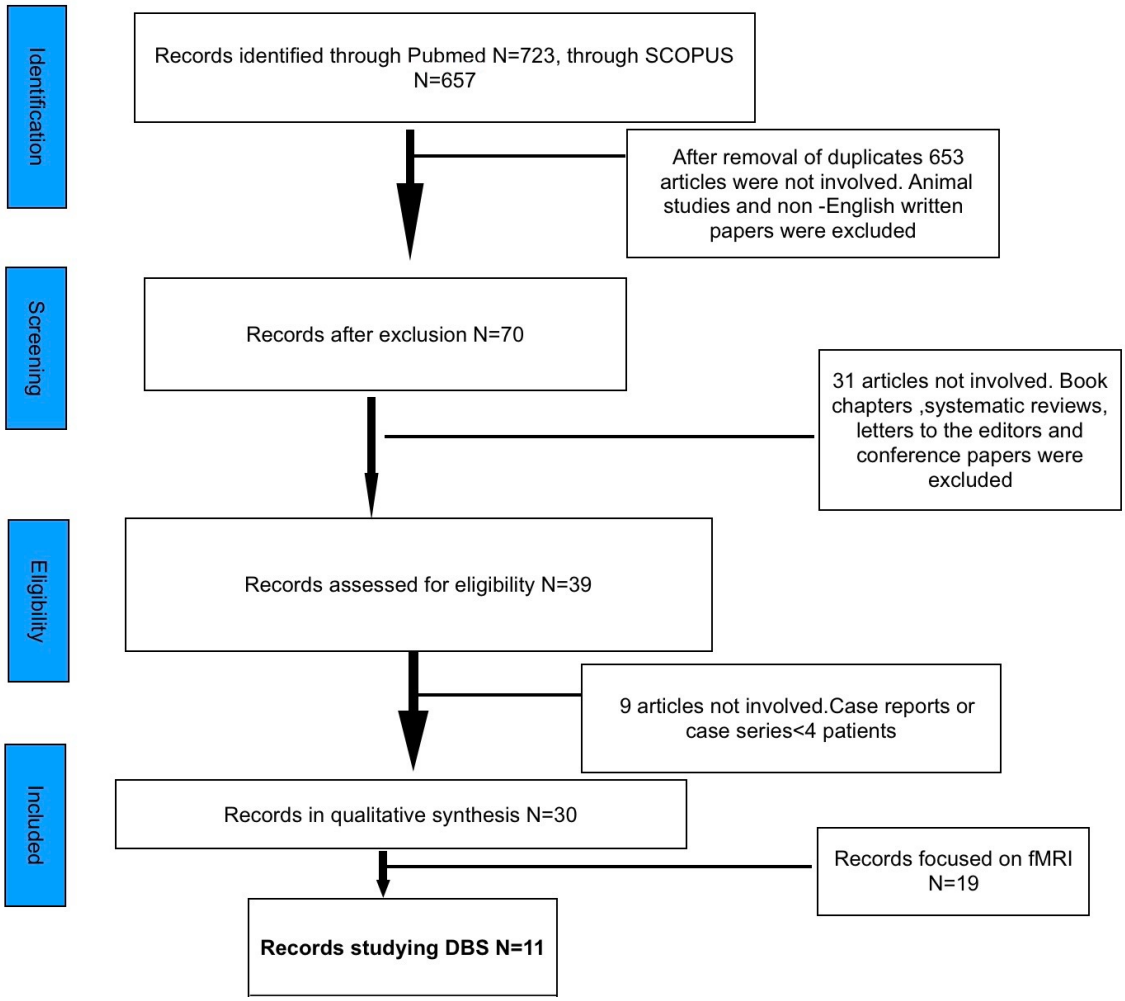

Table 1. page 44. PRISMA diagram for the present study.

Research team	Psychiatric disorder and inclusion criteria	Overall study design	Results synopsis	Adverse neuropsychiatric effects
Luyten et al.[132]	OCD with Y -BOCS ⩾30) and (GAF) ⩽45) for at least 5 years	24 patients ALIC-BNST stimulation. Blinded ON and OFF phases. 17 underwent crossover. HAMD and GAF scores	8 patients non- responders. Improvement on ON phases. YBOCS 66% at 4 years and 45% at last follow-up. HAMD at 4 years 67% and 49% at last follow-up. GAF 30 points at both 4 years and at last follow-up Reduction >35%in all questionnaires. Improvement of GAF	5 patients with seizures 4 suicide attempts 2 patients ICH, 2 patients with obstructive apnea
Luyck et al. [204]	OCD with YBOCS >30 for 5 years	9 patients BNST stimulation /blind crossover trial Exhibition of neutral and trigger images BDI and STAI	Acute provocation test evaluation. Reduced obsessive thoughts in moderate-severe OCD No significant benefit of bilateral stimulation	Warmth (7), sweating (4), Nausea (2), absent feeling
Raymaekers et al.[200]	OCD with Y-BOCS ⩾30 and GAF ⩽45 for at least 5 years	24 patients from group of Luyten et al. ALIC-BNST stimulation Follow up 76.5 months.YBOCS, BDI, GAF and HAMD	ON status strongly correlated with YBOCS reduction. Surgery itself associated with GAF improvement	Same to Luyten et al.
Mosley et al.[201]	OCD with YBOCS>24 >2 weeks Treatment refraction to SSRI for 12 weeks+/-antipsychotics	9 patients DBS of BNST/Nacc Double blinded trial YBOCS and MADRS Structural connectivity	12 month follow-up. 7 patients responders . YBOCS 49.6% reduction. MADRS 10 points reduction. Right-sided altered connectivity including orbitofrontal cortex, pars triangularis, parahippocampal gyrus, calcar area, supramarginal region	Parasomnia Reduced libido Mild agitation

Winter et al.[203]	OCD with YBOCS>25 or >32 Time since diagnosis >14 years	6 patients DBS BNST/ALIC YBOCS and WHO-QoL BREF	8 year follow-up. 4 responders 2 non-responders who were not stimulated at BNST contacts	Transient Psychotic reaction (1)
Farrand et al.[207]	OCD with YBOCS>28 25.9 years mean duration of symptoms	7 patients DBS of BNST and NAcc YBOCS, NUCOG,SOFAS, OCI and DASS	3 patients were full responders after 31 months follow-up. YBOCS reduction 30% for BNST group and 29.35% for NAcc group. Reduction of YBOCS and SOFAS	Hypomanic episodes (2) Ageusia (1) Dejá-vu symptoms(1)
Fitzgerald et al.[206]	MDD with Montgomery Asberg test >25 for 5 years	5 patients DBS of BNST/LH/Nacc BDI, HAMD and MADRS	6-,12- and 18 month follow-up. 2 full responders. 2 partial responders. 1 non-responder. 33% overall reduction of HAMD between 18-24 months.75 increase on QoL.No cognitive deficits	Suicidal attempts (2) Anxiety (3), Persistent Insomnia (1)
Philipson et al. [205]	OCD with YBOCS>25 for 5 years	8 patients ALIC/BNST YBOCS Raven's Colored Matrices, Wechsler Adult intelligence Scale Claeson – Dahls test, Brief visuospatial Memory Test, Delis Kaplan Executive Function System Trail Making Test, Color Word Interference test Verbal fluency, Dichotic listening task and IVA	12month follow-up. 3 fully responders.4 partial responders. Improved performance on selective attention/processing speed. Apart from visuospatial cognitive decline no other cognitive deficits	Relative decline of visuospatial cognition and cognitive interference inhibition (Color-word inhibition test)
Mar-Barrutia et al.[209]	OCD with YBOCS>30. No re-	25 patients DBS of ALIC and BNST	5.4 year follow-up .11 responders . YBOCS reduction 44.2% and	Memory complaints (6), headache (10),

	sponse to SSRIs/antipsychotics for 16 weeks, (GAF) <45%. OCD's onset more than 5 years	GAF and HAMD	HAMD reduction 41.5% Lesser follow-up period of ALIC DBS patients. No statistical difference between the two stimulation points	fatigue (9), insomnia (8), weight gain (6),enuresis (2)
Shofty et al.[208]	OCD with YBOCS>28 for >5 years Drug refractoriness. Commobidities, such as MDD, bipolar disorder and Tourette syndrome	8 patients DBS of VC/Vs or BNST YBOCS Titrated increase of currency intensity and amplitude	Mean follow-up duration 21.25 months. 8 responders. Positive valence in VC/VS stimulation more often than BNST. 48,5% reduction of YBOCS in patients with BNST implanted electrodes. Better outcomes in patients with modified parameters	**Bad mood Worry Tiredness**
Naesström et al.[210]	OCD with YBOCS >25 and>5 years duration. Depression with MARDS>29	11 patients BNST bilaterally YBOCS for primary results GAF and MADRS for secondary results	3, 6 month and 12 month follow-up .6 responders. Overall YBOCS reduction 38%. YBOCS reduction 49% for responders .MADRS reduction 27,3%. GAF 12,2% increase	**Anxiety, insomnia** Impulsive medication intoxication

ALIC: anterior limb of internal capsule, BNST: bed nucleus of stria terminalis, BDI: Beck Depression Inventory, DASS: Depression, Anxiety and Stress Scales,
GAF: Global assessment functioning Scale HAMD: Hamilton Deprression Rating Scale, IVA: Integrated visual and auditory continuous performance Test,
MADRS: Montgomery-Asberg Depression Rating ScaleMDD: Major Depressive Disorder Nacc: nuceus accumbens,
NUCOG: Neuropsychiatry Unit Cognitive Assessment, OCI: Obsessive Compulsive Invnetory, QoL: quality of Life, STAI: State-Trait Anxiety Inventory
SOFAS: Social and occupational functioninγ assessment Scale, Vc/Vs: ventral capsule/ventral striatum, WHOQoLBREF: World Health Organization Quality of Life Form,
YBOCS: Yale brown obsessive-compulsive scale

Table 2, page 47-49. Objectives, design and outcomes of studies included in the present review

Abstract

Introduction

The human bed nucleus of stria terminalis (BNST) is a bilateral medial basal forebrain structure of approximately 190mm^3 that is also referred to as part of the extended amygdala. The nucleus is bordered dorsally by the lateral ventricles and caudate nucleus, laterally by the internal capsule and ventrally / ventromedially by the anterior commissure, nucleus accumbens, hypothalamic preoptic area and fornix. The human BNST displays well conserved structural connections with the hypothalamus and additional limbic areas, such as the amygdala, the insula and nucleus accumbens. Neurocircuitry involving the BNST has been previously implicated in anxiety disorders and addiction. Recent evidence-based guidelines for deep brain stimulations for Obsessive-Compulsive Disorder (OCD) by the Congress of Neurological Surgeons indicate the utility of bilateral stimulation of the BSNT. Case series with BNST stimulation as Major Depressive Disorder (MDD) treatment are also published.

Aims

The present study aimed at mapping the available literature on the utility of the BNST as a target of deep brain stimulation in humans.

Material -methods

We employed a systematic review methodology according to PRISMA guidelines. MeSH terms that were selected for a Pubmed search were: (Bed nucleus of stria terminalis) or (BNST) and (Stimulation). Time period was set from January 1973 - March 2024. Animal studies as well as letters to the Editor, conference papers and those written in a language other than English were excluded. Case series involving 4 or less participants were excluded. Studies involving the BNST activation without therapeutic objectives were also not included.

Results

The present systematic review identified 10 manuscripts assessing the therapeutic potential of BNST stimulation in OCD. Only one study assessed the utility of BNST stimulation in MDD. Out of 107 patients with OCD 58 were full responders (>35% YBOCS reduction). Out of 5 patients with MDD 2 patients were responders. Good outcome was associated with the turned-on phases of the system and was observed in the long-term period. Bilateral stimulation was not related to enhanced outcome. 7 patients with OCD had major psychiatric complications, such as suicidal attempts, hypomanic episodes and psychotic reaction. On the contrary 2 patients with MDD attempted suicide.

Conclusions

BNST neurocircuitry is implicated in anxiety and addiction disorders. Bilateral BNST stimulation has been indicated as a putative therapeutic target against OCD. Patient selection based on strict criteria is still debatable. While a benefit of BNST stimulation in OCD is supported by several studies on small numbers of patients, more research is warranted to assess utility in both OCD and other disorders.

➢ Περίληψη

Ο ανθρώπινος κλινοειδής πυρήνας της τελικής ταινίας ως στόχος εν τω βάθει διέγερσης του εγκεφάλου: συστηματική ανασκόπηση οριοθέτησης

Εισαγωγή

Ο κλινοειδής πυρήνας της τελικής ή μεθορίου ταινίας (ΚΠΜΤ) είναι μια αμφοτερόπλευρη δομή της έσω επιφάνειας της βάσης του προσεγκεφάλου. Ο όγκος του κατά προσέγγιση στα 190mm^3. Ο πυρήνας αφορίζεται ραχιαία από τις πλάγιες κοιλίες και τον κερκοφόρο πυρήνα, επί τα εκτός από την έσω κάψα. Στην κοιλιακή και έσω επιφάνεια με τον πρόσθιο σύνδεσμο, τον επικλινή πυρήνα, την υποθαλαμική προοπτική χώρα και την ψαλίδα. Στον άνθρωπο ο πυρήνας παρουσιάζει εμφανείς συνδέσεις με τον υποθάλαμο και επιμέρους περιοχές του μεταιχμιακού συστήματος, όπως η αμυγδαλή, η νήσος και ο επικλινής πυρήνας. Η μελέτη της συνδεσιμότητας του εμπλέκεται στις διαταραχές του άγχους και στον εθισμό. Οι προσφάτως τεκμηριωμένες κατευθυντήριες οδηγίες για τον εν τω βάθει ερεθισμό του εγκεφάλου ως θεραπεία για την ιδεοψυχαναγκαστική διαταραχή από το Κογκρέσο των Νευροχειρουργών προκρίνουν τη χρήση της αμφοτερόπλευρης διέγερσης του κλινοειδή πυρήνα. Σειρές ασθενών με μείζονα κατάθλιψη και διέγερση του ΚΠΜΤ ως θεραπευτική μέθοδο, επίσης υφίστανται στη βιβλιογραφία.

Σκοπός της μελέτης

Η παρούσα μελέτη αποσκοπεί στην ιχνηλάτηση της διαθέσιμης βιβλιογραφίας σχετικά με τη χρήση του κλινοειδή πυρήνα της μεθορίου ταινίας ως στόχου του εν τω βάθει ερεθισμού του εγκεφάλου στον άνθρωπο.

Υλικό και μέθοδος

Εφαρμόσαμε μεθοδολογία συστηματικής ανασκόπησης σύμφωνα με τις οδηγίες PRISMA. Οι ιατρικοί τίτλοι που χρησιμοποιήθηκαν για την έρευνα στην βάση δεδομένων Pubmed: ήταν [(Bed nucleus of stria terminalis) - (κλινοειδής πυρήνας μεθορίου ταινίας **ή** (BNST)-(ΚΠΜΤ) **και (**Διέγερση)]. Το χρονικό διάστημα της μελέτης ήταν από τον Ιανουάριο του 1973 μέχρι τον Μάρτιο του 2024. Μελέτες σε ζωικά πρότυπα, επιστολές σε εκδότη, προφορικές παρουσιάσεις σε συνέδρια, καθώς και εργασίες μη δημοσιευμένες στην αγγλική γλώσσα δεν συμπεριλήφθηκαν. Σειρές τεσσάρων ασθενών ή και λιγότερων επίσης αποκλείστηκαν. Μελέτες που αναφέρονταν σε διέγερση του πυρήνα χωρίς θεραπευτικό σκοπό δεν συμπεριλήφθηκαν.

Αποτελέσματα

Η παρούσα μελέτη ανέδειξε 10 άρθρα που αξιολογούν τη θεραπευτική δυνατότητα της διέγερσης του ΚΠΜΤ στην ιδεοψυχαναγκαστική διαταραχή. Μόνο ένα άρθρο αναφέρονταν στη χρήση της διέγερσης για τη μείζονα καταθλιπτική διαταραχή. Από τους 107 ασθενείς με ιδεοψυχαναγκαστική διαταραχή 58 ανταποκρίθηκαν πλήρως

(μείωση της κλίμακας YBOCS>35%). Από τους 5 ασθενείς με μείζονα κατάθλιψη 2 ανταποκρίθηκαν πλήρως. Η θετική έκβαση σχετίζεται με τη φάση λειτουργίας του συστήματος και ήταν παρούσα στη μακροπρόθεσμη περίοδο. Αμφοτερόπλευρη διέγερση του ΚΠΜΤ δεν σχετίζονταν με τη θετική έκβαση. Μόνο 7 ασθενείς με ιδεοψυχαναγκαστική διαταραχή εμφάνισαν μείζονες ψυχιατρικές επιπλοκές, όπως απόπειρες αυτοκτονίες, υπομανία και ψυχωτικά επεισόδια. Αντιθέτως 2 ασθενείς με μείζονα κατάθλιψη αποπειράθηκαν να αυτοκτονήσουν.

Συμπεράσματα

Η συνδεσιμότητα του ΚΠΜΤ εμπλέκεται στο άγχος και την εξάρτηση. Η αμφοτερόπλευρη διέγερση του ΚΠΜΤ αναδείχθηκε ως γενικά αποδεκτός στόχος έναντι της ιδεοψυχαναγκαστικής διαταραχής. Παρόλο που ανακύπτει όφελος από τη διέγερση του πυρήνα στην ιδεοψυχαναγκαστική διαταραχή αυτό υποστηρίζεται από αρκετές μελέτες με μικρό δείγμα ασθενών. Η επιλογή ασθενών βάσει αυστηρών κριτηρίων είναι προς συζήτηση. Ως εκ τούτου περαιτέρω έρευνα χρειάζεται για την αξιολόγηση της χρησιμότητας της διέγερσης σε αμφότερες τις διαταραχές.

1. Introduction

1.1 The human BNST: gross anatomical data

The human bed nucleus of stria terminalis (BNST) lies in the medial surface of basal forebrain with an approximate volume of 190mm^3 [**1**]. It is demarcated by the internal capsule (IC) on the lateral side, supracapsular region of globes pallidus interna (GPi), and the basal forebrain locus. At its ventromedial region lies the preoptic area of hypothalamus. BNST is located dorsally the nucleus accumbens (NAcc), and ventrally to the thalamus. It also lies beneath the frontal horns and is situated mostly cranially to the anterior commissure. Its lateral regions are detected below the anterior commissure [**Figure 1**].

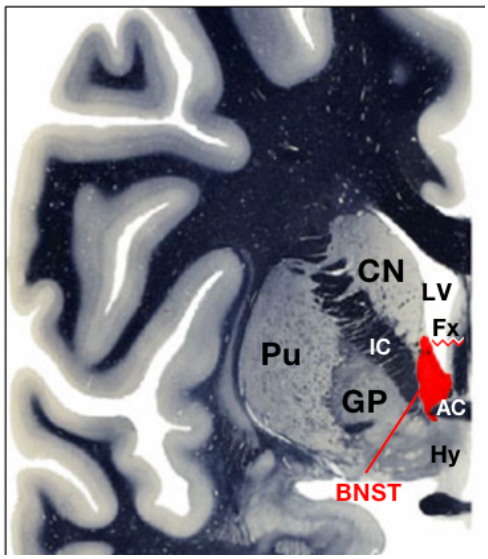

Figure 1. Coronal section of human brain stained for myelin (dark regions). The location of the human (BNST), at the level of the medial hypothalamus (Hy) is identified using a red mask. CN = Caudate Nucleus. Pu = putamen, LV = lateral ventricle. IC = internal capsule, Fx = fornix, AC =anterior commissure. Adopted from the Atlas of the Human Brain (J.K Mai, T. Voss and G. Paxinos, www.thehumanbrain.info).

The human BNST has been divided into lateral, medial, central and ventral segments. The lateral, medial and central regions are clustered frontally to the anterior commissure (AC) becoming thinner and annexing the rostral region posteriorly. It exhibits sexual dimorphism. Male brains demonstrate 2.5 times greater BNST volume than females [**2**]. Relatively recent imaging studies have begun assessing the connections of the BNST with the rest of the brain. Three such discrete, fiber pathways termed the posterior, the ventral and the anterior bundles have been previously described in humans [**3**]. The posterior bundle paces along the stria terminalis towards the lateral amygdala. The ventral bundle courses through the ansa peduncularis to the medial nucleus of amygdala (MeA) and hypothalamus. The anterior bundle has

been only recently described. It transverses the caput of the caudate nucleus and NAcc, proceeding afterwards towards the medial prefrontal cortex (mPFC) and the orbitofrontal cortex (OFC) [**3**] (**Figure 2**).

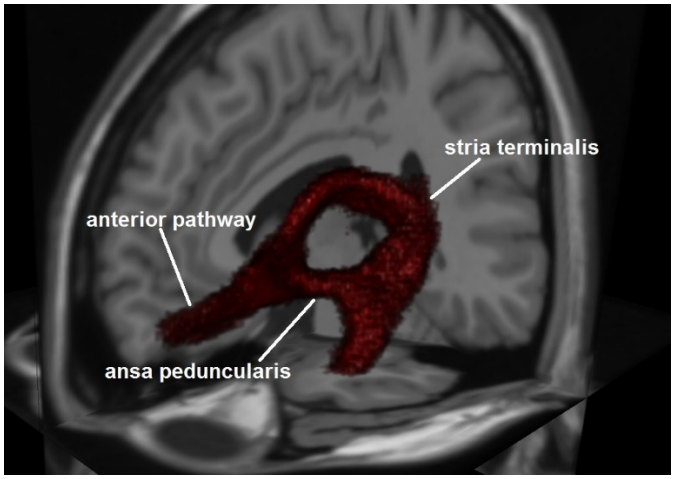

Figure 2. 3D reconstruction of BNST major associative pathways. Stria terminalis, ventral amydalofugal pathway or ansa peduncularis, anterior pathway towards orbitofrontal cortex. [3]

1.2 Anatomical compartmentalization of BNST in rodents

1 The anterior BNST regulates hypothalamus-hypophysis axis (HPA). Within this division are included the oval, anteromedial, dorsomedial, anterolateral, anteroventral, juxtacapsular, fusiform, rhomboid and magnocellular subnuclei.
2. The posterior BNST is involved in reproductive and defensive behaviors. Therein, transverse, intrafascicular and principal subnuclei are located.

1.2.1 Nuclei of the anterior BNST

1.2.1.1 Oval Nucleus (ovBNST)

More specifically, the ovBNST is implicated in stress reactions. Its major cell population includes corticotropin releasing factor (CRF) or corticotropin releasing hormone (CRH) neurons, which also express gamma aminobutyric acid (GABA). CRF expressing neurons are stimulated by visceral sensory stimuli of insula, brainstem and periaqueductal gray (PAG), which are abundant with dopaminergic and glutamatergic neurons [**4**],[**5**]. CRF stimuli derive from the central group of amygdala nucleus (CeA) and paraventricular group of neurons of hypothalamus (PVN) **[4], [5]**. The ovBNST provides significant output. CRF neurons deactivate areas responsible for avoidance-reward pattern and stress responses, as well. As shown in previous animal studies, these areas involve apart from the hypothalamus, the ventral tegmental area (VTA), and the NAcc [**4**], [**5**]. Apart from CRF+ GABAergic neurons [**6**], other neuronal types express either protein kinase C delta (PKCd) or somatostatin (SST). They project bidirectionally to and fro GABAergic CeA nucleus and lateral hypothalamus, as well [**6**] .

CRF receptor 1 (CRF1R) expressing interneurons are inhibitory. This is a conclusion extracted by studies in rodents. Through a positive feedback association CeA neurons enhance ovBNST input to the hypothalamus and this subsequently promotes glucocorticoid elicitation [**7**]. CRF promotes GABA-A receptor expression and the suppressive postsynaptic potentials [**8**].

1.2.1.2 Anteroventral nucleus (avBNST)

The avBNST, according to animal studies, constitutes a minimal portion of glutamatergic neurons sending efferent fibers to the PVN and ventral tegmental area (VTA) [**5**]. This limited population of glutamatergic neurons has a major impact on mood regulation. All of noradrenergic, GABAergic and glutamatergic afferent projections control avBNST function. Central amygdalar (CeA) GABAergic inputs towards avBNST promote suppressive postsynaptic currents enhanced by CRF. mPFC and subiculum produce glutamatergic inputs toward the avBNST [**5**]. In research on rats, it was noticed that the avBNST via projections to amygdala, hypothalamus and brainstem contributes to HPA axis stimulation. The latter modulates the cardiovascular function [**9**]

1.2.1.3 Anteromedial nucleus (amBNST)

In rat anatomical descriptions it was shown that, the amBNST accumulates the majority of BNST afferent projections, especially from the basomedial amygdala (BMA), which exhibits high connectivity with amBNST. Glutamatergic afferent projections sent by hippocampus, BMA, are combined with GABAergic afferent projections from the MeA. Cumulative actions regulate fear context [**10**]. The greatest proportion of amBNST afferents course within the BNST. They are interconnected also with the anterolateral BNST (alBNST) and ovBNST.

1.2.1.4 Dorsomedial nucleus (dmBNST)

The dmBNST accumulates afferent projections sent by various regions of amygdala such as, the BMA, MeA, and CeA. The dmBNST constitutes the major interrelation between BNST and PVN. This association produces a significant GABAergic output, as it was concluded in anatomical studies in rats [**11**]. The magnocellular BNST exhibits functional likeness with dmBNST, contributing significantly to outputs to the PVN. Magnocellular nucleus and dmBNST behave actually as interneurons, which aggregate GABAergic input from the principal BNST.

1.2.1.5 Anterolateral nucleus (alBNST)

Once again based on studies in rats, it has been shown, that the alBNST accumulates various afferent projections. These are glutamatergic afferents sent by the ventral subiculum, serotonergic afferents projected by dorsal raphe, and GABAergic afferent projections from the CeA and BLA [**5**], [**11**]. The alBNST sends efferent axons to areas of somatomotor, central autonomic, thalamocortical feedback, and neuroendocrine systems. The latter involves hypothalamus. A subgroup of neurons bear CRF1R receptors and accumulate CRF afferents projected by ovBNST [**12**]. Inhibition of alBNST connectivity ameliorates stress reaction [**5**].

1.2.1.6. Miscellaneous nuclei

Nuclei of lesser growth were also studied in rats. This group involves juxtacapsular, fusiform and rhomboid nuclei, which are studied in relation to the greater aforementioned groups. Rhomboid and juxtacapsular neurons are GABAergic sending efferent fibers to ovBNST and to CeA, which bear CRF-1 receptors [**12**]. The fusiform BNST bears likeness to ovBNST and exhibits increased transcription of CRF mRNA. CRF derives from the fusiform BNST, CeA, PVN, Nacc, and periaqueductal gray (PAG) [**13**].

1.2.2 Nuclei of Posterior BNST

Further studies in rodents have described the posterior subdivisions of the nucleus and their projections.

1.2.2.1 Principal nucleus (prBNST)

The prBNST constitutes the most extended area of posterior BNST. It is associated with the accessory olfactory system. Posterodorsal medial amygdala mediates this interrelation. It accumulates GABAergic afferents from the lateral septal nuclei and CeA [**12**],[**14**]. The prBNST is predominantly GABAergic [**15**] and sends efferent fibers to septal area, MeA, hypothalamus and PAG [**16**]. The prBNST is also related to the other subgroups of BNST [**12**]. It produces a massive GABAergic output, towards MeA, PVN, PAG, and locus coeruleus(LC) [**15**], [**17**]. 20% of the neurons of this nucleus produce enkephalin and glutamatergic acid. In addition to this, massive expression of both sexual hormones receptors are observed rendering it, thus, as the most sexually dimorphic nucleus [**16**].

1.2.2.2 Intrafascicular nucleus (ifBNST)

The ifBNST collects afferent projections sent by the accessory olfactory system. The Posteromedial amygdala facilitates this association. GABAergic afferent projections originate from the lateral septum, CeA and MeA. The ifBNST neurons express kainate receptors. This expression is modulated by glutamatergic afferents sent by CA1 part of hippocampus, ventral subiculum, paraventricular thalamus and BMA [**15**], [**14**]. The ifBNST sends efferents predominantly to the lateral septum, substantia innominate and VTA. There are also intra-BNST efferent projections [**12**]. The ifBNST also expresses enkephalin, produced mostly by GABAergic neurons [**18**]. The ifBNST does not present sexual dimorphism [**15**].

1.2.2.3 Transverse subnucleus (trBNST) Rodent studies

The trBNST aggregates afferent projections sent by accessory olfactory system. these afferents are GABAergic and glutamatergic. Apart from this, kainite receptors are strongly expressed [**15**], [**14**]. The trBNST sends major GABAergic efferents to the septal area, Nacc, VTA, substantia innominata, CeA, MeA and BMA. Intra-BNST projections are also identified [**12**].

1.2.3 Segmentation of BNST in humans

The anatomical and physiological segmentation of dorsal and ventral human BNST has not been described.
The oval and fusiform/anteroventral nuclei are frequently described in human brain following the advance of MRI, as dorsal and ventral divisions [**19**]. BNST and PVN association is involved in child violent events and emotional dysfunction [**20**]. It is also implicated in abstinence anxiety [**21]**. To sum up, both of these structures participate in emotional symptomatology and anxiety pathophysiology.

1.2.4 Signaling of the subnuclei groups in rodents and canidae

The oval nucleus, contributes to preautonomic signaling based on animal studies, especially in rats. On the other hand, the fusiform and anteroventral (fu/av) nuclei [**22**], dispose the richest network of afferents by solitary tract neurons and noradrenergic efferents in the brain [**23**], [**24**].
Further elaboration on animal models conferred details on the signaling of the ventral subdivisions of the nucleus. The ventral BNST subnuclei (fu/av) that receive viscerosensory afferents innervate the PVN, as well [**22**]. These efferent axonns originate predominantly from CRF neurons [**25]**. PVN function is characteristically regulated by BNST and stress reaction [**26]**. The avBNST promotes the suppression of stress-related HPA activation [**27].**
The noradrenergic efferent fibers, of ventral BNST, may promote contextual and non-contextual fear, as shown in rats [**28]**. These efferent fibers contribute to stress-associated drug pursue [**29]**, mood state upon withdrawal [**24**] and neuroendocrine alterations to anxiety [**30**]. Suppression of this efferent network alleviates psychological stress [**31**]. These noradrenergic projections to the BNST terminate to CRH-affluent, medial parvocellular PVN.
Somatostatin (SST) exists in 2 isoforms, SST-14 and SST-28. Its actions have been thoroughly investigated in rats. The majority of neurons, which express SST are GABAergic and are located in anterior and posterior BNST, apart from the anteromedial part [**32**]. SST and CRH neurons in the BNST regulate intrinsic fear in a contradictory pattern [**33**]. Accordingly, the action of GABA has been clarified in rats. Parvalbumin expressing GABAergic in shell of Nacc regulate avoidance patterns towards anxiety stimuli [**34**].
Neuropeptide Y (NPY) is considered a significant neuromodulator for the preservation of energy homeostasis. Some studies on mice have shed light on its effects. It is mainly located in the anterolateral, posterior and intrafascicular segments of BNST. NPY (+) neurons are active in the anterior BNST. NPY and CRH provoke contradictory effects on emotional states. NPY receptors activation mediate amelioration of anxiety and depression [**35**]. This effect of NPY is attributed to excessive polarization of the pyramidal cells at the BLA. On the contrary, CRH excites the same cells.

Pituitary adenylate cyclase activating polypeptide (PACAP) significantly regulates stress associated behaviors [**36**]. Prolonged non-continuous consumption of alcohol intensified the production of PACAP [**37**]. The aforementioned research programs were based on rat experiments.

Finally, rodent studies have taken place for the elucidation of the action opioids on BNST. Dynorphin belongs to opioid polypeptides and its binding to kappa receptors promotes expression of negative emotions and stress responses. This neuropeptide is mostly aggregated in the anterior BNST. Repeated activation of these receptors hinder presynaptically the glutamatergic afferents from BLA towards the BNST [**38**]. The suppression of GABA elicitation from the central amygdala induces anxiety [**39**]. Taken under consideration that the majority of neuropeptides act inhibitory we may suppose that the inhibitory neurons are suppressed resulting in positive output from BNST.

1.2.5 Functional importance of BNST based on preclinical data

1.2.5.1 BNST–Hypothalamus circuitry in valence surveillance

HPA axis stimulation sustains stress reaction. The interconnection with BNST was clarified based on rodent experiments. The excessive function of this axis involves an instant increase of adrenaline levels in adjunct to glucocorticoid elicitation, tachycardia and hypertension [**7**]. BNST induces evasion responses in fearful setting [**40**],[**41**] and visceral activation [**42**], as well. Ventromedial hypothalamus (VMH)-projecting neurons to the BNST are glutamatergic. GABAergic neurons constitute the major cell group of BNST which terminate to VMH. BNST exerts its action on VMH either with immediate suppression or indirectly via the suppression of shell neurons [**41**]. In animals, connectivity of the nucleus has been studied for many years. Apart from, dmBNST, the MPOA also accumulates GABAergic projections from the rhomboid BNST and prBNST [**43**]. Parallel to this, the amBNST accumulates projections from the MPOA. The VMH is suppressed by the prBNST. GABAergic neurons of amBNST send efferent fibers to VMH shell conferring a contradictory network [**41**]. Efferent fibers toward LH are predominantly GABAergic, springing from CRF + ovBNST [**43**], fuBNST [**22**], and adBNST neurons [**40**], [**44**]. The avBNST contains some glutamatergic projections. GABAergic cells of adBNST express either CRF or cholecystokinin (CCK). These cellular subpopulations have contradictory impact on hypocretin/ orexin-expressing neurons of lateral hypothalamus [**44]**.

1.2.5.2 BNST-amygdalar circuitry

The amygdala regulates the instant stress reactions, whereas the BNST mediates prolonged fear reactions in rodents and men [**42**],[**45**],[**2**],[**46**]. Its “valence surveillance role” has now been established. This also suggests that complementary networks exist in the BNST for both positive and negative emotional states [**40**]. Apart from evasive behaviors, BNST participates in reward responses.

BNST induces acquired fear when an unpleasant event is not sure or unknown. This “valence surveillance” [**2**] includes continuous monitoring of positive and negative stimuli followed by appropriate behaviors. Unpredictable stressors necessitate continuous monitoring via the BNST, which relates to anxiety in humans.

In rodents BMA participates in stress reactions through its association with the hypothalamus. Especially, BMA and VMH are directly interconnected and are able to alter the endocrine function. They are indirectly related to each other with glutamatergic BMA afferents. These activate sequentially amBNST interneurons, which terminate in VMH shell. Therefore, stress reactions are either increased or dampened [**41**]. The reciprocal connectivity with BMA enables the control of the HPA axis function.
The ovBNST confers evasive behaviors via the inhibition anterodorsal region of the BNST, which dampens evasive attempts. Anterodorsal BNST has these properties via its connection with LH and VTA [**40**].

1.2.6 BNST's impact on threat and anxiety expression

1.2.6.1 Threat expression in rodents

GABAergic circuits to the orexin-expressing lateral hypothalamus act toward a contradictory direction, as it was established in mouse experiments. Stimulation of projections from the CRF-expressing adBNST neurons towards the LH is aversive, while those from the CCK- expressing posterior principal nucleus of BNST are rewarding [**44**].
CRF expressing neurons form a network. This observation was corroborated mostly by rodent experiments. They demonstrate alterations of their dendrites, postsynaptic excitation [**47], [48],** CRF signaling [**48]**, and spikes density [**49**],[**50**],[**51**]. The BNST promotes these alterations, which have an indirect impact on the hypothalamus. This is attributed to the interrelation between the BNST and PVN [**52**].

1.2.6.2 Threat expression in humans

Research on men revealed, that neurons expressing CRF are located near those expressing enkephalin, which blocks the action of CRF, cytoarchitecture that may permit the BNST to control approach and avoidance response [**2**].
The involvement of the BNST in persistent threats is preserved in men. Unexpected long-duration (40 s) [**53**] and short-duration 1.75–5.75s threats [**54**], [**55**] induce enhanced human BNST responses. Interestingly, middle term (10–20s) time periods of context expectation evoke the vivid function of the nucleus [**56**]. Nucleus function is proportionate to shock anticipation, time [**57**] and space [**58**] propinquity to danger stimuli, conceived fear [**59**], and frightening pictures [**60**]. The valence supervision function of the nucleus has an impact on maladjustment mood, post-traumatic stress disorder (PTSD), and all valence characteristics of depression. Current literature, concerning human subjects, document the amplified function of the nucleus to unexpected fear patients suffering anxiety disorders [**61**], [**62**], [**63**], [**57**] [**64**].

1.2.6.3 Anxiety expression in rodents

Initial research for anxiety emphasized the role of the amygdala. Lee et al.[**65**] conducting experiments on rats, reported that the CeA impairment eliminated contextual reaction to threat, while it did not have an effect on anxious reactions. Significantly, BNST impairment did not have an impact on threat, indicating a functional uncoupling between the amygdala and the BNST, despite their strong interrelation. BNST functionality was proven to be directly proportionate with the levels of CRF in the cerebrospinal fluid [**65**]. In other experiments in rats, anxiolytic medication demonstrated a distinguished impact on constant threat responses of BNST and periodical ones from the amygdala. Both benzodiazepine and serotonin selective reuptake inhibitors (SSRIs) ameliorated significantly persistent threat activity but had no impact on periodical threat reactions [**66**]. Conversely, the 5HT1A agonists diminished phasic, but not sustained responses. Benzodiazepine uptake diminishes CRF-amplified startle, revealing that this phenomenon relates to BNST-relevant reactions [**67**].

1.2.7 BNST and its role in addiction based on rodent experiments

Apart from pleasant sensation, relevant literature focuses on the negative reinforcement in addiction. Negative reinforcers drive individuals' actions by eliminating negative cues. Hence, addiction perseveres via the evasion of unpleasant emotions, which are present in abstinence periods [**68]**.
Both the HPA network and threat evasion responses controlled by CRF participate in long-term abstinence from all addictive drugs. Amygdala CRF is increased upon abstinence [**67**]. Norepinephrine (NE) receptors participate also in abstinence-relevant stress, as it is documented on both animal and human subjects [**69**], [**70**].
Subjects with anxiety disorders are under the effect of negative reinforcement and not reward. BNST contribution to abstinence responses is marked in addiction pathway, apart from this, the nucleus participates in other stages of addiction [**70**].

1.3 BNST Structural Connectivity Characteristics in humans

BNST of men is usually compartmentalized in a medial to lateral pattern. All parts manifest similarity with common rodent classifications. The nucleus in men may also exhibits a compartmentalization between anterior and posterior divisions [**71**].
The BNST projects mostly to the PVN, ventromedial nucleus, lateral hypothalamus, supraoptic region, and medial preoptic area (MPOA). **The most abundant BNST efferent to the hypothalamus are the inhibitory ones to PVN and VMH. Endocrine reactions are bound to stress stimuli [72]**.

BNST association network is preserved in men throughout the evolution [**1**], [**73**]. In rodents and humans, activation of the BNST–hypothalamus circuitry is thought to mainly disinhibit the hypothalamus, promoting activation of the HPA axis.

1.4 Patterns of anxiety, addiction and memory consolidation (Figure 2)

1.4.1 Human studies

Anxiety and addiction share many attributes. This relationship is established in humans both theoretically and experimentally. They are both triggered by stress [**74**], [**75**], and vice versa altered stress reactivity manifests intensely with both of them [**76**]. Furthermore, they are both highly comorbid [**77**]. The BNST is ideally located to initiate allostatic alterations via its intense connectivity with (PVN), the hub of HPA axis that instigates cortisol activity. The BNST shows common functional associative profile with CeA. Hence, it is subsequently also involved in withdrawal. Resting state fMRI has previously indicated that opioid addicted subjects manifest notably reduced functional connectivity between the two nuclei [**78**].

1.4.2 Rodent studies

Based on rodents' observations, we have three patterns of behaviors against threat stimuli. The circa-strike or imminent responses, post-conflict responses (danger is current, but physically not impending) and pre-conflict responses (recognizable threat- previously confronted). Second and third pattern are elicited by possible or unforeseen threats and constitute a sustained hypervigilant activity, corresponding to anxiety. Thus, the short-term instant reactions or fear abide in the imminence of danger, whereas constant reactions or anxiety appear even when danger is not currently conceivable [**77**].

Further animal experiments demonstrated that CRF cells of BNST reduce dopamine (DA) response of the NAcc, resulting in the depressive mood at abstinence period. Sequentially, CRF efferent fibers of BNST stimulate the NAcc shell promoting memory consolidation [**79**].

CeA accumulates noradrenergic (NA) afferents mostly from the (LC), which is activated at opioid abstinence [**80**].

Multiple rat experiments have robustly verified the assistive role of BNST in memory consolidation. Not only does the basolateral amygdala (BLA) participates in memory consolidation [**81**], but the CeA, as well. CRF1 receptor activation in the BLA is required for consolidation of fear memory [**82**], whereas blockade of protein synthesis, or activation of cannabinoid receptors in the CeA, hinders the long-term storage of fear memory [**83**] and defined taste aversive memory [**84**]. Aversive stimuli enhance CRF neuron responses in the CeA and enable storage of long-term memory [**85**].

The BNST may also interrelate with the amygdala to preserve the long-period emotional memories [**86**]. In addition to that, BNST can also regulate memory consolidation through its direct connections to other memory systems, such as the caudate nucleus [**87**].

Thus, BNST is crucial for the regulation of reminiscence storage by glucocorticoids [88]. NAcc shell participates in the storage process. Therefore, in animal models direct and early NAcc shell injections of NMDA and DA1 blockers hindered hedonistic Pavlovian tuitional tasks [**89**],

whereas microinfusions of glucocorticoids and amphetamine improved memory outcomes for hdonistic and frightful memory tasks [**90**], and D2 activation is necessary for consolidation of fear memory [**91**], [**92**], [**93**].

1.5 BNST contribution in anxiety regulation in humans and non-human primates. Magnetic Resonance Imaging (fMRI) analysis.

Neuroimaging studies in macaques confirmed the contribution of BNST in anxiety behavior. BNST activity involves prolonged freezing at the sight of a human invader [**94**]. Freezing enables peering danger and evading detection. It bears resemblance to rodent anxiety-like responses manifested at the post-conflict period. The uncoupling of anxiety and fear was proven successfully by Alvarez et al. [**52**].

Moreover, research on human individuals, emphasizing on BNST association certifies its malformed plasticity [**95**] ,[**64**], [**96**] under stressful context [**97**]. Recently, the BNST is being defined as an anatomical locus whose modulation may ameliorate dysfunctional mood. Prolonged deep brain stimulation (DBS) of the nucleus decreases the intensity of obsessive–compulsive disorder signs [**98**], refractory anorexia nervosa, and major depressive disorder (MDD) [**99**].

Mobbs et al. examined how proximity affects threat using functional MRI. They employed video projection of a live tarantula motion within a container hurrying to participants' limb. The spider was indiscriminately allocated into divisions at variable distances from the examinee's foot. The BNST response increased as the tarantula moved proximal and vice versa. The BNST in men is prone to upsurge of danger not only to temporal adjacency, but also to spatial closeness [**100**].

Instead of aversive shock stimuli, studies evaluating emotion functioning and anxiety in men utilized threatening pictures. To clarify, whether the BNST reacts to expectation of watching frightening pictures, Grupe et al. projected this kind of pictures and calculated constant expectation within a 2–8s time interval. At neutral image anticipation, the BNST manifested continuously intense activity upon expectation of frightful pictures. Therefore, the BNST responds promptly to threatening stimuli, but it also relates to emotional cues [**101**].

Coaster et al. [**102**] required their subjects to assess the risk of experimental case hypothesis based on the imminence grade of injury. In a rather imminent high injury, BNST function increased, revealing that the nucleus activates upon observation of upcoming serious dangers.

1.6 BNST and behavioral models

1.6.1 Conceptual framework

The BNST assimilates external stimuli into behavioral patterns modulating, thus, a multitude of emotional states. Apart from amygdala connections, three distinct networks are responsible for these properties. First, the network between BNST and lateral hypothalamus (LH). Second the networks toward paraventricular hypothalamus (PVH) and the periaqueductal

gray area (PGA). Third the pathway toward ventral tegmental area (VTA). The last pathway is responsible for reproductive and defensive behaviors [**103**].

The BLA relates to the diencephalon and Broadman areas 10,11 and 47. Therefore, it is regarded as the "sensory" amygdala [**104**]. The BLA can directly activate and suppress the CeA, which confers the efferent pathway, especially in adjunction to fear responses. In addition to this, BLA also interrelates to corticostriatothalamocortical (CSTC) networks, which are particularly comprised by the orbitofrontal and ventromedial prefrontal cortices along with Nacc [**104**], [**105**]. Hence, the BLA has impact on subjective perception and aimed motivation.

Imaging research verifies the fact that, the CeA is affiliated with BNST [**106**] and threat responses, mostly to specific brainstem regions, such as PAG and LC [**107**]. Therefore, the CeA has prominent control of behavioral threat responses. Both, the BLA and the CeA project to the hypothalamus, as it was reported in rat studies [**108**]. Functional connectivity studies in men have corroborated these hypotheses [**109**].

1.6.2 Experiments in rodents

Lateral hypothalamus facilitates different aspects of anxiety behaviors. This is documented in rodent experiments. Particularly, the anterdorsal BNST demonstrates anxiolytic effects via the innervation of LH and VTA [**40**]. Two distinct pathways exist originating from two distinguished subgroups of LH aiming the two different subgroups of GABAergic neurons of BNST, which express either CRH or cholocystokinin. In parallel, glutamatergic projections emanate from the anterior BNST and terminate in arcuate nucleus of hypothalamus. They are considered anxiogenic and are accompanied by glucose increase [**110**].

From research on rodents has been established that, the largest volume of hypothalamic afferents arises from dmBNST. The latter suppresses the magnocellular and parvocellular cell groups within PVN. They also suppress supraoptic area and MPOA [**11**]. Parallel efferent towards PVN coexist with GABAergic projections from fusiform, rhomboid, alBNST, amBNST, and CRF+ ovBNST subnuclei.

Principal and transverse subnuclei, suppress the parvocellular division of PVN, as well [**70**].

The balance between activating and de-activating BNST signals is thoroughly elaborated in rodent models. The anteroventral BNST sends both glutamatergic and GABAergic efferent fibers to the non-dopaminergic segment of VTA. Stimulation of this pathway promotes anxiety, whereas the GABAergic activation had anxiolytic effects [**110**]. Glutamatergic afferents originate from insular cortex [**112**]. It is believed that the GABAergic neurons of BNST exert their effects through the amygdalar pathways [**113**]

1.7 Functional MRI studies of human BNST connectivity

Sommerville et al. showed that the inferior frontal gyrus, insula, and BNST promote the preservation of fear condition via BNST's constant stimulation. The inferior frontal gyrus and anterior insula (AI) manifest more vivid function in more stressful context and are massively associated with areas of temporal and orbital cortex, as well. The ventromedial prefrontal cortex (vmPFC) has been involved in the suppression of conditioned fear. Sustained activation of vmPFC via predictive knowledge based on current and future environmental events may ameliorate anxiety status of individuals [**57**].

Klumpers et al. correlated this network with ventral striatum (VS)/ (BNST), and thalamus/mid-brain circuitry. Interestingly, the amygdala was not included in this loop. BNST was associated stronger with striatum, anterior cingulate cortex (ACC) and hypothalamus **[55**]. Alvarez et al. presented in their study that BNST, midcingulate cortex (MCC) and anterior insula form a network, which is activated under unpredictable threat [**53**].

Herrmann et al. described a positive coactivation among the amygdala, auditory and visual cortices. Therefore, they stressed the crucial function of the amygdala in the alerting response system which regulates the perception and mood status to aversive occasion. On the contrary, sustained anticipatory responses were observed in the BNST, insula, thalamus and periaqueductal gray. Functional connectivity of BNST, insula and prefrontal cortex were significant in later stages of threat anticipation. In general, **both BNST and amygdala have different functional connectivity networks [114].**

Hur et al. performed their fMRI study with visual, auditory and electrical stimuli. They described the threat anticipation network, which is comprised of midcingulate cortex (MCC), AI, OFC, dorsolateral PFC (dlPFC) and frontal pole. BNST and dorsal amygdala (CeA) were coactivated at certain threat anticipation, in the context of their anatomic and histological affinity [**115**]. From this coactivation, saccades orientation to threat signals can be explained [**116**].

Pedersen et al. compared healthy subjects and patients suffering posttraumatic stress disorder (PTSD). They identified activation of lateral and medial PFC in patients' group along with the hyperactivation of amygdala. Right BNST, especially, develops action synchronization with vmPFC, while the left one exhibited reduced synchronization with dorsal medial PFC (dmPFC). The CeA conveys the response to short-term, distinct threat stimuli, whereas the BNST conveys responses to long-term and general threat [**116**]. Pedersen et al. documented in a parallel study that BNST responds to novel and negative images proving that the BNST does not present habituation [**118**].

Both the CeA and BNST were responding to an area within thalamus compatible with the interthalamic adhesion. Furthermore, medial dorsal thalamus demonstrates functional connectivity (FC) with both the CeA and BNST. The aforementioned nuclei are both associated with the caudate nucleus, ventral striatum, hippocampus and mPFC [**54**].

The intense functional junction between BNST and striatum clarifies the relation of stress and prompted actions. The paracingulate region (PCC) more coupled with the BNST than CeA was located within the dorsal mPFC. The PCC is especially involved in self-orientation and pondering. As a consequence of this, BNST is selectively implicated in cognitive characteristics anxiety, relative to the amygdala [**119**].

McMenamin et al. examined the temporal sequence of threat and safe cues on twenty-four healthy subjects. Upon the early (within 5seconds) phase, increased responses were recorded in thalamus, anterior insula and visual cortex. Responses were decreased in default network areas. In the intermediate phase posterior cingulate cortex (PCC) and dmPFC were activated (7,5-17,5 seconds). Ventral striatum and NAcc associations, especially with medial OFC were activated, upon threat **stimulation at the third temporal phase (20-40seconds)** [**56**].
Murty et al. assessed individuals, who were informed visually, that they will receive either intense-threatening- electrical stimulation or moderate-safe stimulations within two hours. Default network reveals dampened activation at frightful stimuli. **The anterior dorsal insula, especially on right hemisphere, exhibited sustained responses that were greater at threat. On the contrary, BNST responses were not sustained for threat, despite their intensity. Greater responses relative to threat were observed in both amygdala** [**120**].
Limbachia et al. compared the effect of controllable versus uncontrollable electrical stimuli. In their fMRI analysis they observed that **both BNST along with left dorsal AI demonstrated intense responses in uncontrollable stimuli.** In controllable stimulation group the diminished responses of BNST responded to reduced aversiveness or noticed impact [**121**].
Straube et al. compared the fMRI responses of spider phobic individuals versus healthy ones, when they expected images of spiders. The sufferers exhibited amplified function during expectancy **in the dorsal ACC bilaterally, in right AI and left BNST** [**61**].
OCD anxiety correlates with BNST hyperactivation, and enhanced functional connectivity with the frontopolar cortex (FPC) . Anxiety is imputed to inadequate cortical downregulation of this hyperactivation. This deficient inhibition is the result of restricted functional connectivity between subthalamic nucleus (STN) and the internal part of the Globus Pallidus. **Activity in the FPC downregulates hyperactivation of subcortical limbic structures. Hence, increased functional connectivity between the FPC and the amygdala is documented in frightful context and indistinguishable findings are found in FPC-BNST coactivation throughout the periods of constant fear** [**122**].
Figel et al. evaluated 22 individuals with social anxiety disorder (SAD) and 22 disorder-free individuals. **SAD sufferers in contradiction with control persons exhibited enhanced periodic function in the left CeA and BNST.** During sustained threat expectation, no difference in BNST function for subjects with the disorder and control population was noticed [**63**].
Dagher et al. observed a large bilateral **deactivation upon stressful mental changes in smokers population of the NAcc [123**].
German et al. evaluated 5 OCD patients using voxel-wise analysis aiming to elucidate the hubs of OCD. Deep brain stimulation (DBS) of inferior thalamic peduncle resulted in improvement of symptomatology. Acquired functional connectivity with amygdala bilaterally resulted in better outcomes. The advantage of DBS as therapeutic method was achieved with ALIC/ventral striatum stimulation adjacent to BNST [**124**].
Baas et al. evaluated the startle response in patients having underwent NAcc-DBS and having the system turned on. No statistically significant reduction of startle response was reported

either under predictable or unpredictable shock situations. Patients reported subjective anxiety during the examination. **Therefore, the authors concluded that the defensive state mechanisms are not associated with anxiolysis.** They recorded amplified progressive unresponsiveness to stimulation at high-frequencies, when the locus was the dorsomedial ventral striatum [**125**].

Neumann et al. recorded long field potentials in 23 patients with major depressive and obstructive compulsive disorder. They gained their results by externalizing DBS electrodes. **They exhibited that α-oscillations (8-14Hz) in subcallosal area (GC25) and BNST predispose to desolate emotional condition in major depression [126].**

1.8 Recommendations for BNST stimulation in OCD

Two recommendations for DBS in OCD exist: (1) Bilateral Subthalamic nucleus stimulation should be employed as a treatment for pharmaceutical persistent OCD (level I evidence). (2) Bilateral NAcc or BNST DBS as therapy measure for patients with pharmaceutical persistent OCD may be utilized (level II evidence) [**127**], (**Figure 3**).

Throughout the sequent paragraphs the principles/mechanisms of DBS and the **pathophysiological processes implicated in OCD are introduced.**

1.9 Mechanism of Deep Brain Stimulation (DBS) (Figure 3)

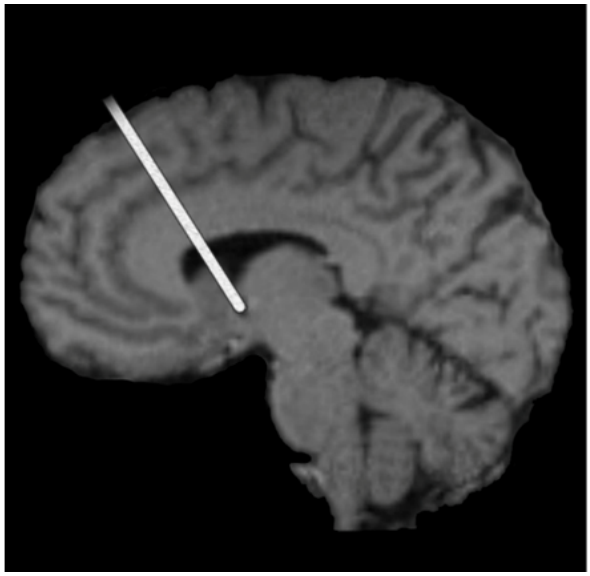

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Figure 3. Typical trajectory of a BNST and ALIC deep brain stimulation electrode [**132**

1.9.1 General aspects

The mechanism of DBS can be perceived in two phases [**128**]:

1) The short-period excitation of axons centripetally located to the stimulation locus.

2) Non-specific synaptic suppression associated with short-period plasticity.

The synaptic driving relies on the kind and equilibrium of afferent neurotransmitters, which is proportionate to the volume of the stimulated tissue. DBS elicits action potentials in axons even when frequencies reach 200Hz [**129**]. It predominantly regulates the centrifugal impulses toward the target. Consequently, stimulation of areas, which receive primarily glutamatergic excitatory input results in an instant excitation of stimulated area's neurons [**130**]. On the contrary in areas with primarily GABAergic input, stimulation evokes an instant suppression, which can surpass DBS period [**131**].

Membrane hyperpolarization occurs at the most proximal to stimulation point electrode, whereas nearby areas will be hypopolarized and function as a negative electrode. Anodic stimulation is based on the negative electrode-like areas to produce current in axons. Hence, anodic stimulation warrants higher stimulation intensities and is less effective than cathodic stimulation [**133**], [**134**], [**135**]. Anatomy remains the most important prognosticator for beneficial stimulation. Anodic stimulation of cortex necessitates lesser intensities. This phenomenon is attributed to due to the posterior and caudal trajection of pyramidal axons.

Overall, the longitudinal stimulation achieves the greatest excitation (**Figure 4**).

Constant high-frequency stimulation leads to a sequence of instant synaptic driving [**129**] by non-specific synaptic dampening. Afterwards, cell excitation ceases at the stimulation locus [**136**]. This synaptic dampening is characteristic to stimulation frequency and appears significantly at approximately 100Hz or higher. Experimentally, it is revealed that thalamocortical synaptic transmission is not prolonged at high frequencies [**137**].

Short-term stimulation leads to depression of target structures attributed to presynaptic decrease of neurotransmitter concentration and their release pattern, along with presynaptic calcium depletion [**128**].

All axons cross the Volume of Activated Tissue, therefore the same locus may be crossed by downstream or upstream currents. Hence, long-term and distal polysynaptic network effects are associated with focal synaptic suppression of stimulated neurons [**138**].

Structural connectivity functions as predictor of DBS outcome. It has greater significance if modulated fiber tracts are along to information current. **Here, downstream suppression of synaptic input to the target structure is likely one of the mechanisms of high-frequency DBS [138].**

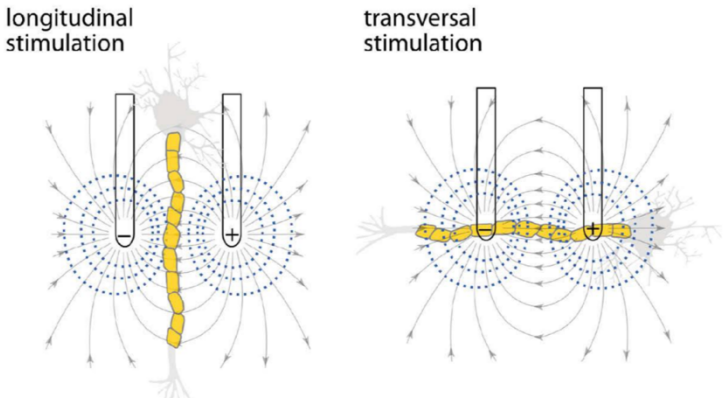

Figure 4. Differences between longitudinal and transverse stimulation. Greater amount of neuraxons are involved in longitudinal stimulation [**139**]

1.9.2 Modulation of oscillatory local field potential activity

The local field potential (LFP) describes the accumulation of potentials of neurons proximal to the recording electrode and relate to transmembrane ion flow [**140**]. LFP coordinate neural firing recording, which responds to pre-and post- synaptic flow from neurons directly situated in the anatomical area of interest [**141**]. Enhanced synchronization in the beta frequency band portends to Parkinson's disease [**142**]. The hypodopaminergic condition leads to amplified oscillations within 13–35Hz or beta frequency band, both in the STN and GPi [**143**]. **DBS induces local suppression of this rhythm [144] via the dampening of beta frequency, which further responds to clinical signs amelioration [145]. Therefore, the hypothesis was raised that DBS functions via regulation of oscillation types.** Beta activity in LFP relates to increased spike firing [**146**]. Suppression of beta power is accompanied by a decrease in firing rates [**147**]. The exact etiology of oscillatory dysregulation is debatable. Modification of abnormal patterns is a putative stimulation effect, inasmuch as LFP documentation constitute biomarkers in diseases other than PD, such as dystonia [**148**], Tourette's syndrome [**149**], [**150**], OCD [**151**] and MDD [**131**]. Standardized δ, β and γ frequency bands in the right BNST interrelate to OCD. Oscillations in δ rhythm are amplified and in γ rhythm diminished, respectively at compulsion initiation. On the contrary β frequency increased when compulsions ceased. Furthermore, the outcome after BNST DBS, regarding compulsions control, was markedly dependent on the degree of oscillations alteration [**152**].

Record of cortical activity during DBS is feasible along with subcortical structures stimulation [**153**]. According to these studies the suppression of beta power is recorded at both areas of interest (STN or GPi) [**153**]. These studies utilized EEG, magnetoencephalography (MEG), and electrocorticography (ECoG) [**154**]. Cortical broad rhythm activity coincides with particular periods of the beta oscillation [**155**]. This phenomenon is usual in the motor cortex during hypodopaminergic OFF state [**156**].

According to the aforementioned literature regulation of only one hub of the network results in functional changes of the rest of the network. Apart from the coactivation of hubs of oscillatory networks orientation of information current is also evaluated. DBS regulates synchrony but does not alter orientation of information current [**145**].

1.9.3 Connectomic perspective of DBS

Under pathological conditions local aberrant neuronal excitation is adjusted to LFP oscillations and dissociate interregional networks.
This abnormal cerebral connectivity is hindered by electrical stimulation. As a whole, DBS was shown to be implicated in global brain connectivity patterns, as it is described by the theorem of network centrality of graph-theory–relevant metrics [**157**]. The neuromodulation effects among brain areas is actually a neurophysiological desynchronization. In OCD, this effect is attributed to the reduction of the so far abnormally intense association between the frontal cortex and Nacc [**158**].
Detailed knowledge of DBS effects derives from the movement pathology, where high- frequencies (>100 Hz) are enforced in vertical pulses via electrode. This mechanism regards:

1) Regional regulation of neurotransmitter release and consequent transmembrane activity and pulse propagation.
2) Regional regulation of oscillatory field potentials.
3) Distant regulation of oscillatory synchronicity.
4) Regulation of whole-brain network connectivity.

Individual pulses excite presynaptic terminals of all efferent fibers. In targets with mostly GABAergic inputs stimulation leads to a net hyperpolarisation. **In a mesoscale assessment DBS induces suppression of beta activity [159].**
Stimulation settings for MDD and OCD were customized based on the ones of Parkinson disease [**160**]. Hence, PD DBS ranges between 100–130 Hz. 130 Hz compensates energy depletion and symptom control [**161**]. Apart from this, it is relatively safe. Furthermore, brain functionality is recordable by the stimulatory electrodes within time period often exceeding one year [**162**]. None of the studies estimates the geometry of the pathways. Selecting different parameters a specific pathway may be stimulated more than the others.
Evaluation of outcome is difficult in psychiatric disorders. Term such as “depression” is hard to measure. Accordingly, the establishment of prognosticators is laborious. [**163**]. Therefore, cognitive aspects including cognitive restraint, reward valence and negative emotions should be estimated for proper tailoring of treatment [**164**]. Trials that are used in animals include approach- avoidance contexts [**165**], [**166**].

Assessing cognitive networks reveals the physiologic aim for efficacious stimulation: periodic oscillations of the local field potential (LFP), and the coactivation among brain areas. LFP oscillations, lower than 25 Hz, are often coupled even when the loci are distant. This was the

rule for movement disorders [**167**] and its efficacy on emotional circuits has been demonstrated [**168**].

1.10 Pathophysiology of obsessive-compulsive disorder

OCD pathophysiology relies on a dysfunction of cortico-striato-thalamo-cortical circuit (CSTC). This network encompasses executive and limbic cortices [**169**]. Anterior cingulate cortex (ACC) contributes in motivation, conflict control and acknowledgement between desired and anticipated conditions [**170**], (**Figure 3**). Hence, one may deduce, that obsessions and compulsions originate from an aberrant reward process leading to an impaired distinction between expected and present conditions. PET and fMRI research indicated the excessive ACC function with either symptoms triggering and fallacies or hindered distinction situations [**171**]. Selective serotonine reuptake inhibitors (SSRI) administration reduced ACC metabolismo, as it is evaluated by PET. This observation was reflected to better behavioral outcomes [**171**]. Anterodorsal cingulotomy leads to long-term amelioration refractory OCD symptoms. OFC and ACC exert combined influence on action valence and selection [**172**].

Caudate nucleus participates in procedural learning and this may explain the loss of actional sequence sustained by frontal subcortical associations that are assumingly present in OCD [**172**]. **Excessive caudate activity is parallel to the grade of symptomatology, as it is documented with PET and fMRI studies [173]. OCD patients demonstrate reduced dopamine D2 receptor binding [174] and elevated dopamine transporter accumulation in the caudate [175].** Thalamic activity is increased in OCD together with OFC activity estimated by PET along with ipsilateral caudate nucleus [**171**].

Hippocampus and amygdala are interconnected together with the PFC. Amygdala associates significantly external cues with emotional importance and contextual fear responses [**171**]. Hippocampus incorporates spatial and mood data [**176**] and participates in the behavioral patterns to stress [**177**]. **Therefore, aberrant functionality of these loci may underpin the anxiety** caused to patients by the impelling to execute compulsions.

OCD patients manifest abnormal connections in functional MRI analysis between ventral striatum (VS) and OFC that are relevant to disease's degree [**178**]. On the other hand, the activity in these structures diminishes with medical treatment and cognitive behavioral therapy [**179**]. Furthermore, medium spiny neurons in the caudate, which present efferent fibers to OFC, tend to depolarize intensely during exacerbation of OCD [**180**]. Continuous and exclusive optogenetic stimulation of the OFC-VS efferent fibers in animal models promote OCD-relevant symptomatology [**181**]. In addition to that, the orbitofrontal branch of CSTC is involved in motion execution aligned with emotional cues; therefore, this excessive activity promotes the urgent and formalistic characteristics of OCD [**182**].

In PET studies OFC activity is reduced with medical treatment. This reduction relates to OCD symptoms alleviation [**182**]. The medial OFC (mOFC) and lateral OFC (lOFC) participate differently in disorder's manifestation. The first one provides regulation of feelings and positive

appraisal procedures, whereas the second one mediates aversive stimuli and reactions to threat [**183**].

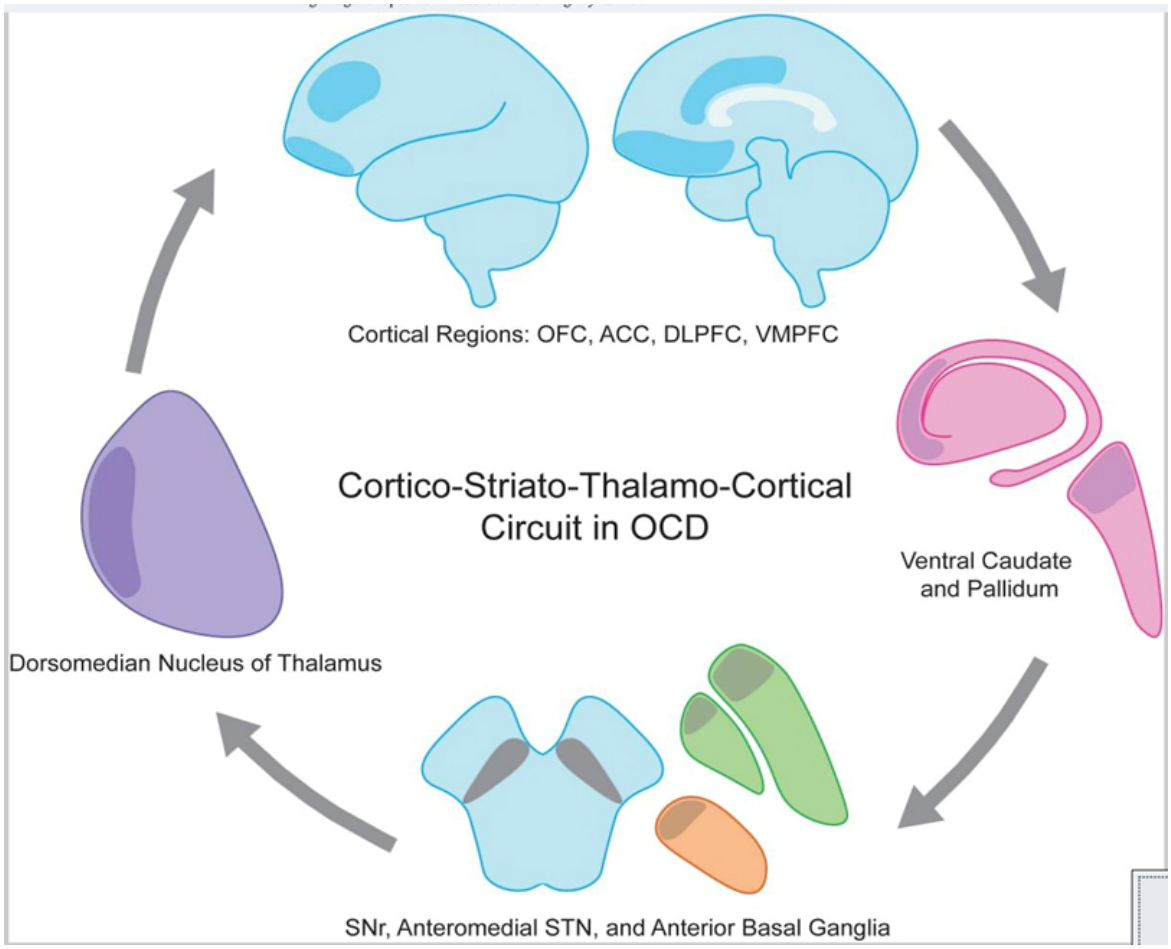

Figure 5. OFC, ACC, dlPFC, and vmPFC (colored blue), ventral caudate and pallidum (colored pink), anterior GPi and GPe (colored green), anteriomedial STN (colored orange), SNr, and dorsomedian nucleus of the thalamus (colored purple). ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; OFC, orbitofrontal cortex; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; VMPFC, ventromedial prefrontal cortex. [**169**]

Reduced activity of the dlPFC and dorsolateral caudate are present in the disorder, as well [**184**], (**Figure 5,6**). The dlPFC forms a loop with dorsal segment of caudate nucleus, lateral GPi, rostral substantia nigra reticulata (SNr), and the ventral anterior thalamus [**185**]. Dampened functionality of this loop hinders the transition and sequence between actions, a pathognomonic sign of the disorder [**186**].

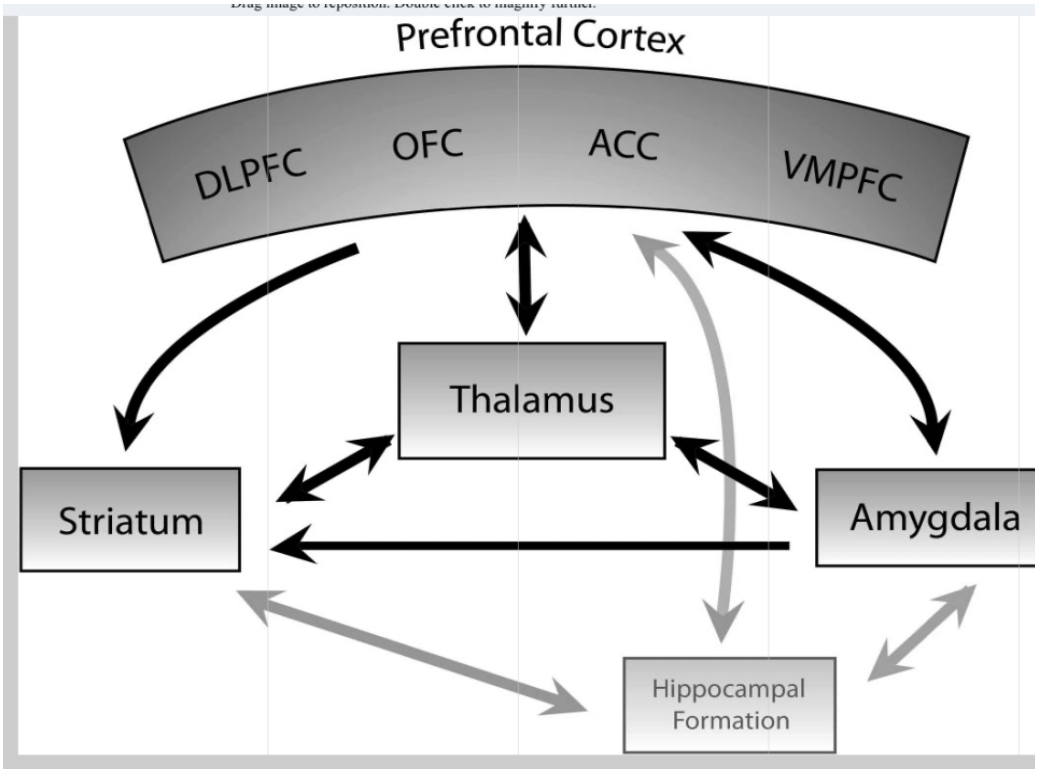

Figure 6. Cortico-striato-thalamocortical network. In DBS for OCD, high frequency stimulation modulates the functionality of this network. DLPFC, dorsolateral prefrontal cortex; ACC, anterior cingulate cortex; OFC, orbitofrontal cortex; VMPFC, ventromedial prefrontal cortex. Arrowheads denote the traectory of neural input. Black vectors respond to major connections. Gray vectors respond to additional connections [**171**].

1.11 Scales for assessing-OCD

The YBOCS is a semi-structured interview introduced by Goodman and colleagues to evaluate obsessive compulsive symptoms [**187**]. Scale grading does not rely on distinct types of symptoms, but on the characteristics of the symptoms as referred during the interview, such as their length, encroaching or resistance. The scale involves two segments of five items each, the Obsessions category and the Compulsions one. Each category evaluates the characteristic of the disorder within a range from 0 (lack of signs) to 4 (exacerbation of signs). These involve (1) temporal duration of the disorder, (2) severity of interference, (3) anxiety, (4) refractoriness, and (5) assumed restrain of the disorder. YBOCS attributes lesser grading to marked refractoriness. Grading extracted from the subscales provide a YBOCS Total score [**188**].
The signs catalogue includes fifty-four dualistic questions estimating the presence or remission of the disorder. Problems which occur are the subjective perception of the “refractoriness to obsessions” item. There is also reduced sensitivity regarding the slight alteration in extreme symptomatology and low discriminant validity regarding depressive feelings [**188**].

Refractoriness to Compulsions, was slightly associated with the rest of the inventory. Clinically sufferers themselves are not able to discern between their maximal efforts of resistance and positive outcome. It has excellent inter-rater reliability in long-term, or among distinct interviewers [**188**].

The scale demonstrates low discriminative validity, as long as, it is strongly related to depression compared to other aspects of the disorder. This problem is present in other OCD inventories, as well [**189**], [**190**]. These collateral depressive symptoms denote the desolation in severe disorder and not a comorbidity.

State-trait anxiety inventory (STAI) This is a forty item self-evaluation inventory, which estimates the existence of anxiety signs [**191**]. It is made up of by two subscales: the STAI-state and the STAI-trait. Trait anxiety responds to perception of stressful conditions, which is a constant personality characteristic [**191**], [**192**]. Elevated trait anxiety grading responds to misconception of situations as perilous. State anxiety ranges in the lapse of time temporally and depends on the stressful stimuli. Subjects with high trait anxiety scores appear to possess higher state anxiety scores [**191**], [**192**].

Depression anxiety stress scale (DASS-21). This instrument evaluates depression, anxiety and stress. The DASS-D describes a person's despair, positive emotions and self-confidence [**193**]. The DASS-A describes autonomous nerve system status, contextual anxiety, musculoskeletal signs, perception of anxiety agitation and contextual anxiety. At last, DASS-S describes agitation, emotional strain and negative emotions [**194**]. The individual segments involve seven questions which rate from 0 ("did not assign to me at all") to 3 ("assign to me a lot, or usually") seven days before the interview. The total score varies from 0 to 21. Recent literature, was not able, though, to present border zones for the intensity of the disorder [**195**].

1.12 Diagnostic and statistical manual of mental disorders: fourth edition (DSM-IV)

The DSM-IV is the horse shoe for identifying psychiatric diseases. The Structured Clinical Interview for DSM-IV (SCID) utilizes categorical items to classify psychiatric diseases. The presence of experienced interviewers to employ the SCID are necessary. Diagnosis itself is established by clinical judgement [**196**].

The Global Assessment of Functioning (GAF) [**197**] is an instrument which evaluates the communal and vocational activity along with psychiatric signs in adult population. One significant drawback of this questionnaire is the ineptitude to discern clinical signs from the normal functioning. The requirement for a specialized evaluation instrument of global functioning, not directly associated with psychopathology, resulted in the establishment of the Social and Occupational Functioning Assessment Scale (SOFAS) [**198**].

The SOFAS evaluates the communal and vocational functioning, but not psychological impairment. It also includes effects of a medical context and applies to the assessment at the current time. Both inventories' scores rely on a sequence of actions. Greater sum implies better performance. Both GAF and SOFAS are utilized for the daily performance evaluation [**199**].

Aims:

The aim of the present study was to conduct a systematic literature review mapping and analyzing the available literature on all clinical studies utilizing BNST stimulation.

2. Materials and Methods

The hitherto literature includes some case series with variable participants. To further elucidate this observation, we conducted our study. We employed a systematic review according to PRISMA 2009 guidelines, medical subject headings (MeSH) terms that were selected were: (Bed nucleus of stria terminalis) or (BNST) and (Stimulation). Time period was set from January 1973 to March 2024. All animal studies were excluded. We did not include Case series involving 4 or less participants. Finally, studies focusing exclusively on BNST activation without therapeutic objective were also not included.

3. Results

The process of systematic review is presented schematically (**Table. 1**). The review extended in two databases Pubmed and Scopus led to the recognition of 653 articles after duplication exclusions. Among them, animal studies and studies not written in the English language were excluded. After the screening of the remaining 70 articles, book chapters, conference papers and reviews articles were excluded. From the remaining 39 studies case reports or case series involving less than four patients were also not included. Finally, thirty articles remained, of which only 11 were on DBS.

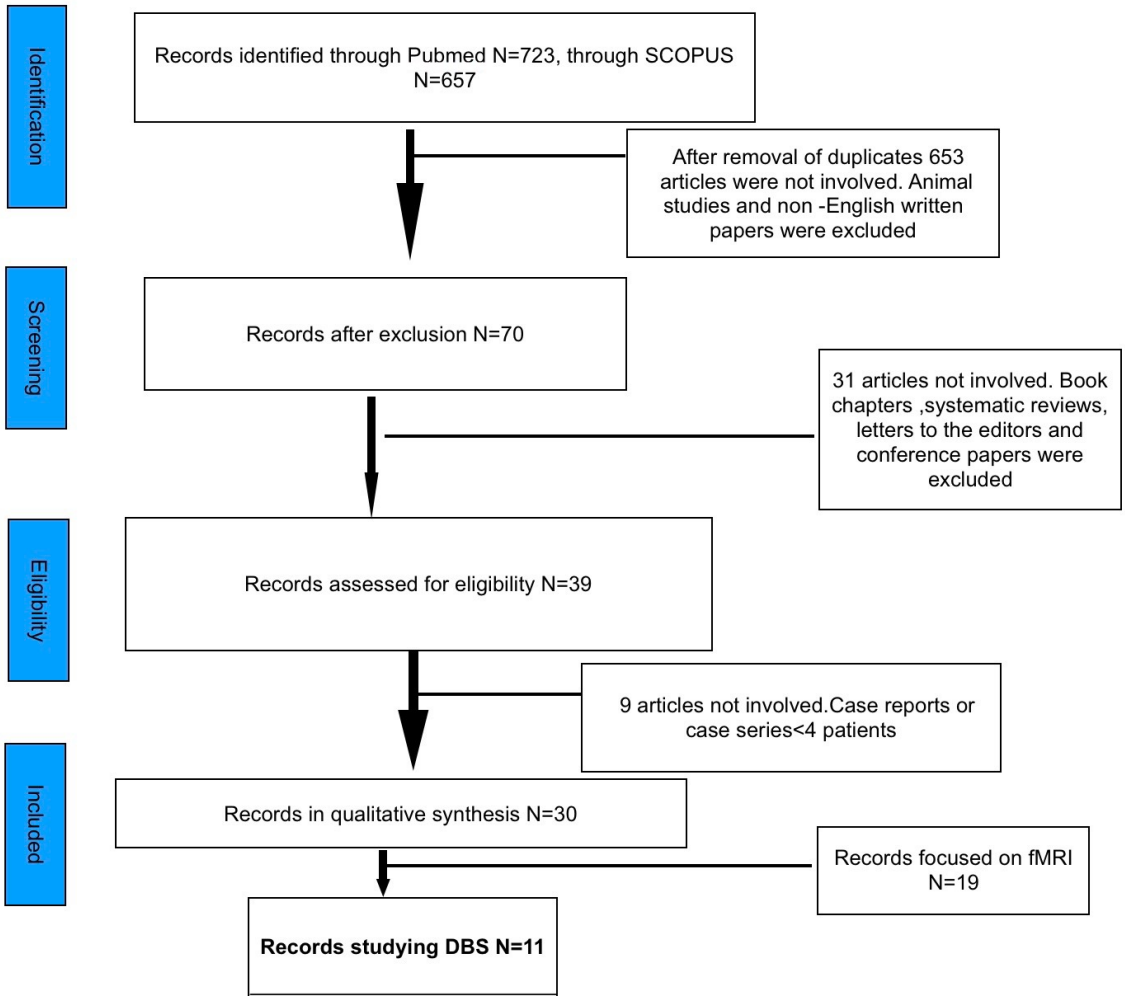

Table 1. PRISMA diagram for the present study.

Studies which have utilized DBS of BNST Region (also see Table 1) Luyten et al. were the first to report that electrical stimulation in the ALIC/BNST region alleviates significantly OCD signs in the so-far medication-recalcitrant patients. They observed 24 patients within a 4-year period. Ten of them underwent exclusive DBS of BNST, whereas 15 patients had adjunct stimulation of ALIC and BNST. Electrical stimulation led to reduced anxiety and depression symptoms. **BNST seemed to be a more effectual target compared to ALIC. One-third of the patients developed epilepsy** [**132**].

Raymaekers et al. evaluated these patients within a period of 12 years. A strong and preserved reduction of the Y-BOCS was rapidly **noticed within the first months. On the contrary when stimulation was off Y-BOCS score was increased. A more severe depressive impact at the starting point of observation portended minimal reduction of the Y-BOCS over time**.

Eight patients had received less dose of medication and half of them warranted no medication upon last follow-up control. The patients after initial rapid improvement regained slowly their previous activity and thus present a progressive downgrade of Y-BOCS scores [**200**].

Mosley et al. studied nine OCD sufferers after DBS at BNST and NAcc interface. The authors studying altered functional and structural connectivity with fMRI isolated a pathway on **right hemisphere crossing the midbrain and reaching the ventrolateral prefrontal cortex** and another one **associating the anatomical locus of stimulation with amygdala, as well.** Fibers of this area were crossing the hippocampal white matter and regress to BNST via the ST proximal to fornix [**201**].

Mar-Barutia et al. compared the outcome of a group of six sufferes who underwent ventral ALIC-Nacc stimulation and a second cohort of 19 patients, who received DBS at BNST. Upon 12 months all patients considered either full or partial responders not only in the severity of OCD but in global assessment functioning, as well. The first cohort was observed for approximately nine years whereas the patients of the second group for approximately five years. **The authors reported a non-statistically noticeable greater reduction of Y-BOCS scores in the BNST patients** [**202**].

Winter et al. evaluated a cohort of six OCD patients in a long-term period at 4 and 8 years, respectively. All patients underwent either ALIC stimulation exclusively or joined BNST and ALIC stimulation. They compared the outcome of patients' cohort who underwent DBS of ALIC exclusively and concluded that stimulation of BNST may not have a particular benefit [**203**].

Luyck et al. assessed the outcomes in 9 patients suffering from OCD. They included cases with uni- and bilateral DBS employing a blinded crossover study design. They evaluated anxiety, avoidance, wellbeing, apart from obsession, compulsions and mood. Patients were allocated according to the intensity of OCD when the. Research program commenced. Bilateral BNST stimulation was beneficial in cases of moderate to severe disorder, concerning obsessions [**204**].

Philipson et al. further supported that DBS of BNST provides alleviation of OCD symptoms measured with Y-BOCS rating 32,6%. They have also studied the cognitive alteration that DBS

brings. **Decline in visuospatial cognition and selective attention been reported in this series** [**205**].

Fitzgerald et al. performed DBS of BNST, just posterior to NAcc and laterally to anterior hypothalamus, as an alternative. The intervention resulted in reduction of physical signs of MDD, essential mood dysfunction and improvement of overall quality of life in 5 sufferers assessed within a maximum period of 2 years [**206**].

DBS of BNST and NAcc for severe intractable OCD results in 27,3% reduction of Y-BOCS and approximately 45% of patients achieve full response. The variation of effectiveness is attributed to the fact that, most studies are series of cases. In addition to that, the definition of 'full response 'responding to 35% reduction or more of YBOCS does not seem to promote the control of the disorder, as long as serotonin reuptake inhibitors may also achieve a 38% YBOCS improvement according to the same criteria [**207**]. It is also associated with cases of negative valence, such as bad mood, tiredness or prolonged worry [**208**].

Mar-Barutia et al also, evaluated the long-period impacts of DBS, within a time span of 20 years. This was one of the largest patients' series and responders superseded the fifty percent of the participants. They studied the outcome of their subjects, who had undergone either ventral ALIC or BNST stimulation. Both of these subgroups were juxtaposed with a sham group. Outcome was evaluated in both OCD and depressive symptomatic, as well. There was a significant decline more than 40% in the patients' group and less than 5% in control group. The new contribution of this study was the fact that none among the unoperated individuals presented full remission of symptoms. DBS thus constitutes a necessary culmination of tailored treatment for OCD. They could not detect predictors, though. Scarcely did their subjects report complications and the majority of them were light and temporary [**209**].

Naesström et al. in their study whose time span was 12 months observed that more than half of the cases, exhibited response and depressive symptoms alleviation, as well. After a review of the pertinent literature they detect a large variance in the traces of improvements. Intuitively expected factors, such as age or duration of symptoms were not proved predictors [**210**].

Research team	Psychiatric disorder and inclusion criteria	Overall study design	Results synopsis	Adverse neuropsychiatric effects
Luyten et al.[132]	OCD with Y -BOCS ⩾30) and (GAF) ⩽45) for at least 5 years	24 patients ALIC-BNST stimulation. Blinded ON and OFF phases. 17 underwent crossover. HAMD and GAF scores	8 patients non- responders. Improvement on ON phases. YBOCS 66% at 4 years and 45% at last follow-up. HAMD at 4 years 67% and 49% at last follow-up. GAF 30 points at both 4 years and at last follow-up Reduction >35%in all questionnaires. Improvement of GAF	5 patients with seizures 4 suicide attempts 2 patients ICH, 2 patients with obstructive apnea
Luyck et al. [204]	OCD with YBOCS >30 for 5 years	9 patients BNST stimulation /blind crossover trial Exhibition of neutral and trigger images BDI and STAI	Acute provocation test evaluation. Reduced obsessive thoughts in moderate-severe OCD No significant benefit of bilateral stimulation	Warmth (7), sweating (4), Nausea (2), absent feeling
Raymaekers et al. [200]	OCD with Y-BOCS ⩾30 and GAF ⩽45 for at least 5 years	24 patients from group of Luyten et al. ALIC-BNST stimulation Follow up 76.5 months. YBOCS, BDI, GAF and HAMD	ON status strongly correlated with YBOCS reduction. Surgery itself associated with GAF improvement	Same to Luyten et al.
Mosley et al. [201]	OCD with YBOCS>24 >2 weeks Treatment refraction to SSRI for 12 weeks+/-antipsychotics	9 patients DBS of BNST/Nacc Double blinded trial YBOCS and MADRS Structural connectivity	12-month follow-up. 7 patients responders with YBOCS 49.6% reduction. MADRS 10 points reduction. Right-sided altered connectivity including orbitofrontal cortex, pars triangularis, parahippocampal gyrus, calcar area, supramarginal region	Parasomnia Reduced libido Mild agitation

Winter et al. [203]	OCD with YBOCS>25 or >32 Time since diagnosis >14 years	6 patients DBS BNST/ALIC YBOCS and WHO-QoL BREF	8-year follow-up. 4 responders 2 non-responders who were not stimulated at BNST contacts	Transient Psychotic reaction (1)
Farrand et al. [207]	OCD with YBOCS>28 25.9 years mean duration of symptoms	7 patients DBS of BNST and NAcc YBOCS, NUCOG, SOFAS, OCI and DASS	3 patients were full responders after 31 months follow-up. YBOCS reduction 30% for BNST group and 29.35% for NAcc group. Reduction of YBOCS and SOFAS	Hypomanic episodes (2) Ageusia (1) Dejá-vu symptoms(1)
Fitzgerald et al. [206]	MDD with Montgomery Asberg test >25 for 5 years	5 patients DBS of BNST/LH/Nacc BDI, HAMD and MADRS	6-,12- and 18-month follow-up. 2 full responders. 2 partial responders. 1 non-responder. 33% overall reduction of HAMD between 18-24 months. 75 increase on QoL. No cognitive deficits	Suicidal attempts (2) Anxiety (3), Persistent Insomnia (1)
Philipson et al. [205]	OCD with YBOCS>25 for 5 years	8 patients ALIC/BNST YBOCS Raven's Colored Matrices, Wechsler Adult intelligence Scale Claeson –Dahls test, Brief visuospatial Memory Test, Delis Kaplan Executive Function System Trail Making Test, Color Word Intererence test Verbal fluency, Dichotic listening task and IVA	12-month follow-up. 3 fully responders.4 partial responders. Improved performance on selective attention/processing speed. Apart from visuospatial cognitive decline no other cognitive deficits	Relative decline of visuospatial cognition and cognitive interference inhibition (Color-word inhibition test)

Mar-Barrutia et al. [209]	OCD with YBOCS>30. No response to SSRIs/antipsychotics for 16 weeks, (GAF) <45%. OCD's onset more than 5 years	25 patients DBS of ALIC and BNST GAF and HAMD	5.4 year follow-up . 11 responders. YBOCS reduction 44.2% and HAMD reduction 41.5% Lesser follow-up period of ALIC DBS patients. No statistical difference between the two stimulation points	Memory complaints (6), headache (10), fatigue (9), insomnia (8), weight gain (6), enuresis (2)
Shofty et al. [208]	OCD with YBOCS>28 for >5 years Drug refractoriness. Commobidities, such as MDD, bipolar disorder and Tourette syndrome	8 patients DBS of VC/Vs or BNST YBOCS Titrated increase of currency intensity and amplitude	Mean follow-up duration 21.25 months**.** 8 responders. Positive valence in VC/VS stimulation more often than BNST. 48,5% reduction of YBOCS in patients with BNST implanted electrodes. Better outcomes in patients with modified parameters	**Bad mood Worry Tiredness**
Naesström et al. [210]	OCD with YBOCS >25 and>5-years duration. Depression with MARDS>29	11 patients BNST bilaterally YBOCS for primary results GAF and MADRS for secondary results	3, 6 month and 12-month follow-up .6 responders. Overall YBOCS reduction 38%. YBOCS reduction 49% for responders. MADRS reduction 27,3%. GAF 12,2% increase	**Anxiety, insomnia** Impulsive medication intoxication

ALIC: anterior limb of internal capsule, BNST: bed nucleus of stria terminalis, BDI: Beck Depression Inventory, DASS: Depression, Anxiety and Stress Scales,
GAF: Global assessment functioning Scale HAMD: Hamilton Deprression Rating Scale, IVA: Integrated visual and auditory continuous performance Test,
MADRS: Montgomery-Asberg Depression Rating ScaleMDD: Major Depressive Disorder Nacc: nuceus accumbens,
NUCOG: Neuropsychiatry Unit Cognitive Assessment, OCI: Obsessive Compulsive Invnetory, QoL: quality of Life, STAI: State-Trait Anxiety Inventory
SOFAS: Social and occupational functioniny assessment Scale, Vc/Vs: ventral capsule/ventral striatum, WHOQoL-BREF: World Health Organization Quality of Life Form,
YBOCS: Yale brown obsessive-compulsive scale

Table 2. Objectives, design and outcomes of studies included in the present review

4.Discussion

4.1 DBS in OCD

OCD is considered resistant when patient has less than 25% reduction in YBOCS, despite a cycle of at least 12 weeks at the maximal acceptable administration of SSRIs or clomipramine, adjunct with 30 hours of cognitive behavioral therapy (CBT). Refractory OCD denotes the non-response at a schema of three antidepressant drugs within half a year combined with atypical antipsychotics [**211**].
These functional terms remain, though, ambiguous in the pertinent trials [**212**]. Despite administration of adequate treatment, persistence of symptoms and serious handicap, in the context OCD is present in 10% of the cases [**213**].
DBS is a neuromodulation method with well-documented efficacy for OCD [**214**]. In the hitherto studies the researchers do not include their patients, according to commonly established and accepted criteria. They conclude, though, that DBS is a last-tier therapy [**215**]. Both fully and partially treated patients refer an overall amelioration of their symptoms, their self-esteem and their handicaps in the social intercourse [**216**].
Therefore, DBS has been established as a practicable method for refractory OCD. Current research data from Sweden emphasize, that less than one third of OCD sufferers are conscious of their problem. Paradoxically, treating psychiatrists do not frequently regard their patients as potential candidates for surgery. In addition to this, they do not consider themselves adequate of setting strict indications [**217**].
Luyten et al were the first who introduced the stimulation of BNST as a target for OCD treatment. They utilized four-polar electrodes. They employed a range of frequencies stimulation and they performed a crossover and blinded study. They added to their armamentarium structural and functional MRI, CT and in a few cases 18F-fluorodeoxyglucose positron emission tomography (PET). Their assessment took place both before and after the implantation and turning-on of the system. Specifically, they noticed that the vast majority of the benefitted patients was undergoing actually stimulation of BNST. Improvement was verified according to YBOCS scale. They ascribed the efficacy to anxiety amelioration and not to basal ganglia modulation [**132**].
In long term observation of Luyten's group's patients it was shown, that sustained stimulation is necessary for OCD control. The relapse phenomenon was mostly marked in cases of battery depletion. Furthermore, high charge densities are warranted for OCD treatment. Interestingly age, gender or duration of symptoms were not predictive factors for the outcome compared to the meticulous stimulation adjustment [**200**].
Luyck et al. controlled the effects of BNST stimulation under visual provocation of anxiety. Their patients had initially undergone a habituation phase involving anxiogenic images exposure and self-assessment of symptoms with disease- specific inventories. The examiners evaluated the outcome of unilateral, bilateral and sham stimulation, while patients were not

acquainted with the settings. Patients reported benefit after BNSTs stimulation, regardless of its being uni-or bilateral. The authors had, therewith, proven that BNST stimulation efficacy was not a placebo phenomenon [**204**].

As more long-term results of DBS were being presented, there appeared studies which evaluated the quality of life in treated OCD patients. Herein, patients exhibited advanced quality of life estimated by generic inventories. The time span of these observations were between four and eight years. No peri-interventional complications or chronic adverse effects of stimulation were reported [**203**].

In addition to this, connectomic studies indicated the benefits of BNST. Regions with strong connectivity related to good outcome. BNST was both structurally and functionally ratified as a hub between CSTC network and limbic system **[201].** The right lateralization aligns with the right-sided corticostriatal circuits, which are involved in inhibition of [**218**] impulsivity [**201**]. Hardware infection and device removal was the most significant adverse events [**201**]. Psychiatric side effects such as severe anxiety, impulsivity and hypomania are also reported.

It remains dubious whether best results are achieved by the stimulation of axonal or terminal end points, namely BNST, STN or NAcc.

In all studies which estimated the long-term outcomes of stimulation improvement, variability in the results is apparent. The 35% YBOCS reduction was set as the lowest cut-off for full response based on the hitherto pharmacological studies [**219**]. Therein, DBS is considered as a last tier treatment, stressing, thus, its efficacious results. The discrepancy can be attributed to the so far limited number of participants [**220**]. Furthermore, the contribution of regular psychiatric review and therapeutic rapport alleviated symptoms and functionality [**221**].

The aggravation of anxiety persists, though, despite the anxiolytic effects of DBS [**220**] . This may be ascribed to the maximal levels of anxiety of these patients. On the other hand, several patients exhibit a constancy of symptoms, due to the chronicity of their disease. This fact deteriorates self- and social requirements, that further aggravate anxiety. Finally, hypomania is a recognized and serious potential side effect in DBS [**207**].

DBS for refractory OCD bears relatively few negative cognitive sequels during the first twelve months after the surgery. Philipson et al. appraised elaborately the negative impact of prolonged stimulation. They utilized disease-specific inventories [**222**]. They reported that inhibition during tasks was restricted and the overall cognitive adeptness was achieved. Their results were comparable with the side effects of subthalamic nucleus (STN) stimulation and not VC/VS stimulation [**223**]. The most remarkable observation was a mild decrease in visual spatial learning. The short-term memory results were improved, though. This pattern of effects was ascribed to the more posterior implantation of the electrodes (and therefore inferiority and caudally to Nacc), in order to optimize the outcomes [**224**].

The visuospatial working memory involves a wide network of brain areas. This structure includes the inferior- and superior-order visual hubs, medial side of temporal lobe, the dlPFC and the posterior inferior-frontal gyrus (pIFG) [**225**].
Adverse effects can be allocated into three categories: complications relevant to procedure or hardware. Complications attributed to inappropriate stimulation-and miscellaneous ones [**217**].
The first category entails electrode transposition or infections. The incidence rates were from 1 to 15%. They constitute the major cause of device removal. Postoperative hemorrhage is a detrimental complication ranging from 4.8 to 7.7%. Epileptic seizures are sporadically reported and coexist usually with the aforementioned side effects [**217**]. The sequel with the highest incidence is hypomania. It frequently recedes when settings are altered. The rest of the sequels are obesity, hyposomnia, inaccurate memory recollection and intense worry. The high propensity to suicide is contended. This tendency can be imputed to antecedent comorbidities or despondency, due to deficient response to the device implantation [**226**]. Structural Connectivity among the anterior cingulate cortex, insula, and precuneus was a prognosticator of a propitious result, which was not related to the selected anatomical locus [**224**]. According to this research program anterior hypothalamus adjacent to ITP and BNST are considered the most appropriate anatomical loci. BNST DBS is more efficient compared to the Nacc stimulation [**205**].
Shofty et al. focused on the extracting of predictors within a period of approximately 21 months. They also advocated the benefits according to YBOCS Scale to the whole cohort. They concluded that proper and frequent evaluation by specialized team and the respective alterations were correlated with improved outcome. They also observed that when stimulation was relevant with Nacc then patients tended to have more volatile mood, especially when pulse generator was about to deplete [**208**].

4.2 Pathophysiology of Major Depressive Disorder

Ventral striatum and amygdala contribute in the proper response to reward stimuli and forming judgments in vmPFC. vmPFC and ventral striatum manifest robust functional and combined connectivity at rest and during reward processing tasks, as well [**227**].
Rodent studies have indicated that vmPFC emit glutamatergic efferent fibers toward ventral striatum [**228**]. The subsequent inhibition of vmPFC modifies the function of ventral striatum. Impairment of both vmPFC and ventral striatum has impact on reactions related to reward. This implies that adjustment of judgements necessitates the function of both areas [**229**]
A second area where vmPFC is the protagonist is the modification of aversive feelings. Rodent studies implementing fear context and extinction pattern corroborated this model of vmPFC function. vmPFC lesion hinders recollection of gradually decreased tuition, at high context fear responses during the extinction period [**230**]. A similar research program using neurophysiology revealed that vmPFC cells fire upon the recollection of gradually weakened tuition

diminish conditioned fear responses [**229**]. This result is joined with findings documenting that amygdala's role is crucial for the expression of conditioned fear [**231**]. Apart from that vmPFC activation inhibits amygdala function [**232**]. All these findings stress the existence of a mechanism according to which fear occurs after vmPFC inhibition of amygdala [**233**]. **Human functional imaging studies have contributed further advocation of this observation. Moreover, vmPFC and amygdala functionality are inversely variated when contextual threat gradually weakens [234] , [235].**
Structural differences are noticed in MDD. These involve dwindling of the left anterior cingulate and paracingulate gyrus along with bilateral prefrontal regions diminishing [**236**].

4.3 Rationale for DBS stimulation in MDD

DBS treatment for major depression remains under speculation and is not considered a recommended procedure. Treatment of major depression remains multimodal involving medication and psychotherapy, as well [**237**]. The majority of the relevant studies are small sample research programs. The subcallosal genu (SCG) constituted the primary objective. Dopaminergic nuclei, such as the medial forebrain bundle, the vALIC, the VC/VS, the NAcc or habenula with monoaminergic neurotransmission are targets, as well [**238**].
Mosley et al. performed a strict scrutinization of the literature evaluating the effect of electrical stimulation on depression. More than fifty percent of the sufferers were responders and one third of them exhibited recess. On the contrary recurrence rated 14%. Unfortunately, the adverse events, such as seizures or infection occurred in two -thirds of the patients (67%). Suicidal attempts or suicide were presents in the patients who received this treatment [**239**]. Dougherty et al., 2015 [**240**] and Puigdemont et al., [**241**] refined the methodology in their trials and revealed no statistically notable discrepancy in the outcome between the stimulated and control populations. A common phenomenon in the included studies was the variance in the remission percentages both in the short and long -term period [**242**].
In addition to this, DBS promotes psychiatric dysfunction including manic bursts. These events are impermanent and invertible by alternating the parameters [**243**].
Actual discrepancies between the operative and control population might be recorded, though, within 1 year after the procedure depending on the target [**244**]. On the other hand, cease of stimulation leads generally to quantifiable regression. The scales that assess a wide range of antidepressant outcomes do not properly evaluate a circuit-tailored procedure like DBS, which potentially ameliorates circuit-relevant clinical signs [**245**]. HRDS and MADRS, which are usually used to appraise the gravity of depression, but not to discern symptoms indicating relapse. The most significant is the deficient mood variability [**246**].
Hardware adverse effects incidence is comparable to those of motor disorders. Safety issues are raised when device turns off accidentally. Symptoms recur within days or weeks [**247**], with their preprocedural sequences when the system is switched off [**244**]. Overall, one third of the sufferers with TRD attempt suicide [**247**].

Suicide attempts in DBS treated patients reviewed here rate 6.7%, implying that the risk is not increased.

Fitzgerald et al. in their recent study of eight patients found that within the double-blind crossover phase over a one -year period, no standard antdepressant results were observed. Regardless of the four stimulation points settings their subjects did not exhibit any improvement or recession [**248**]. They did not perform connectomic analysis, though.

Conversely, Wang et al. presented a study with 7 remitters among 23 patients and 14 responders. They stressed particularly the role of the volume of the activated tissue to the beneficial outcome [**249**]. When BNST was encased in the stimulation then the results were the optimal

Structural analysis studies [**250**] detected four fascicles which interrelate with the outcome in refractory depression: forceps minor, cingulum fascicles, dorsal and medial midcingulate gyri, and uncinate fasciculus. The latter binds the lateral orbitofrontal area with the limbic system of the anterior temporal lobes [**250**].

It is accepted that in cases of exacerbated depression accompanied by anhedonia, deficient vivacity, excessive anxiety the DBS outcome is not optimal. Reported that the distance between the epicentre of stimulated tissue and the fascicle associating the VTA-ALIC alters in full responders and non-responders. Hence, the personalized structural alterations on DBS modulation, confer evidence for the prognosis after the procedure in sufferers of TRD [**251**]. Proper myelination of white matter bundles interconnecting frontal and subcortical structures was predictive of the outcome [**249**]. The relations were observed in fascicles, such as thalamic radiation and the reticulospinal pathway. Inadequate myelination deters transmission of serial antidromic spikes at the initiation of DBS [**252**]. The same presuppositions exist for the fibers of ALIC area, whose integrity relate to proper function of the NAcc and reward-associated reaction of the ventral striatum [**253**].

The anterior thalamic radiation and superolateral medial forebrain bundle (slMFB) are the major fascicles that propagate the impulses in the ALIC [**254**]. Past research programs revealed that DBS close to ALIC and these fascicles leads to favorable outcome [**254**]. These correlations were documented in the setting of long-term DBS and optimization of the treatment framework [**254**].

Therefore, the grade of the disorder along with the duration of medical treatment do not constitute a sufficient indication for DBS indication. Radiological parameters should also be co-evaluated.

Compared to movement disorders, the setting of parameters in MDD is hindered, owing to the absence of evidence-based mood and physical outcomes. There is an interval of 2 weeks between adaptation and noticeable results. In some cases, final adaptation may need a period of twelve months. In OCD, DBS patients necessitate time to identify differences and incorporate them successfully into their daily life [**255**].

Overall, BNST stimulation is a technique that has been presented and appraised within the last eight years. The first studies assessed its outcome and how it could be optimized. The late ones focus on patient's quality of life and potential sequels. DBS hardware is tolerated well concerning appearance. Some patients may express discomfort in posture alterations but they progressively habituate themselves. Stimulation settings varied according to patients' geographical position, access to treating physicians and patients' fondness [**256**].

5 Limitations of the study

Some limitations have to be acknowledged, though. First, there had not be a common sum of YBOCS and duration of symptoms in the mentioned studies, which were considered strong indications for DBS. Second, follow up controls did not use the same scales for evaluating mood disorders and cognitive deficits. Third, not all studies involved blinded control of sub-groups and when this took place the randomization criteria were not clearly reported.
These facts stress the need for additional multi-institutional clinical trials, which will reduce the risk of bias.

6. Conclusions

- BNST neurocircuitry is implicated in anxiety and addiction disorders. Apart from being a part of extended amygdala BNST has dense connectivity with ventral striatum. Therefore, is implicated in CSTC network and reward reinforcement.

- Bilateral BNST stimulation has been indicated as a putative therapeutic target against OCD. The latter derives from CSTC network dysregulation.

- The present systematic review identified 10 manuscripts assessing the therapeutic potential of BNST stimulation in OCD. Most of the studies use joined stimulation of adjacent areas, such as Nacc and ALIC. No strong correlation is extracted among stimulation parameters and therapeutic outcomes.

- Only one study assessed the utility of BNST stimulation in major depressive disorder.

- Patient selection based on strict criteria is still debatable. Both the severity of OCD and the duration of conservative treatment varies among the studies. Therapeutic protocols are based on the experience with Parkinson's syndromes treatment.

- None of the studies provide an individualized protocol of DBS settings based on the severity of the disorder.

- While a benefit of BNST stimulation in OCD is supported by several studies on small numbers of patients, more research is warranted to assess utility in both OCD and other disorders.

References

1. Avery SN, Clauss JA, Blackford JU The human BNST: functional role in anxiety and addiction. Neuropsychopharmacology 2016; 41: 126–141.
2. Lebow MA, Chen A. Overshadowed by the amygdala: the bed nucleus of the stria terminalis emerges as key to psychiatric disorders. Mol Psychiatry. 2016 Apr;21(4):450-63. doi: 10.1038/mp.2016.1. Epub 2016 Feb 16. Erratum in: Mol Psychiatry. 2021 Aug;26(8):4561.
3. Krüger Oliver "Examination of the structural connectivity profile of the Bed Nucleus of the Stria Terminalis in the human brain using probabilistic fiber tracking of diffusion weighted magnetic resonance imaging data." Inaugural-Dissertation zur Erlangung des Doktorgrades der Medizin der Medizinischen Fakultät der Eberhard Karls Universität zu Tübingen 2016
4. Taha SA, Fields HL Encoding of palatability and appe- titive behaviors by distinct neuronal populations in the nucleus accumbens. J Neurosci 2005; 25: 1193–1202.
5. Gungor NZ, Pare D Functional heterogeneity in the bed nucleus of the stria terminalis. J Neurosci 2016;36: 8038- 8038-49.
6. Forray MI, Gysling K . Role of noradrenergic projections to the bed nucleus of the stria terminalis in the regulation of the hypothalamic-pituitary-adrenal axis. Brain Res Brain Res Rev. 2004; 47: 145–160.
7. Dong HW, Petrovich GD, Watts AG et al. Basic organization of projections from the oval and fusiform nuclei of the bed nuclei of the stria terminalis in adult rat brain. J Comp Neurol 2001; 436: 430–455.
8. Gungor NZ, Yamamoto R, Pare D (2018). Glutamatergic and gabaergic ventral BNST neurons differ in their physiological properties and responsibilities. Neuropsychopharmocol 2019;43: 2126–2133.
9. Choi DC, Evanson NK, Furay AR et al. The anteroven- tral bed nucleus of the stria terminalis differentially regulates hypothalamic-pituitary-adrenocortical axis responses to acute and chronic stress. Endocrinology 2008;149: 818–826.
10. Haufler D, Nagy FZ, Pare D (2013). Neuronal correlates of fear conditioning in the bed nucleus of the stria terminalis. Learn Mem 2013; 20: 633–641.
11. Dong HW, Swanson LW. Projections from bed nuclei of the stria terminalis, dorsomedial nucleus: implications for cerebral hemisphere integration of neuroendocrine, autonomic, and drinking responses. J Comp Neurol 2006;494:75–107
12. Dong HW, Swanson LW. Organization of axonal pro- jections from the anterolateral areas of the bed nuclei of the stria terminalis. J Comp Neurol 2004a;468: 277–298.
13. Daniel SE, Rainnie DG. Stress modulation of opposing circuits in the bed nucleus of the stria terminalis. Neuropsychopharmacology 2015; 41: 103–125.
14. Myers B, Dolgas CM, Kasckow J et al. Central stress- integrative circuits: forebrain glutamatergic and GABAergic projections to the dorsomedial hypothalamus, medial pre- optic area, and bed nucleus of the stria terminalis. Brain Struct Funct 20134; 219: 1287–1303
15. Bota M, Sporns O, Swanson LW. Neuroinformatics analysis of molecular expression patterns and neuron populations in gray matter regions: the rat BST as a rich exemplar. Brain Res 2012;1450: 174–193.

16. Gu G, Cornea A, Simerly RB. Sexual differentiation of projections from the principal nucleus of the bed nuclei of the stria terminalis. J Comp Neurol 2003; 460: 542–562.
17. Henckens MJAG, Printz Y, Shamgar U et al. CRF receptor type 2 neurons in the posterior bed nucleus of the stria terminalis critically contribute to stress recovery. Mol Psychiatry 2017; 22: 1691–1700.
18. Poulin JF, Arbour D, Laforest S et al. Neuroanatomical characterization of endogenous opioids in the bed nucleus of the stria terminalis. Prog Neuropsychopharmacol Biol Psychiatry 2009; 33: 1356–1365.
19. Sibbach BM, Karim HT, Lo D, et al. Manual segmentation of the paraventricular nucleus of the hypothalamus and the dorsal and ventral bed nucleus of stria terminalis using multi-modal 7 Tesla structural MRI: probabilistic atlases for a stress-control triad. Brain Struct Funct. 2024 Mar;229(2):273-283.
20. Banihashemi L, Peng CW, Rangarajan A, et al. Childhood threat is associated with lower resting-state connectivity within a central visceral network. Front Psychol. 2022 Mar 3;13:805049.
21. Flook EA, Feola B, Benningfield MM, et al. Alterations in connectivity of the bed nucleus of the stria terminalis during early abstinence in individuals with alcohol use disorder. Alcohol Clin Exp Res 2021;45(5):1028–1038.
22. Dong H-W, Petrovich GD, Watts AG, Swanson LW. Basic organization of projections from the oval and fusiform nuclei of the bed nuclei of the stria terminalis in adult rat brain. J Comp Neurol 2001; 436:430–455
23. Fendt M, Siegl S, Steiniger-Brach B Noradrenaline transmission within the ventral bed nucleus of the stria terminalis is critical for fear behavior induced by trimethylthiazoline, a component of fox odor. J Neurosci 2005;25(25):5998–6004
24. Delfs J, Zhu Y, Druhan JP, Aston-Jones G Noradrenaline in the ventral forebrain is critical for opiate withdrawal-induced aversion. Nature 2000;403(27):430–434
25. Herman JP, Cullinan WE, Watson SJ Involvement of the bed nucleus of the stria terminalis in tonic regulation of paraventricular hypothalamic CRH and AVP mRNA expression. J Neuroendocrinol 1994;6(4):433–442
26. Crestani CC, Alves FHF, Gomes FV, Resstel LBM, Correa FMA, Herman JP Mechanisms in the bed nucleus of the stria terminalis involved in control of autonomic and neuroendocrine functions: a review. Curr Neuropharmacol 2013;11(2):141–159.
27. Johnson SB, Emmons EB, Anderson RM, Glanz RM, Romig-Martin SA, Narayanan NS, LaLumiere RT, Radley JJ A basal forebrain site coordinates the modulation of endocrine and behavioral stress responses via divergent neural pathways. J Neurosci 2016;36(33):8687–8699
28. Schweimer J, Fendt M, Schnitzler HU Effects of clonidine injections into the bed nucleus of the stria terminalis on fear and anxiety behavior in rats. Eur J Pharmacol 2005;507:117–124
29. Leri F, Flores J, Rodaros D, Stewart J Blockade of stress- induced but not cocaine-induced reinstatement by infusion of noradrenergic antagonists into the bed nucleus of the stria terminalis or the central nucleus of the amygdala. J Neurosci 2002;22(13):5713–5718
30. Cecchi M, Khoshbouei H, Javors M, Morilak DA Modulatory effects of norepinephrine in the lateral bed nucleus of the stria terminalis on behavioral and neuroendocrine responses to acute stress. Neuroscience 2002;112(1):13–21
31. Banihashemi L, Rinaman L Noradrenergic inputs to the bed nucleus of the stria terminalis and paraventricular nucleus of the hypothalamus underlie hypothalamic-pituitary-adrenal axis but

not hypophagic or conditioned avoidance responses to systemic yohimbine. J Neurosci 2006;26(44):11442–11453
32. Uematsu M, Hirai Y, Karube F, et al. Quantitative chemical composition of cortical GABAergic neurons revealed in transgenic venus expressing rats. Cerebral Cortex 2008;18(2):315-330
33. Nguyen AQ, Dela Cruz JA, Sun Y, et al. Genetic cell targeting uncovers specific neuronal types and distinct subregions in the bed nucleus of the stria terminals. The journal of comparative neurology 2016;524(12):2379-2399
34. Xiao Q, Zhou X, Wei P, et al. A new GABAergic somatostatin projection from the BNST onto accumbal parvalbumin neurons controls anxiety 2021; Molecular Psychiatry 2021;26(9):4719-4741
35. Sparrow AM, Lowery- Gionta EG, Pleil KE, et al. Central neuropeptide Y modulates binge-like ethanol drinking in C57BL/6J mice via Y1 and Y2 receptors.neuropsychopharmacology 2012;37(6): 1409-1421
36. Seiglie MP, Huang L, Cottone P, et al. Role of the PACAP system of the extended amygdala in the acoustic startle response in rats. Neuropharmacology 2019;160: 107761
37. Ferragud A, Velazquez- Sanchez C, Minnig MA, et al. Pituitary adenylate cyclase activating polypeptide (PACAP) modulates dependence-induced alcohol drinking and anxiety-like behavior in male rats. Neuropsychopharmacology 2021;46(3):509-518
38. Crowley NA, Bloodgood DW, Hardaway JA,et al. Dynorphin controls the gain of an amygdalar anxiety circuit. Cell Reports 2016;14(12):2774-2783
39. Li C, Pleil KE, Stamatakis AM, et al. Presumptive inhibition of gamma-aminobutyric acid release in the bed nucleus of the stria terminalis by kappa opioid receptor signaling Biological Psychiatry 2012;71(8): 725-732
40. Kim S, Adhikari A, Lee SY et al. Diverging neural pathways assemble a behavioral state from separable features in anxiety. Nature 2013; 496: 219–223
41. Yamamoto R,Ahmed N,ItoT.et al.Optogenetic study of anterior BNST and basomedial amygdala projections to the ventromedial hypothalamus. 2018; eNeuro 5. https://doi.org/ 10.1523/ENEURO.0204-18.2018.
42. Song Y, Meng Q, Wu K et al. Disinhibition of PVN-projecting GABAergic neurons in AV region in BNST participates in visceral hypersensitivity in rats. Psychoneuroendocrinology 2020; 117: 104690.
43. Dong HW, Swanson LW. Projections from bed nuclei of the stria terminalis, posterior division: implications for cerebral hemisphere regulation of defensive and reproductive behaviors. J Comp Neurol 2004b; 471: 396–433.
44. Giardino WJ, Eban-Rothschild A, Christoffel DJ et al. Parallel circuits from the bed nucleus of the stria terminalis to the lateral hypothalamus driven opposing emotional states. Nat Neurosci 2018; 21: 1084–1095.
45. Pang X, Fan S, Zhang Y, et al. Alterations in neural circuit dynamics between the limbic network and prefrontal/default mode network in patients with generalized anxiety disorder. Neuroimage Clin. 2024;43:103640.
46. Goode TD, Maren S. Role of the bed nucleus of the stria terminalis in aversive learning and memory. Cold Spring Harbor Lab Press 2019; 24: 480–491.
47. Smith SM, Vale WW. The role of the hypothalamic-pituitary-adrenal axis in neuroendocrine responses to stress. Dialogues Clin Neurosci. 2006;8(4):383-95.

48. Hu P, Maita I, Kwok C et al. Chronic stress induces anxiety-associated negative valence behavior by activating a Corticotropin-releasing hormone-related molecular signature in the oval bed nucleus of the Stria terminalis. J Neurosci 2020a; 40: 2519–2537.
49. Conrad KL, Louderback KM, Gessner CP et al. Stress- induced alteration in anxiety-like behavior and adaptations in plasticity in the bed nucleus of the stria terminalis. Physiol Behav 2011; 104: 248–256.
50. Glangetas C, Georges F. Pharmacology of the bed nucleus of the stria terminalis. Curr Pharmacol Rep 2016; 2: 262–270
51. Hu P, Maita I, Phan ML et al. Early-life stress alters affective Behaviors in adult mice through persistent activa- tion of CRH-BDNF Signaling in the oval bed nucleus of the Stria terminalis. Transl Psychiatry. 2020 Nov 11;10(1):396https://doi.org/10.1038/ s41398-020-01070-3.
52. Tartar JL, King MA, Devine DP. Glutamate- mediated neuroplasticity in a limbic input to the hypothalamus. Stress 2006; 9: 13–19.
53. Alvarez RP, Chen G, Bodurka J, Kaplan R, Grillon C. Phasic and sustained fear in humans elicits distinct patterns of brain activity. Neuroimage 2011; 55: 389–400
54. Choi JM, Padmala S, Pessoa L. Impact of state anxiety on the interaction between threat monitoring and cognition. Neuroimage 2012; 59: 1912–1923.
55. Klumpers F, Kroes MC, Heitland I, et al. Dorsomedial prefrontal cortex mediates the impact of serotonin transporter linked polymorphic region genotype on anticipatory threat reactions. Biol Psychiatry 2014; 14: 1–8
56. McMenamin BW, Langeslag SJE, Sirbu M, et al. Network organization unfolds over time during periods of anxious anticipation. J Neurosci 2014; 34: 11261–11273.
57. Somerville LH, Whalen PJ, Kelley WM. Human bed nucleus of the stria terminalis indexes hypervigilant threat monitoring. Biol Psychiatry 2010; 68: 416–424
58. Mobbs D, Yu R, Rowe JB, Eich H, FeldmanHall O, Dalgleish T. Neural activity associated with monitoring the oscillating threat value of a tarantula. Proc Natl Acad Sci USA 2010; 107: 20582–20586
59. Coaster M, Rogers BP, Jones OD et al. Variables influencing the neural correlates of perceived risk of phys- ical harm. Cogn Affect Behav Neurosci 2011; 11: 494–507
60. Grupe DW, Oathes DJ, Nitschke JB. Dissecting the anticipation of aversion reveals dissociable neural networks. Cereb Cortex 2013; 23: 1874–1883.
61. Straube T, Mentzel H, Miltner WHR. Waiting for spi- ders: brain activation during anticipatory anxiety in spider phobics. Neuroimage 2007; 37: 1427–1436.
62. Brinkmann L, Buff C, Feldker K et al. Distinct phasic and sustained brain responses and connectivity of amygdala and bed nucleus of the stria terminalis during threat anticipation in panic disorder. Psych Med 2017; 47: 2675–2688.
63. Figel B, Brinkmann L, Buff C et al. Phasic amygdala and BNST activation during the anticipation of temporally unpredictable social observation in social anxiety disorder patients. NeuroImage Clin 2019; 22: 101735.
64. Brinkmann L, Buff C, Feldker K et al. Inter-individual differences in trait anxiety shape the functional connectivity between the bed nucleus of the stria terminalis and the amygdala during brief threat processing. Neuroimage 2018; 166: 110–116
65. Lee Y, Davis M. Role of the hippocampus, the bed nucleus of the stria terminalis, and the amygdala in the excitatory effect of corticotropin-releasing hormone on the acoustic startle reflex. J Neurosci 1997;17: 6434–6446

66. Miles L, Davis M, Walker D. Phasic and sustained fear are pharmacologically dissociable in rats. Neuropsychopharmacology 2011;36: 1563–1574 Classic review of the pharmacological dissociation between 'fear' and 'anxiety' in rodents.
67. Swerdlow NR, Geyer MA, Vale WW, Koob GF. Corticotropin-releasing factor (CRF) potentiates acoustic startle reflex (ASR) in rats. Blockade by chlordiazep- oxide. Psychopharmacology 1986; 88: 147–152
68. Koob GF, Volkow ND. Neurocircuitry of addiction. Neuropsychopharmacology 2010; 35: 217–238.
69. Aston-Jones G, Kalivas PW (2008). Brain norepinephrine rediscovered in addiction research. Biol Psychiatry 63: 1005–1006.
70. Logrip ML, Koob GF, Zorrilla EP. Role of corticotropin-releasing factor in drug addiction: potential for pharmacological intervention. CNS Drugs 2011; 25: 271–287
71. Walter A, Mai JK, Lanta L, Görcs T. Differential distribution of immunohis- tochemical markers in the bed nucleus of the stria terminalis in the human brain. J Chem Neuroanat 1991;4: 281–298.
72. Kash TL, Pleil KE, Marcinkiewcz CA et al. Neuropeptide regulation of signaling and behavior in the BNST. Mol Cells 2015;38: 1–13.
73. Tillman RM, Stockbridge MD, Nacewicz BM et al. Intrinsic functional connectivity of the central extended amygdala. Hum Brain Mapp 2008;39: 1291–1312
74. Koob GF. Brain stress systems in the amygdala and addiction. Brain Res 2009; 1293: 61–75
75. McEwen BS. Brain on stress: how the social environment gets under the skin. Proc Natl Acad Sci USA 2012;109: 17180–17185.
76. Villada C, Hidalgo V, Almela M, Salvador A. Individual Differences in the Psychobiological Response to Psychosocial Stress (Trier Social Stress Test): The Relevance of Trait Anxiety and Coping Styles. Stress Health. 2016 Apr;32(2):90-9
77. Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005b; 62: 617–627.
78. Upadhyay, J., Maleki, N., Potter, J., et al.. Alterations in brain structure and functional connectivity in prescription opioid-dependent patients. Brain 2010;133(7):2098–2114
79. Frenois, F., Stinus, L., di Blasi, F., Cador, M., le Moine, C. A specific limbic circuit underlies opiate withdrawal memories. J. Neurosci. 2005; 25(6);1366–1374.
80. Ivanov, A., Aston-Jones, G.,. Local opiate withdrawal in locus coeruleus neurons in vitro. J. Neurophysiol. 2001;85 (6), 2388–2397. https://doi.org/10.1152/ jn.2001.85.6.2388.
81. Beldjoud, H., Barsegyan, A., Roozendaal, B. Noradrenergic activation of the basolateral amygdala enhances object recognition memory and induces chromatin remodeling in the insular cortex. Front. Behav. Neurosci. 2015; 9 (APR), 108.
82. Roozendaal, B., Brunson, K.L., Holloway, B.L., et al., Involvement of stress-released corticotropin-releasing hormone in the basolateral amygdala in regulating memory consolidation. Proc. Natl. Acad. Sci. U. S. A. 2002; 99(21):13908–13913.
83. Ghiasvand, M., Rezayof, A., Zarrindast, M.R., et al. Activation of cannabinoid CB1 receptors in the central amygdala impairs inhibitory avoidance memory consolidation via NMDA receptors. Neurobiol. Learn. Mem. 2011; 96(2):333–338.
84. Bahar, A., Dorfman, N., Dudai, Y. Amygdalar circuits required for either consolidation or extinction of taste aversion memory are not required for reconsolidation. Eur. J. Neurosci. 2004;19(4):1115–1118.

85. Pitts, M.W., Todorovic, C., Blank, T., et al. The central nucleus of the amygdala and corticotropin-releasing factor: insights into contextual fear memory. J. Neurosci. 2009; 29(22): 7379–7388.
86. McGaugh, J.L., The amygdala modulates the consolidation of memories of emotionally arousing experiences. Annu. Rev. Neurosci. 2004; 27(1):1–28.
87. Packard, M.G., Introini-Collison, I., McGaugh, J.L., Stria terminalis lesions attenuate memory enhancement produced by intracaudate nucleus injections of oxotremorine. Neurobiol. Learn. Mem.1996; 65(3);278–282
88. Roozendaal, B., McGaugh, J.L., 1996. The memory-modulatory effects of glucocorticoids depend on an intact stria terminalis. Brain Res. 1996;709(2): 243–250.
89. Dalley, J.W., Lääne, K., Theobald, D.E.H., Armstrong, H.C., Corlett, P.R., Chudasama, Y., Robbins, T.W. Time-limited modulation of appetitive Pavlovian memory by D1 and NMDA receptors in the nucleus accumbens. Proc. Natl. Acad. Sci. U. S. A. 2005;102(17):6189–6194.
90. Wichmann, R., Fornari, R.V., Roozendaal, B., Glucocorticoids interact with the noradrenergic arousal system in the nucleus accumbens shell to enhance memory consolidation of both appetitive and aversive taste learning. Neurobiol. Learn. Mem. 2012;98(2);197–205
91. Managò, F., Castellano, C., Oliverio, A., et al. Role of dopamine receptors subtypes, D1-like and D2-like, within the nucleus accumbens subregions, core and shell, on memory consolidation in the one-trial inhibitory avoidance task. Learn. Mem. 2009;16 (1):46–52.
92. Kerfoot, E.C., Williams, C.L. Contributions of the nucleus Accumbens Shell in mediating the enhancement in memory following noradrenergic activation of either the amygdala or Hippocampus. Front. Pharmacol. 2018;9 (FEB): 47.
93. LaLumiere, R.T., Nawar, E.M., McGaugh, J.L. Modulation of memory consolidation by the basolateral amygdala or nucleus accumbens shell requires concurrent dopamine receptor activation in both brain regions. Learn. Mem. 2005;12 (3):296–301.
94. Kalin NH, Shelton SE, Fox AS, Oakes TR, Davidson RJ. Brain regions associated with the expression and contextual regulation of anxiety in primates. Biol Psychiatry 2005;58: 796–804.
95. Andreescu C, Sheu LK, Tudorascu D et al. Emotion reactivity and regulation in late-life generalized anxiety disorder: functional connectivity at baseline and post- treatment. Am J Geriatr Psychiatry 2015; 23: 200–214.
96. Clauss JA, Avery SN, Benningfield MM et al. Social anxiety is associated with BNST response to unpredictabilty. Depress Anxiety 2019; 36: 666–675.
97. Torrisi S, Alvarez GM, Gorka AX et al. Resting-state connectivity of the bed nucleus of the stria terminalis and the central nucleus of the amygdala in clinical anxiety. J Psychiatry Neurosci 2019; 44: 313–323.
98. Winter L, Heitland I, Saryyeva A et al. Acute Effects of electrical stimulation of the bed nucleus of the stria termi- nalis/internal capsule in obsessive-compulsive disorder. World Neurosurg 2018;111: e471–e477.
99. Blomstedt P, Naesstrom M, Bodlund O. 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. Clinical Case Reports 2017; 5: 679–684.
100. Mobbs D, Yu R, Rowe JB, Eich H, FeldmanHall O, Dalgleish T. Neural activity associated with monitoring the oscillating threat value of a tarantula. Proc Natl Acad Sci USA 2010;107: 20582–20586
101. Grupe DW, Oathes DJ, Nitschke JB. Dissecting the anticipation of aversion reveals dissociable neural networks. Cereb Cortex 2013;23: 1874–1883.

102. Coaster M, Rogers BP, Jones OD, Viscusi WK, Merkle KL, Zald DH et al. Variables influencing the neural correlates of perceived risk of physical harm. Cogn Affect Behav Neurosci 2011;11: 494–507.103
103. Wang X, Ge S, Zhang C. Bed nuclei of the stria terminalis: A key hub in the modulation of anxiety. Eur J Neurosci. 2023 Mar;57(6):900-917.
104. LeDoux J, Daw ND. Surviving threats: neural circuit and computational implications of a new taxonomy of defensive behaviour. Nat Rev Neurosci 2018;19: 269–282105
105. LeDoux JE, Brown R. A higher-order theory of emo- tional consciousness. Proc Natl Acad Sci U S A 2017;114: E2016–E2025.
106. Shackman AJ, Fox AS. Contributions of the central extended amygdala to fear and anxiety. J Neurosci 2016;36: 8050–8063.
107. Isaac O, Thiemer K. Biochemical studies on camo- mile components/III. In vitro studies about the antipeptic activity of (–)-alpha-bisabolol (author's transl). Arzneimittelforschung 1975; 25: 1352–1354.
108. Reppucci CJ, Petrovich GD. Organization of connec- tions between the amygdala, medial pre- frontal cortex, and lateral hypothalamus: a single and double retrograde tracing study in rats. Brain Struct Funct 2016;221: 2937–2962.
109. Bickart KC, Dickerson BC, Barrett LF. The amygdala as a hub in brain networks that support social life. Neuropsychologia 2014;63: 235–248.
110. Mia X, Chen S, Li X, et al. Divergent neurocircuitry dissociates two components of the stress response: Glucose mobilization and anxiety-Like behavior Cell Reports 2022;41(6):111586
111. Jennings JH, Rizzi G, Stamatakis AM, Ung RL, Stuber GD. The inhibitory circuit architecture of the lateral hypothalamus orchestrates feeding. Science. 2013;341(6153):1517-21.
112. Girven KS, Aroni S, Navarrete J, et al. Glutamatergic input from the insula to the ventral bed nucleus of the stria terminalis controls reward-related behavior. Addict Biol. 2021 May;26(3):e12961
113. Tian G, Hui M, Macchia D, et al. An extended amygdala-midbrain circuit controlling cocaine withdrawal-induced anxiety and reinstatement. Cell Rep. 2022 May 3;39(5):110775
114. Herrmann MJ, Boehme S, Becker MP, et al. Phasic and sustained brain responses in the amygdala and the bed nucleus of the stria terminalis during threat anticipation. Hum Brain Mapp. 2016 Mar;37(3):1091-102
115. Hur J, Smith JF, DeYoung KA, et al. Anxiety and the Neurobiology of Temporally Uncertain Threat Anticipation. J Neurosci. 2020 Oct 7;40(41):7949-7964
116. Koller K, Hatton CM, Rogers RD, et al. Stria terminalis microstructure in humans predicts var- iability in orienting towards threat. Eur J Neurosci. 2019 Dec;50(11):3804-3813
117. Pedersen WS, Muftuler LT, Larson CL. Disentangling the effects of novelty, valence and trait anxiety in the bed nucleus of the stria terminalis, amygdala and hippocampus with high resolu- tion 7T fMRI. Neuroimage. 2017 Aug 1;156:293-301
118. Pedersen WS, Balderston NL, Miskovich TA, et al The effects of stimulus novelty and negativ- ity on BOLD activity in the amygdala, hippocampus, and bed nucleus of the stria terminalis. Soc Cogn Affect Neurosci. 2017 May 1;12(5):748-757
119. Gorka AX, Torrisi S, Shackman AJ, Grillon C, Ernst M. Intrinsic functional connectivity of the central nucleus of the amygdala and bed nucleus of the stria terminalis. Neuroimage. 2018 Mar;168:392-402.

120. Murty DVPS, Song S, Morrow K, Kim J, Hu K, Pessoa L. Distributed and Multifaceted Effects of Threat and Safety. J Cogn Neurosci. 2022 Feb 1;34(3):495-516.
121. Limbachia C, Morrow K, Khibovska A, et al. Controllability over stressor decreases responses in key threat-related brain areas. Commun Biol. 2021 Jan 5;4(1):42. doi: 10.1038/s42003-020-01537-5.
122. Cano M, Alonso P, Martínez-Zalacaín I, Subirà M, Real E, Segalàs C, Pujol J, Cardoner N, Menchón JM, Soriano-Mas C. Altered functional connectivity of the subthalamus and the bed nucleus of the stria terminalis in obsessive-compulsive disorder. Psychol Med. 2018 Apr;48(6):919-928
123. Dagher A, Tannenbaum B, Hayashi T, et al. An acute psychosocial stress enhances the neural response to smoking cues. Brain Res. 2009 Oct 13;1293: 40-8.
124. Germann J, Boutet A, Elias GJB, et al. Brain Structures and Networks Underlying Treatment Response to Deep Brain Stimulation Targeting the Inferior Thalamic Peduncle in Obsessive-Compulsive Disorder. Stereotact Funct Neurosurg. 2022;100(4):236-243.
125. Baas JM, Klumpers F, Mantione MH, et al. No impact of deep brain stimulation on fear-potentiated startle in obsessive-compulsive disorder. Front Behav Neurosci. 2014 Sep 9;8:305.
126. Neumann WJ, Huebl J, Brücke C, et al. Different patterns of local field potentials from limbic DBS targets in patients with major depressive and obsessive compulsive disorder. Mol Psychiatry. 2014 Nov;19(11):1186-92.
127. Staudt MD, Pouratian N, Miller JP, et al Congress of Neurological Surgeons Systematic Review and Evidence-Based Guidelines for Deep Brain Stimulations for Obsessive-Compulsive Disorder: Update of the 2014 Guidelines. Neurosurgery. 2021 Mar 15;88(4):710-712.
128. Milosevic L, Kalia SK, Hodaie M,et al. A theoretical framework for the site-specific. And frequency -dependent neuronal effects of deep brain stimulation. BioRxiv 2020;2020
129. Krauss JK, Lipsman N, Aziz T, et al. Technologgy of deep brain stimulation: current status and future directions. Nat Rev Neurol 2020
130. Milosevic L, Kalia SK, Hodaie M, et al. Physiological mechanisms of thalamic ventral intermediate nucleus stimulation for tremor suppression. Brain 2018;141(7):2142-2155
131. Milosevic L, Gramer R, Kim TH, et al. Modulation of inhibitory plasticity in basal ganglia output nuclei of patients with Parkinson's disease. Neurobiol Dis 2019;124:46-56
132. Luyten L. The Bed Nucleus of the Stria Terminalis: Translational Deep Brain Stimulation to Reduce Anxiety. The Neuroscientist 2020;26(3):278-284
133. Ranck. JB. Which elements are excited in electrical stimulation of mammalian central nervous system: a review. Brain Res 1975; 98;417– 440.
134. BeMent SL, Ranck JB. A quantitative study of electrical stimulation of central myelinated fibers. Exp Neurol 1969;24:147–170
135. Stoney SD, Thompson WD, Asanuma H. Excitation of pyramidal tract cells by intracortical microstimulation: effective extent of stimulating current. J Neurophysiol 1968;31: 659–669
136. Kim J, Criaud M, Cho SS, et al. Abnormal intrinsic brain functional network dynamics in Parkinson's disease. Brain 2017;140(11):2955-2967
137. Steiner LA, Barreda Tomas FJ, Planert H, et al. Connectivity and dynamics underlying synaptic control of the subthalamic nucleus. J Neurosci. 2019;39(13):2470-2481
138. Johnson LA, Wang J, Nebeck Sd, et al. Direct activation of primary motor cortex during subthalamic but not pallidal deep brain stimulation. J Neurosci 2020;40(10):2166-2177

139. Deep Brain Stimulation. Indications and Applications Editors Lee KH, Duffy PS, Bieber AJ. Pa Stanford Publishing;Taylor Francis, Singapore: 2017
140. Buzsáki G, Anastassiou CA, Koch C. The origin of extracellular fields and currents-EEG, ECoG, LFP and spikes. Nat Rev Neurosci. 2012;13(6):407–420.
141. Buzsaki G. Rhythms of the Brain. USA: Oxford University Press; 2011
142. Brown P. Abnormal oscillatory synchronization in the motor system leads to impaired movement.Curr Opin Neurobiol. 2007.
143. Eusebio A, Brown P.Synchronisation in the beta frequency-band--the bad boy of parkinsonism or an innocent bystander? Exp Neurol. 2009;217(1):1–3.
144. Wang D D,de Hemptinne C,Miocinovic S,et al. Pallidal deep-brain stimulation disrupts Pallidal Beta oscillations and coherence with primary motor cortex in Parkinson's disease. J Neurosci. 2018;38(19): 4556–4568
145. Oswal A, Beudel M, Zrizo L, et al. Deep brain Stimulation modulates synchrony within spatially and spectrally. Distinct resting state networks. In Parkinsonn's disease Brain 2016 May;139(Pt 5):1482-96.
146. Kuhn AA, Trottenberg T, Kivi A,et al. The relationship between local field potential and neuronal discharge in the subthalamic nucleus of patients with Parkinnson's disease. Exp. Neurol 2005;194(1):212-220
147. Pavlides A, Hogan SJ, Bogacz R. Computational models describing possible mechanisms for generation of excessive Beta oscillations in Parkinson's disease. PLoS Comput Biol. 2015;11(12).
148. Neumann WJ, Horn A, Ewert S, et al. A localized pallidal physiomarker in cervical dystonia. Ann Neurol. 2017;82(6):912–924.
149. Shute JB, Okun MS, Opri E, et al. Thalamocortical network activity enables chronic tic detection in humans with Tourette syndrome. Neuroimage Clin. 2016;12:165–172
150. Neumann W-J, Huebl J, Brücke C, et al. Pallidal and thalamic neural oscillatory patterns in Tourette syndrome. Ann Neurol. 2018;15.
151. Rappel P, Marmor O, Bick AS,etal.Subthalamicthetaactivity:a novel human subcortical biomarker for obsessive compulsive disorder. Transl Psychiatry. 2018;8(1):118.
152. Wu H, Tambuyzer T, Nica I, et al.Field Potential Oscillations in the Bed Nucleus of the Stria Terminalis Correlate with Compulsion in a Rat Model of Obsessive-Compulsive Disorder. J Neurosci. 2016 Sep 28;36(39):10050-9
153. Crowell AL, Ryapolova-Webb ES, Ostrem. JL,et al. Oscillations in sensorimotor cortex. In movement disorders: an electrocorticography study. Brain. 2012;135(Pt2):615-630
154. Abbasi O, Hirschmannn J, Storzer L, et al. Unilateral deep brain stimulation suppresses alpha and beta oscillations in sensorimotor cortices. Nneuroimage 2018;174:201-207
155. Cole SR, van der Meij R, Petersen EJ, et al. onsiusoidal beta oscillatios reflect cortical pathophysiology in Parkinnson's disease. J Neurosci 2017;37(18):4830-4840
156. Swann N, Poizner H, Houser M ,et al. Deep brain stimulation of the subthalamic ucleus alters the cortical profile of response inhibition in the beta frequency band: a scalp EEG study. In Parkinson's disease. J Neurosci. 2011;3§(15):5721-5729
157. Horn A, Wezel G, Irmen F, et al. Deep brain stimulation induced normalization of the human fuctional connectome. In Parkinson's disease Brain 2019;142(10):3129-3143
158. Figee M ,Luigjes J, Smolders R, et al. Deep rain stimulation restores frontostriatal network activity Nat Neurosci 2013;16(4):386-387

159. Georgiev D, Akram H, Jahanshahi M. Deep brain stimulation for psychiatric disorders: role of imaging in identifying/confirming DBS targets, predicting, and optimizing outcome and unravelling mechanisms of action. Psychoradiology. 2021 Oct 4;1(3):118-151.
160. StoneySD, ThompsonWD, Asanuma H.Excitation of pyramidal tract cells by intracortical microstimulation: effective extent of stimulating current. J Neurophysiol 1968;31: 659–669
161. Ramasubbu R, Lang S, Kiss ZHT. Dosing of electrical parameters in Deep Brain Stimulation (DBS) for intractable depression: a review of clinical studies. Front. Psychiatry 2018;9.
162. Stanslaski S, Afshar P, Cong P, et al. 2012. Design and validation of a fully implantable, chronic, closed-loop neuromodulation device with concurrent sensing and stimulation. IEEE transactions on neural systems and rehabilitation engineering. Publ IEEE Eng. Med. Biol. Soc 2012; 20(4): 410–421.
163. Widge AS, Bilge MT, Montana R, et al. Electroencephalographic biomarkers for treatment response prediction in major depressive illness: a meta-analysis. Am. J. Psychiatry 2018;176 (1): 44–56
164. Monteggia LM, Heimer H, Nestler EJ. Meeting report: can we make animal models of human mental illness? Biol. Psychiatry 2018;84 (7):542–545.
165. Diehl MM, Bravo-Rivera C, Quirk G. The study of active avoidance: a platform for discussion. Neurosci. Biobehav. Rev 2019;107: 229–237
166. Zorowitz S, Rockhill AP, Ellard KK, et al.The neural basis of approach-avoidance conflict: a model based analysis. 2019; eNeuro ENEURO.0115-19.2019
167. 290 Little S, Brown P. What brain signals are suitable for feedback control of deep brain stimulation in Parkinson's disease? Annals of the New York Academy of Sciences 2012; 1265:9–24.
168. Veerakumar A, Tiruvadi V, Howell B, et al. Field potential 1/f activity in the subcallosal cingulate region as a candidate signal for monitoring deep brain stimulation for treatment-resistant depression. J. Neurophysiol 2019;122 (3): 1023–1035
169. Karas PJ, Lee S, Jimenez-Shahed J, et al. Deep Brain Stimulation for Obsessive Compulsive Disorder: Evolution of Surgical Stimulation Target Parallels Changing Model of Dysfunctional Brain Circuits. Front Neurosci. 2019(8);12:998.
170. Del Casale A., Kotzalidis G. D., Rapinesi C., et al.Functional neuroimaging in obsessive-compulsive disorder. Neuropsychobiology 2011;64: 61–85
171. Bourne SK, Eckhardt CA, Sheth SA, Eskandar EN. Mechanisms of deep brain stimulation for obsessive compulsive disorder: effects upon cells and circuits. Front Integr Neurosci. 2012; 14(6):29.
172. Graybiel A. M., Rauch S. L. Toward a neurobiology of obsessive-compulsive disorder. Neuron 2000;28:343–347
173. Simon D., Kaufmann C., Musch K., et al.Fronto-striato-limbic hyperactivation in obsessive-compulsive disorder during individually tailored symptom provocation. Psychophysiology 2010; 47: 728–738
174. Denys D., Van Der Wee N., Janssen J., et al. Low level of dopaminergic D2 receptor binding in obsessive-compulsive disorder. Biol. Psychiatry 2004;55:1041–1045
175. van der Wee N. J., Stevens H., Hardeman J. A., et al. Enhanced dopamine transporter density in psychotropic-naive patients with obsessive-compulsive disorder shown by [123I]{beta}-CIT SPECT. Am. J. Psychiatry 2004;161: 2201–2206

176. Sesack S. R., Grace A. A. Cortico-Basal Ganglia reward network: microcircuitry. Neuropsychopharmacology 2010; 35: 27–47
177. Bouton M. E., King D. A. Contextual control of the extinction of conditioned fear: tests for the associative value of the context. J. Exp. Psychol. Anim. Behav. Process.1983; 9: 248–265
178. Beucke J. C., Sepulcre J., Talukdar T., Linnman C., Zschenderlein K., Endrass T., et al. Abnormally high degree connectivity of the orbitofrontal cortex in obsessive-compulsive disorder. JAMA Psychiatry 2013;70 :619–629.
179. Nakao T., Nakagawa A., Yoshiura T., et al. . Brain activation of patients with obsessive-compulsive disorder during neuropsychological and symptom provocation tasks before and after symptom improvement: a functional magnetic resonance imaging study. Biol. Psychiatry 2005;57 :901–910.
180. Guehl D., Benazzouz A., Aouizerate B., Cuny E., Rotgé J.-Y., Rougier A., et al. (2008). Neuronal correlates of obsessions in the caudate nucleus. Biol. Psychiatry 2008; 63: 557–562.
181. Ahmari S. E., Spellman T., Douglass N. L., Kheirbek M. A., Simpson H. B., Deisseroth K., et al. Repeated cortico-striatal stimulation generates persistent OCD-like behavior. Science 2013; 340 :1234–1239. 10.1126/science.1234733
182. Swedo S. E., Pietrini P., Leonard H. L., et al. Cerebral glucose metabolism in childhood-onset obsessive-compulsive disorder. revisualization during pharmacotherapy. Arch. Gen. Psychiatry 1992;49,:690–694
183. Kringelbach M. L., Rolls E. T. The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. Prog. Neurobiol. 2004; 72: 341–372
184. Levine J. B., Gruber S. A., Baird A. A., Yurgelun-Todd D. Obsessive-compulsive disorder among schizophrenic patients: an exploratory study using functional magnetic resonance imaging data. Compr. Psychiatry 1998;39:308–311
185. Alexander G. E., DeLong M. R., Strick P. L. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu. Rev. Neurosci. 1986; 9:357–381
186. van den Heuvel O. A., van der Werf Y. D., Verhoef K. M. W., et al. Frontal-striatal abnormalities underlying behaviours in the compulsive-impulsive spectrum. J. Neurol. Sci. 2010; 289:55–59
187. Goodman WK, Price LH,Rasmussen SA, et al. The Yale Obsessive Compulsive Scale I. Development, use and reliability . Archives of General Psychiatry 1989a;46:1006-1011
188. Woody SR, Steketee G, Chambless DL. Reliability and validity of the Yale-Brown Obsessive-Compulsive Scale. Behav Res Ther. 1995 Jun;33(5):597-605.
189. Emmelkamp PMG Leyton Obsessional Inventory. In Hersen M and Bellack AS (Eds) Dictionary of Behavioral Assessment techniques (pp.287-291). New York;1988a: Pergamon Press
190. Emmelkamp PMG Maudsley Obsessional Compulsive Inventory. In Hersen M and Bellack AS (Eds) Dictionary of Behavioral Assessment techniques (pp.294-296). New York; 1988b: Pergamon Press
191. Dhamnetiya D, Jha RP, Shalini S, Bhattacharyya K. How to Analyze the Diagnostic Performance of a New Test? Explained with Illustrations. J Lab Physicians. 2021 Sep 8;14(1):90-98.
192. Hanlon C, Medhin G, Selamu M, et al. Validity of brief screening questionnaires to detect depression in primary care in Ethiopia. J Affect Disord. 2015;186:32–39.
193. Moussa MT, Lovibond P, Laube R, Megahead HA. Psychometric Properties of an Arabic Version of the Depression Anxiety Stress Scales (DASS) Res Soc Work Pract. 2017;27:375–386

194. Tran TD, Tran T, Fisher J. Validation of the depression anxiety stress scales (DASS) 21 as a screening instrument for depression and anxiety in a rural community-based cohort of northern Vietnamese women. BMC Psychiatry. 2013 Jan 12;13:24.
195. Taber KS. The Use of Cronbach's Alpha When Developing and Reporting Research Instruments in Science Education 2018; 1273–1296. 10.1007/s11165-016-9602-2
196. Moya E, Larson LM, Stewart RC, et al. Reliability and validity of depression anxiety stress scale (DASS)-21 in screening for common mental disorders among postpartum women in Malawi. BMC Psychiatry. 2022 May 24;22(1):352
197. Lehman AF. The effects of psychiatric symptoms on quality of life assessments among the chronic mentally ill. Evaluation and Program Planning. 1983 Jan 1;6(2):143-51.
198. Goldman HH, Skodol AE, Lave TR. Revising axis V for DSM-IV: a review of measures of social functioning. Am J Psychiatry. 1992 Sep;149:9.
199. Turkoz I, Fu DJ, Bossie CA, et al. Relationship between the clinical global impression of severity for schizoaffective disorder scale and established mood scales for mania and depression. J Affect Disord. 2013 Aug 15;150(1):17-22
200. Raymaekers S, Vansteelandt K, Luyten L, et al. Long-term electrical stimulation of bed nucleus of stria terminalis for obsessive-compulsive disorder. Mol Psychiatry. 2017 Jun;22(6):931-934
201. Mosley PE, Windels F, Morris J, et al. A randomised, double-blind, sham-controlled trial of deep brain stimulation of the bed nucleus of the stria terminalis for treatment-resistant obsessive-compulsive disorder. Transl Psychiatry. 2021 Mar 29;11(1):190.
202. Mar-Barrutia L, Ibarrondo O, Mar J, Real E, et al. Long-term comparative effectiveness of deep brain stimulation in severe obsessive-compulsive disorder. Brain Stimul. 2022 Sep-Oct;15(5):1128-1138.
203. Winter L, Saryyeva A, Schwabe K, et al. Long-Term Deep Brain Stimulation in Treatment-Resistant Obsessive-Compulsive Disorder: Outcome and Quality of Life at Four to Eight Years Follow-Up. Neuromodulation. 2021 Feb;24(2):324-330
204. Luyck K, Bervoets C, Deblieck C, et al. Deep brain stimulation in the bed nucleus of the stria terminalis: A symptom provocation study in patients with obsessive-compulsive disorder. J Psychiatr Res. 2022 Jul;151:252-260. doi: 10.1016/j.jpsychires.2022.04.031
205. Philipson J, Naesstrom M, Johansson JD, et al. Deep brain stimulation in the ALIC-BNST region targeting the bed nucleus of stria terminalis in patients with obsessive-compulsive disorder: effects on cognition after 12 months. Acta Neurochir (Wien). 2022 Sep 2. doi: 10.1007/s00701-022-05351-2
206. Fitzgerald PB, Segrave R, Richardson KE, et al. A pilot study of bed nucleus of the stria terminalis deep brain stimulation in treatment-resistant depression. Brain Stimul. 2018 Jul-Aug;11(4):921-928.
207. Farrand S, Evans AH, Mangelsdorf S, Loi SM, et al. Deep brain stimulation for severe treatment-resistant obsessive-compulsive disorder: An open-label case series. Aust N Z J Psychiatry. 2018 Jul;52(7):699-708.
208. Shofty B, Gadot R, Viswanathan A, et al. Intraoperative valence testing to adjudicate between ventral capsule/ventral striatum and bed nucleus of the stria terminalis target selection in deep brain stimulation for obsessive-compulsive disorder. J Neurosurg. 2022 Dec 9:1-9.

209. Mar-Barrutia L, Ibarrondo O, Mar J, Real E, et al. Long-term comparative effectiveness of deep brain stimulation in severe obsessive-compulsive disorder. Brain Stimul. 2022 Sep-Oct;15(5):1128-1138.
210. Naesström M, Hariz M, Strömsten L, et al. Deep Brain Stimulation in the Bed Nucleus of Stria Terminalis in Obsessive-Compulsive Disorder-1-Year Follow-up. World Neurosurg. 2021 May;149:e794-e802.
211. Piccinelli M, Pini S, Bellantuono C, Wilkinson G. Effectiveness of drug treatment in OCD: a metanalytic review. B J P. 1995; 166:424–43.
212. Pallanti S, Hollander E, Bienstock C, Koran L, Leckman J, Marazziti D, et al. Treatment non-response in OCD: methodological issues and operational definitions. Int J Neuropsychopharmacol. 2002;5:181–91.
213. Denys D. Pharmacotherapy of obsessive-compulsive disorder and obsessive-compulsive spectrum disorders. Psychiatr Clin North Am. 2006;29:553–84
214. Beszłej J, Wieczorek T, Kobyłko A, Piotrowski P, Siwicki D, Weiser A, et al. Deep brain stimulation: new possibilities for the treatment of mental disorders. Psychiatr Pol. (2019) 53:789–806
215. Alonso P, Cuadras D, Gabriëls L, Denys D, Goodman W, Greenberg B, et al. Deep brain stimulation for obsessive-compulsive disorder: a meta-analysis of treatment outcome and predictors of response. PLoS One. (2015) 10:e0133591
216. Schüpbach M, Gargiulo M, Welter ML, Mallet L, Béhar C, Houeto JL, et al. Neurosurgery in Parkinson disease: a distressed mind in a repaired body? Neurology. 2006;66:1811–1816
217. Swierkosz-Lenart K, Dos Santos JFA, Elowe J, et al. Therapies for obsessive-compulsive disorder: Current state of the art and perspectives for approaching treatment-resistant patients. Front Psychiatry. 2023 Feb 16;14:1065812.
218. Rae CL, Hughes LE, Anderson MC, Rowe JB. The prefrontal cortex achieves inhibitory control by facilitating subcortical motor pathway connectivity. Journal of neuroscience. 2015 Jan 14;35(2):786-94.
219. Dougherty DD. Will deep brain stimulation help move precision medicine to the clinic in psychiatry?. Biological Psychiatry. 2019 May 1;85(9):706-7.
220. Li N, Baldermann JC, Kibleur A, et al. A unified connectomic target for deep brain stimulation in obsessive-compulsive disorder. Nature communications. 2020 Jul 3;11(1):3364
221. Mantione M, Nieman DH, Figee M, Denys D. Cognitive–behavioural therapy augments the effects of deep brain stimulation in obsessive–compulsive disorder. Psychological medicine. 2014 Dec;44(16):3515-22.
222. Naesström M, Blomstedt P, Hariz M, Bodlund O. Deep brain stimulation for obsessive-compulsive disorder: knowledge and concerns among psychiatrists, psychotherapists and patients. Surg Neurol Int. 2017;8:298–298
223. Huff W, Lenartz D, Schormann M, et al. Unilateral deep brain stimulation of the nucleus accumbens in patients with treatment-resistant obsessive-compulsive disorder: outcomes after one year. Clin Neurol Neurosurg. 2010;112:137–143.
224. Greenberg BD, Gabriels LA, Malone DA, et al. Deep brain stimulation of the ventral internal capsule/ventral striatum for obsessive-compulsive disorder: worldwide experience. Mol Psychiatry. 2010;15:64–79.
225. Menzies L, Chamberlain SR, Laird AR, et al. Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: the orbitofronto-striatal model revisited. Neurosci Biobehav Rev. 2008;32:525–549.

226. Mar-Barrutia L, Real E, Segalás C, et al. Deep brain stimulation for obsessive-compulsive disorder: a systematic review of worldwide experience after 20 years. World J Psychiatry. 2021;11:659–80.
227. Cauda F, Cavanna AE, D'Agata F, et al. Functional connectivity and coactivation of the nucleus accumbens: a combined functional connectivity and structure-based meta-analysis. *J Cogn Neurosci.* 2011;23:2864–2877
228. Voorn P, Vanderschuren LJ, Groenewegen HJ, et al. Putting a spin on the dorsal-ventral divide of the striatum. *Trends in neurosciences.* 2004;27:468–474.
229. Hiser J, Koenigs M. The Multifaceted Role of the Ventromedial Prefrontal Cortex in Emotion, Decision Making, Social Cognition, and Psychopathology. Biol Psychiatry. 2018 Apr 15;83(8):638-647.
230. Milad MR, Quirk GJ. Neurons in medial prefrontal cortex signal memory for fear extinction. *Nature.* 2002;420:70–74.
231. LeDoux J. The emotional brain, fear, and the amygdala. *Cell Mol Neurobiol.* 2003;23:727–738.
232. Rosenkranz JA, Moore H, Grace AA. The prefrontal cortex regulates lateral amygdala neuronal plasticity and responses to previously conditioned stimuli. *J Neurosci.* 2003;23:11054–11064.
233. Ghashghaei HT, Barbas H. Pathways for emotion: interactions of prefrontal and anterior temporal pathways in the amygdala of the rhesus monkey. *Neuroscience.* 2002;115:1261–1279
234. Kalisch R, Korenfeld E, Stephan KE, et al. Context-dependent human extinction memory is mediated by a ventromedial prefrontal and hippocampal network. *J Neurosci.* 2006;26:9503–9511
235. Delgado MR, Nearing KI, Ledoux JE, Phelps EA. Neural circuitry underlying the regulation of conditioned fear and its relation to extinction. *Neuron.* 2008;59:829–838
236. Hibar DP, Westlye LT, Doan NT,et al . Cortical abnormalities in bipolar disorder: an MRI analysis of 6503 individuals from the ENIGMA Bipolar Disorder Working Group. Mol Psychiatry. 2018 Apr;23(4):932-942.
237. Kennedy SH, Lam RW, McIntyre RS, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 3. Pharmacological treatments. The Canadian Journal of Psychiatry. 2016 Sep;61(9):540-60.
238. Sartorius A, Kiening KL, Kirsch P, et al. Remission of major depression under deep brain stimulation of the lateral habenula in a therapy-refractory patient. Biological psychiatry. 2010 Jan 15;67(2):e9-11.
239. Mosley PE, Marsh R, Carter A. Deep brain stimulation for depression: Scientific issues and future directions. Australian & New Zealand Journal of Psychiatry. 2015 Nov;49(11):967-78.
240. Dougherty DD, Rezai AR, Carpenter LL, et al. A randomized sham-controlled trial of deep brain stimulation of the ventral capsule/ventral striatum for chronic treatment-resistant depression. Biological psychiatry. 2015 Aug 15;78(4):240-8.
241. Puigdemont D, Pérez-Egea R, Portella MJ, et al. Deep brain stimulation of the subcallosal cingulate gyrus: further evidence in treatment-resistant major depression. International Journal of Neuropsychopharmacology. 2012 Feb 1;15(1):121-33.
242. Wu Y, Mo J, Sui L, et al. Deep Brain Stimulation in Treatment-Resistant Depression: A Systematic Review and Meta-Analysis on Efficacy and Safety. Front Neurosci. 2021 Apr 1;15:655412.

243. Fitzgerald P. Brain stimulation techniques for the treatment of depression and other psychiatric disorders. Australasian Psychiatry. 2008 Jun;16(3):183-90.
244. Bergfeld IO, Mantione M, Hoogendoorn ML, et al. Deep brain stimulation of the ventral anterior limb of the internal capsule for treatment-resistant depression: a randomized clinical trial. JAMA psychiatry. 2016 May 1;73(5):456-64.
245. Jiang Z, Harati S, Crowell A, et al. Classifying major depressive disorder and response to deep brain stimulation over time by analyzing facial expressions. IEEE transactions on biomedical engineering. 2020 Jul 20;68(2):664-72
246. Scangos KW, Makhoul GS, Sugrue LP, et al. State-dependent responses to intracranial brain stimulation in a patient with depression. Nature medicine. 2021 Feb;27(2):229-31.
247. Figee M, Riva-Posse P, Choi KS, et al. Deep Brain Stimulation for Depression. Neurotherapeutics. 2022 Jul;19(4):1229-1245.
248. Fitzgerald PB, Hoy K, Richardson KE, Gainsford K, Segrave R, Herring SE, Daskalakis ZJ, Bittar RG. No Consistent Antidepressant Effects of Deep Brain Stimulation of the Bed Nucleus of the Stria Terminalis. Brain Sci. 2024 May 15;14(5):499.
249. Wang T, Dai L, Lai Y, et al. Parameter-based analysis of clinical efficacy of combined bed nucleus of the stria terminalis-nucleus accumbens deep brain stimulation for treatment-resistant depression. J Neurosurg. 2024 Jan 12;140(6):1630-1640.
250. Riva-Posse P, Choi KS, Holtzheimer PE, et al. Defining critical white matter pathways mediating successful subcallosal cingulate deep brain stimulation for treatment-resistant depression. Biol Psychiatry. 2014 Dec 15;76(12):963-9.
251. Wang F, Dai L, Wang T, et al. Presurgical structural imaging and clinical outcome in combined bed nucleus of the stria terminalis-nucleus accumbens deep brain stimulation for treatment-resistant depression. Gen Psychiatr. 2024 Jun 21;37(3):e101210.
252. Chomiak T, Hu B. Axonal and somatic filtering of antidromically evoked cortical excitation by simulated deep brain stimulation in rat brain. The Journal of physiology. 2007 Mar 1;579(2):403-12.
253. Koch K, Wagner G, Schachtzabel C, et al. Association between white matter fiber structure and reward-related reactivity of the ventral striatum. Human brain mapping. 2014 Apr;35(4):1469-76.
254. Coenen VA, Panksepp J, Hurwitz TA, et al.. Human medial forebrain bundle (MFB) and anterior thalamic radiation (ATR): imaging of two major subcortical pathways and the dynamic balance of opposite affects in understanding depression. J Neuropsychiatry Clin Neurosci 2012;24:223–36.
255. Thomson CJ, Segrave RA, Fitzgerald PB, et al "Nothing to Lose, Absolutely Everything to Gain": Patient and Caregiver Expectations and Subjective Outcomes of Deep Brain Stimulation for Treatment-Resistant Depression. Front Hum Neurosci. 2021 Sep 29;15:755276.
256. Thomson CJ, Segrave RA, Fitzgerald PB, et al. Personal and relational changes following deep brain stimulation for treatment-resistant depression: A prospective qualitative study with patients and caregivers. PLoS One. 2023 Apr 6;18(4):e0284160