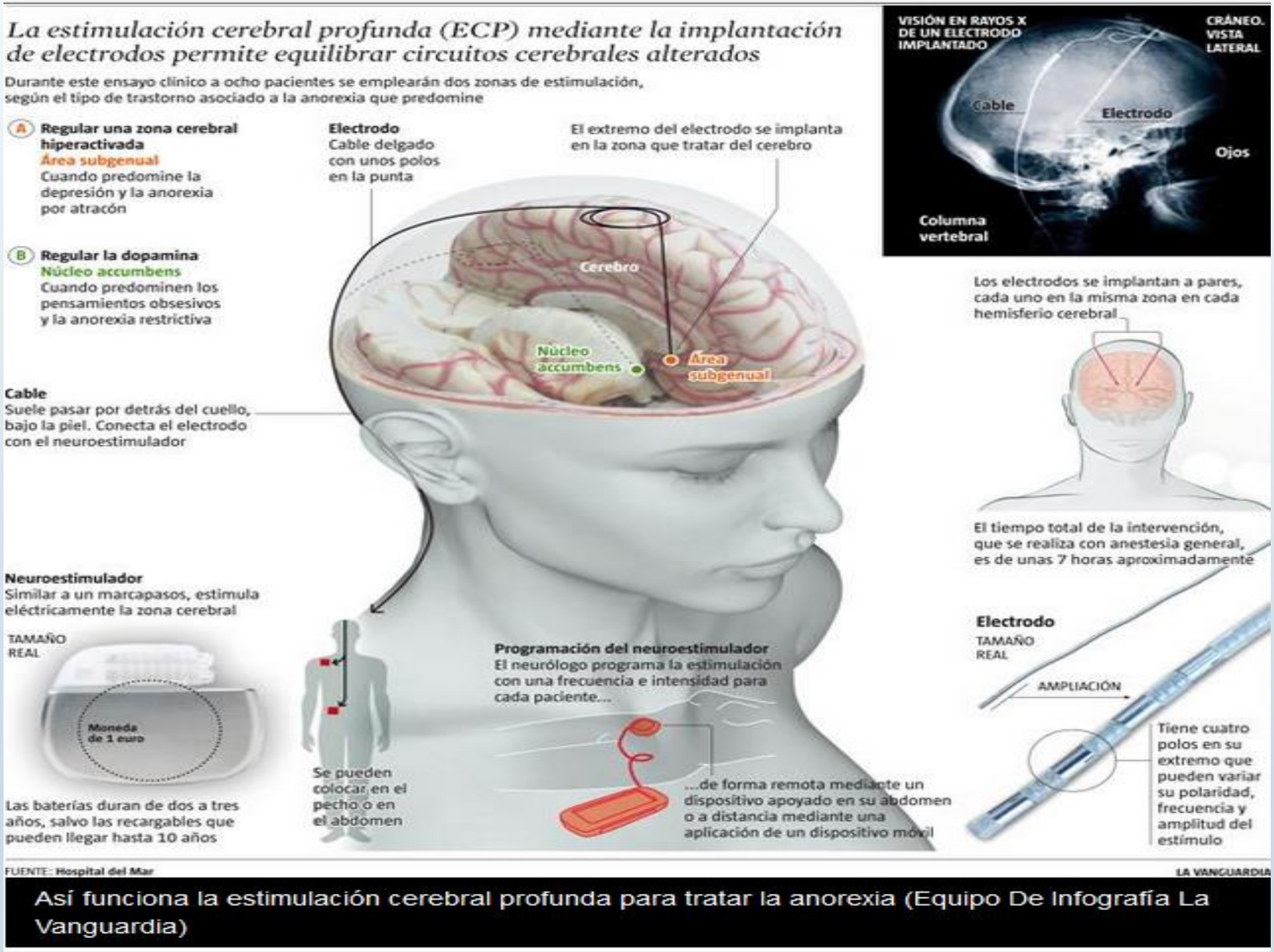
1 -12 de abril de 2019
INTERPSIQUIS
XX Congreso Virtual Internacional de Psiquiatría, Psicología y Salud Mental

""La Estimulación Cerebral Profunda en la Depresión, la Esquizofrenia o los Trastornos de la Alimentación"

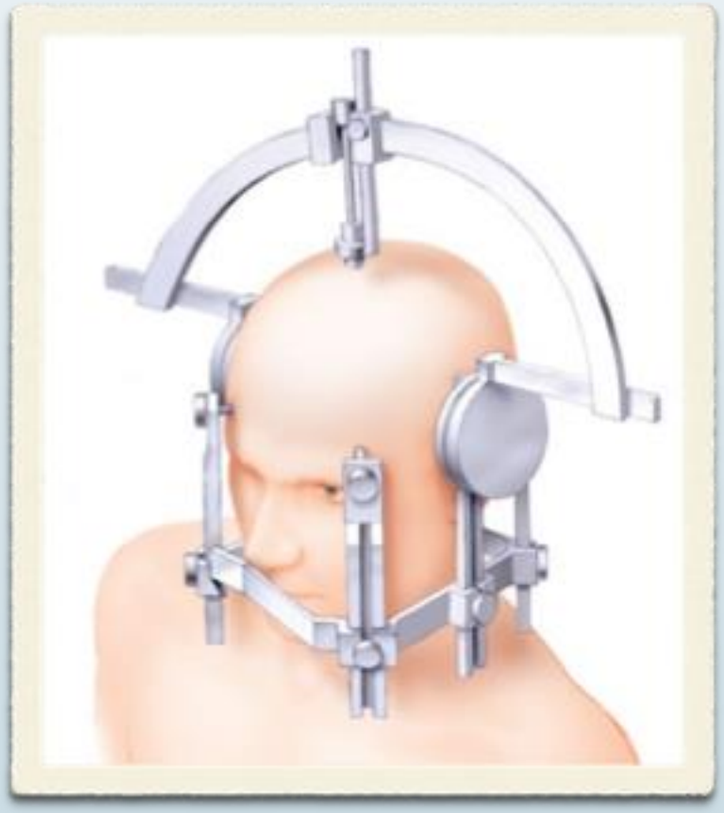
Víctor Pérez Sola

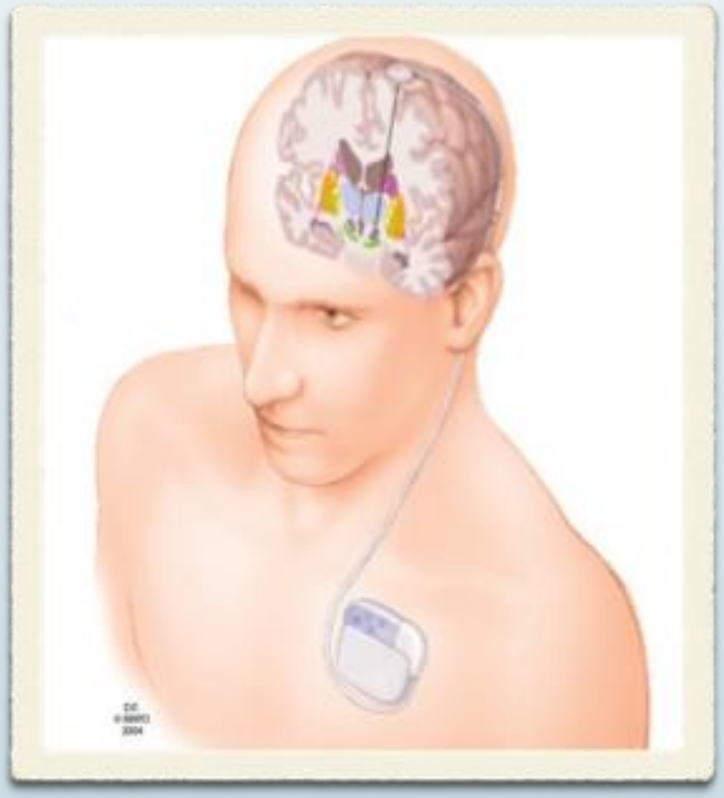
INAD Hospital del Mar. CIBERSAM



Así funciona la estimulación cerebral profunda para tratar la anorexia (Equipo De Infografía La Vanguardia)

Técnica





- Colocación guía estereotáxica
- Cálculo coordenadas target TC, RM y neuronavegador
- Implante electrodo con anestesia local
- Microrregistro actividad neuronal
- Estimulación intraoperatoria
- Implante del generador (anestesia general)
- RMN cerebral post-operatoria

Estructuras cerebrales relacionadas con la enfermedad mental

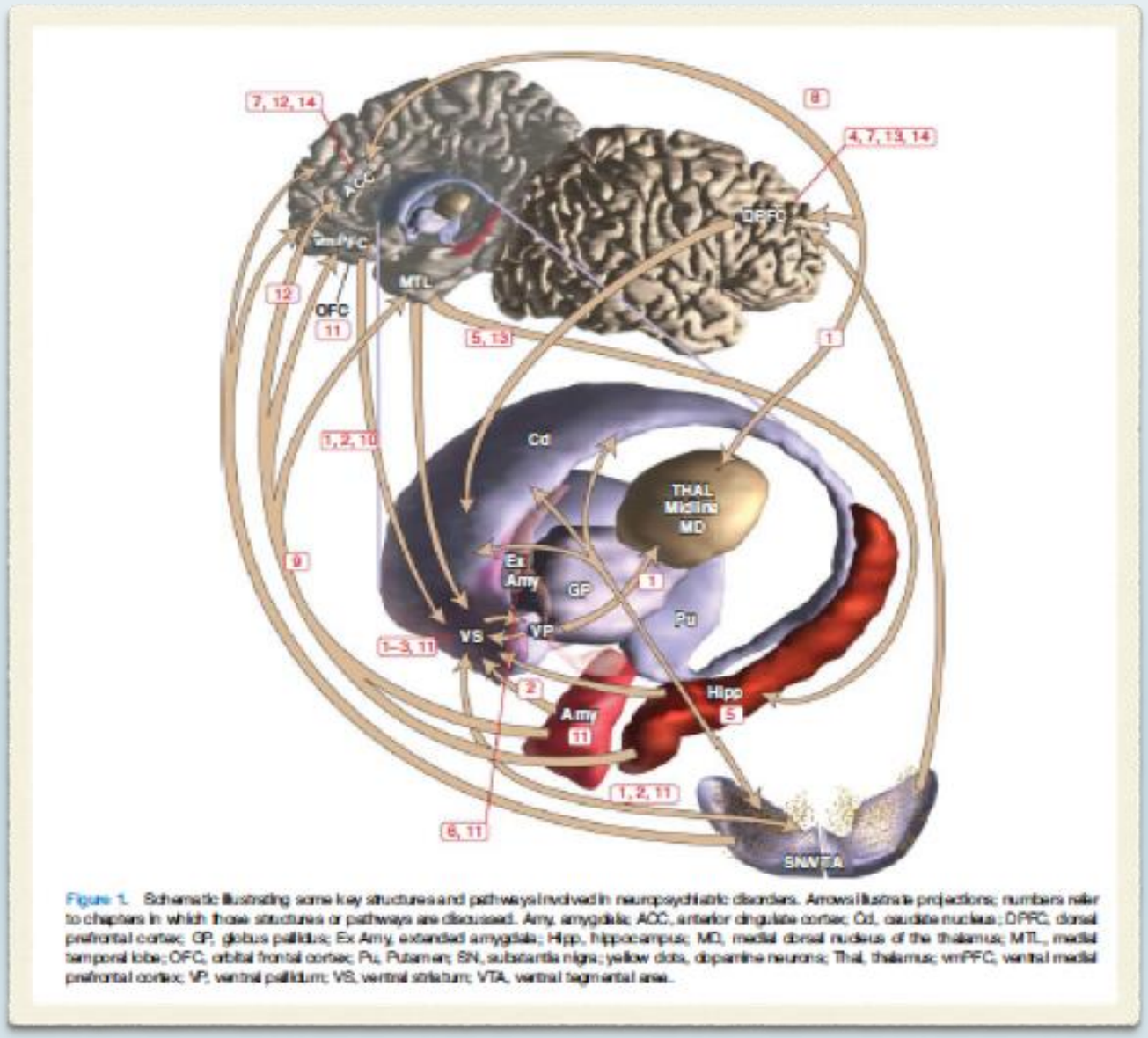


Figure 1. Schematic illustrating some key structures and pathways involved in neuropsychiatric disorders. Arrows illustrate projections; numbers refer to chapters in which those structures or pathways are discussed. Amy, amygdala; ACC, anterior cingulate cortex; Cd, caudate nucleus; DPFC, dorsal prefrontal cortex; GP, globus pallidus; Ex Amy, extended amygdala; Hipp, hippocampus; MD, medial dorsal nucleus of the thalamus; MTL, medial temporal lobe; OFC, orbital frontal cortex; Pu, Putamen; SN, substantia nigra; yellow dots, dopamine neurons; Thal, thalamus; vmPFC, ventral medial prefrontal cortex; VP, ventral pallidum; VS, ventral striatum; VTA, ventral tegmental area.

S.Haber & Rauch.
Neupsypharma Reviews (2010) 35, 1-3

Posibles Indicaciones en Psiquiatría

* Trastorno obsesivo - compulsivo
* Esquizofrenia
* Trastorno depresivo
* Anorexia Nerviosa
* Tr. por consumo de sustancias

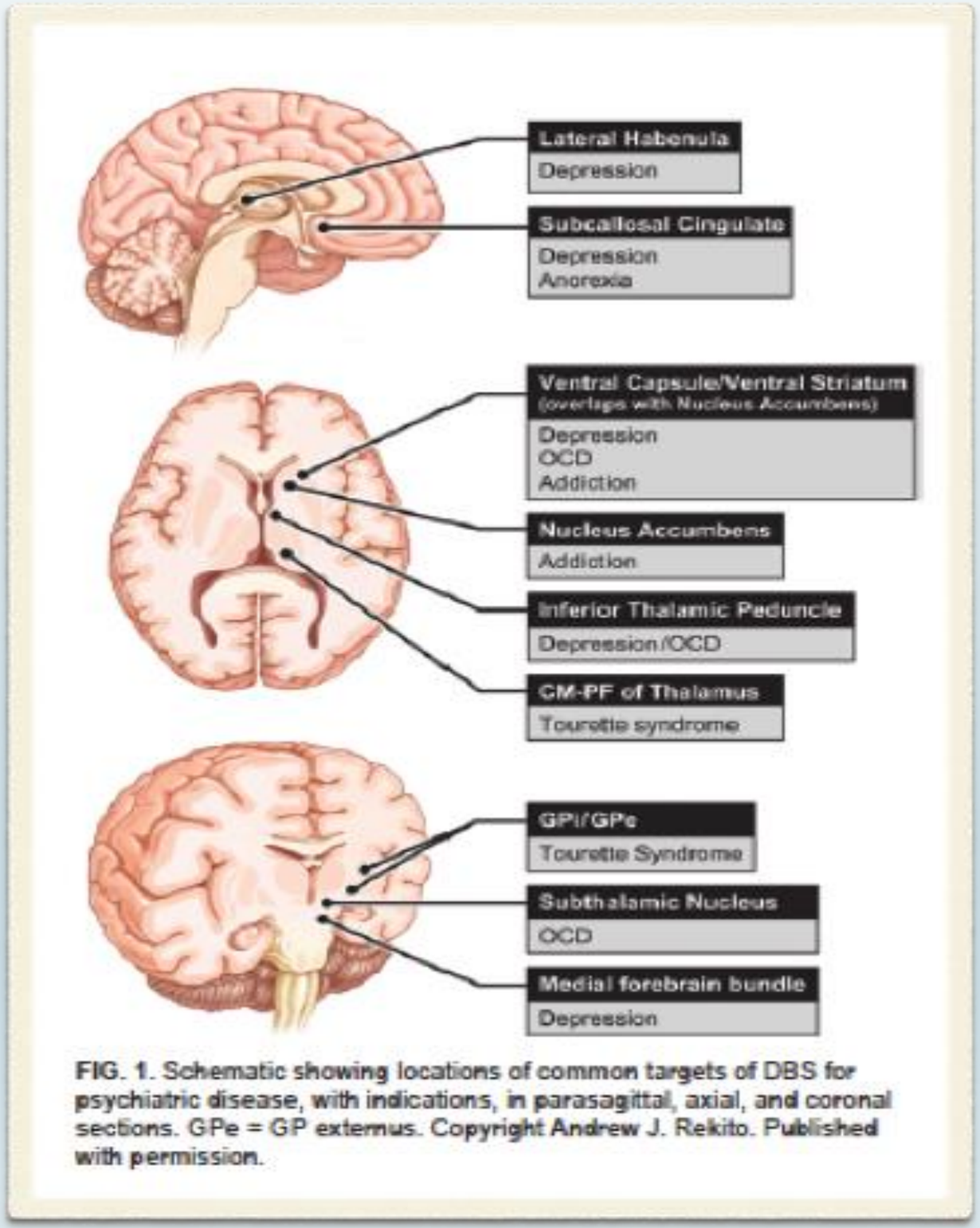


FIG. 1. Schematic showing locations of common targets of DBS for psychiatric disease, with indications, in parasagittal, axial, and coronal sections. GPe = GP externus. Copyright Andrew J. Reikito. Published with permission.

CRITERIOS SELECCIÓN DE LA DIANA A ESTIMULAR EN AN

. Implicada en circuitos del estado de animo, ansiedad, y motivacion/recomprensa

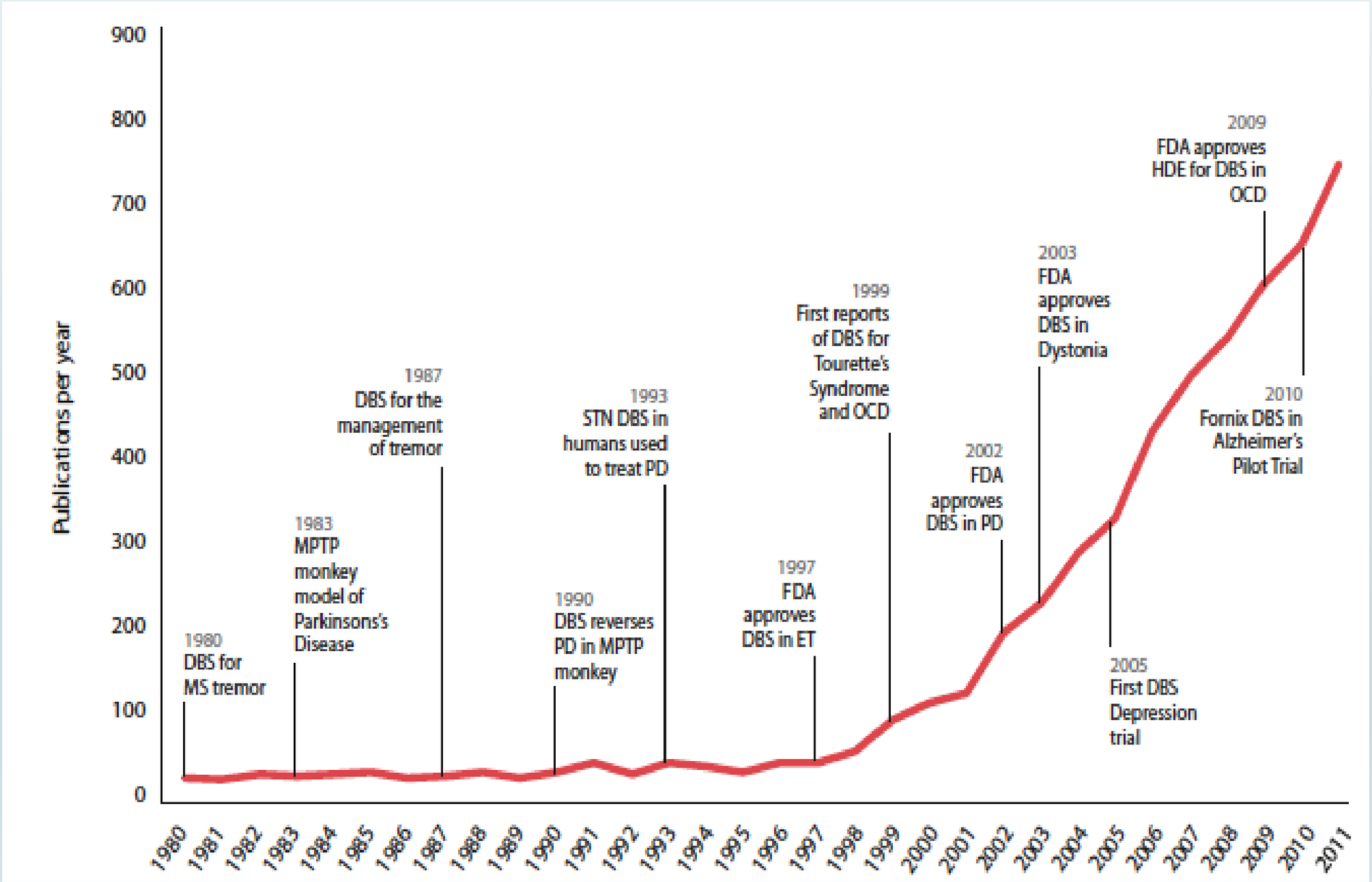
(Estudios de imagen funcional y preclínicos)

. Estructura donde los circuitos neuronales se concentren y convergen ("Key node")

. Estructura con facilidad para acceder quirúrgicamente

. Estructura donde haya experiencia previa en otras enfermedades mentales y DBS

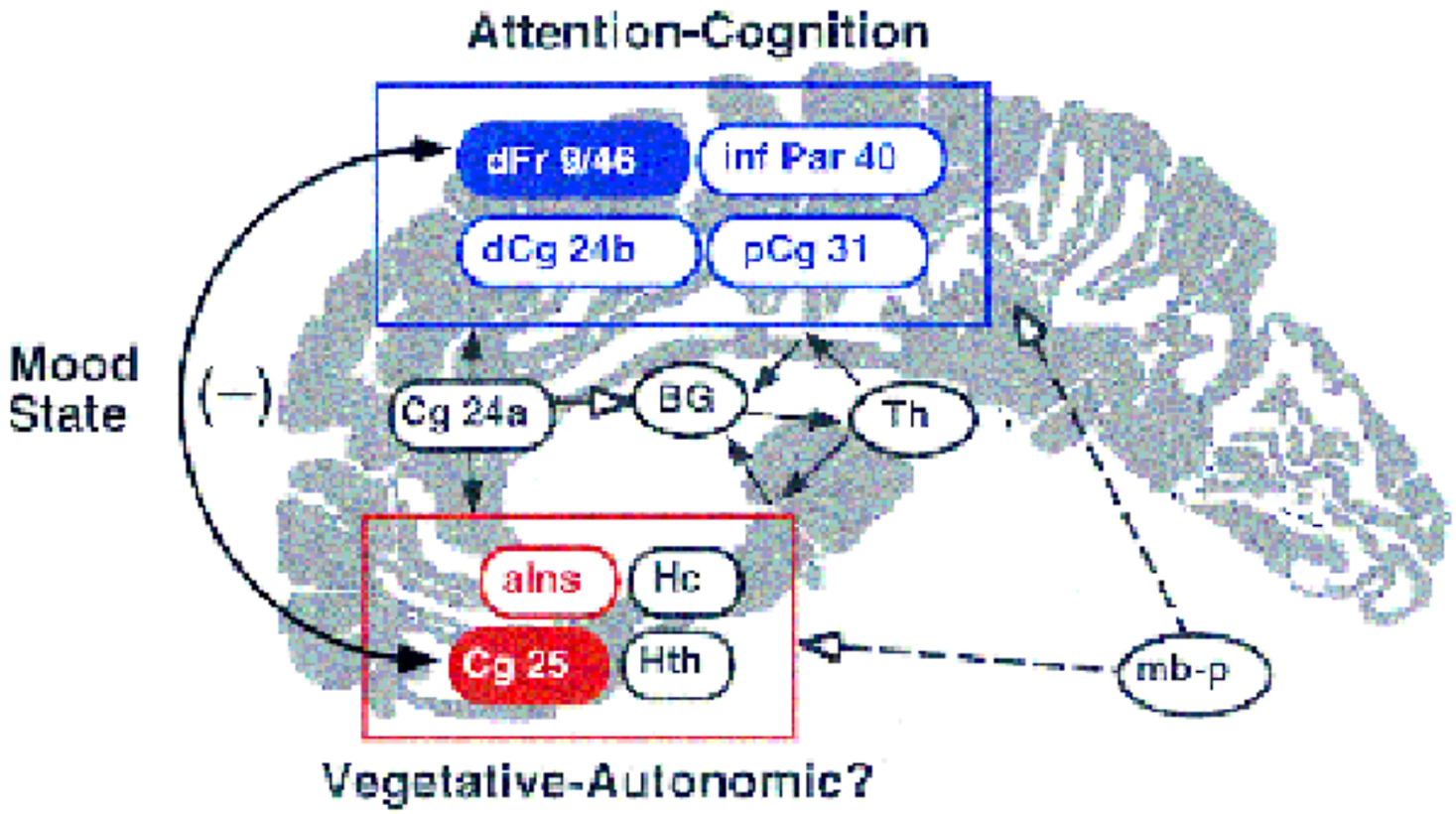
Indicación de DBS y Numero de publicaciones(año)



DBS en Depresión

Los estudios de Neuroimagen señalaron las zonas mas implicadas en la depresión

FIGURE 2. Schematic Model Illustrating Relationships Among Regions Mediating Shifts in Negative Mood State[a]

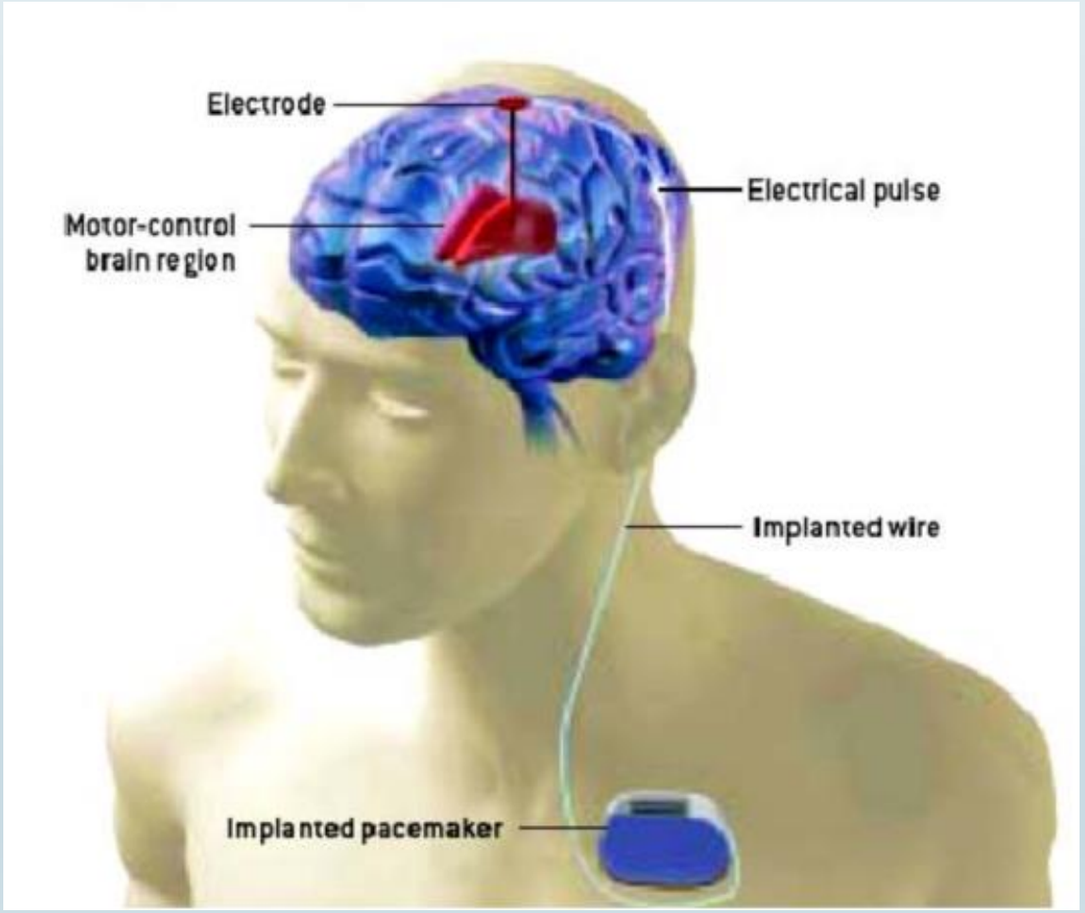


[a] Regions with known anatomical connections that also show synchronized changes (with PET) with both provocation and resolution of negative mood are grouped into two compartments: dorsal (blue) and ventral (red). The dorsal-ventral segregation also defines the brain regions where an inverse relationship is seen across the two PET paradigms (table 1, figure 1). Curved black arrows and color-filled regions further emphasize the significant inverse correlation between right dorsal prefrontal cortex (dFr 9/46, in blue) and subgenual cingulate (Cg 25, in red) seen with both transient sadness in healthy volunteers (Fr decreases, Cg increases) and mood symptom resolution in depressed patients (Fr increases, Cg decreases). Noncolored regions delineate brain areas potentially critical to the schematic model but where changes were not identified in both experiments. Short black arrows indicate known subcortical pathways. Numbers are Brodmann area designations. Abbreviations: in blue: dFr=dorsolateral prefrontal; inf Par=inferior parietal; dCg=dorsal anterior cingulate; pCg=posterior cingulate; in red: Cg25=subgenual cingulate; aIns=anterior insula; in black: Cg 24a=rostral anterior cingulate; BG=basal ganglia; Th=thalamus; Hc=hippocampus; Hth=hypothalamus; mb-p=midbrain-pons.

Deep Brain Stimulation for Treatment-Resistant Depression

Clinical Study

Mayberg et al., Neuron 2005



Criterios de inclusión

- Edad entre 18 y 70 años.
- Episodio Depresivo Mayor según DSM IV-TR.
- Resistentes a tratamiento farmacológico con un nivel 4 del Índice de Resistencia Thase o en los que esté contraindicada la TEC o pacientes en los que la mejoría obtenida con TEC no se mantiene.
- HDRS igual o mayor de 18.
- Los pacientes no deben haber modificado su pauta de tratamiento antidepresivo en el último mes.

International Journal of Neuropsychopharmacology, Page 1 of 13. © CINP 2011
doi:10.1017/S1461145711001088

ARTICLE

CINP

Deep brain stimulation of the subcallosal cingulate gyrus: further evidence in treatment-resistant major depression

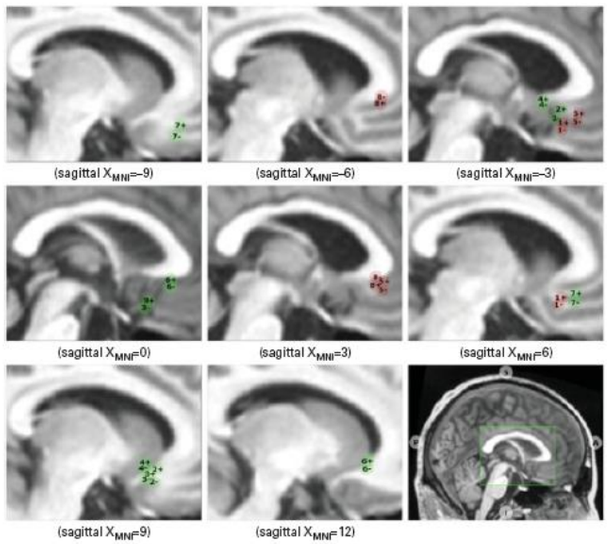
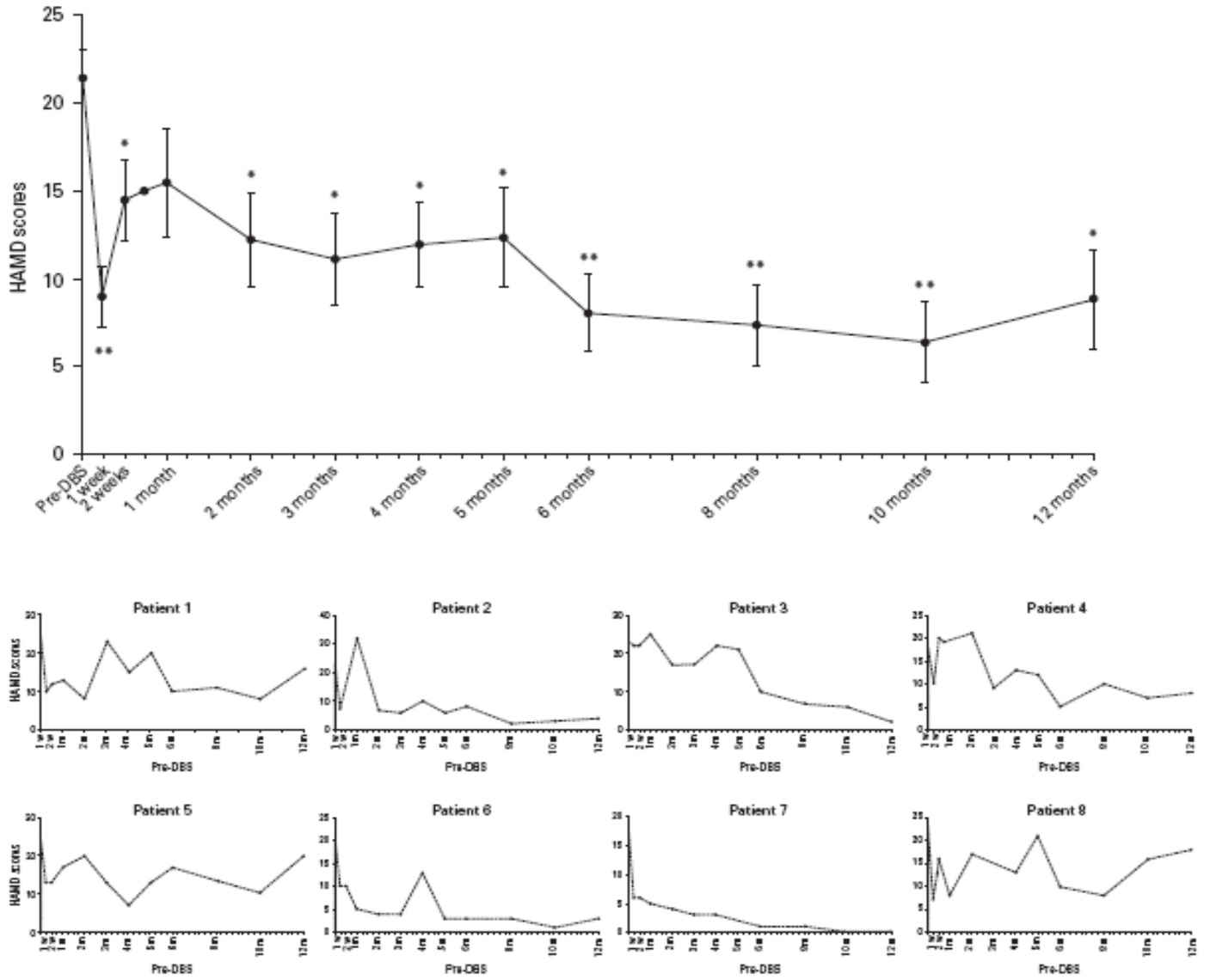
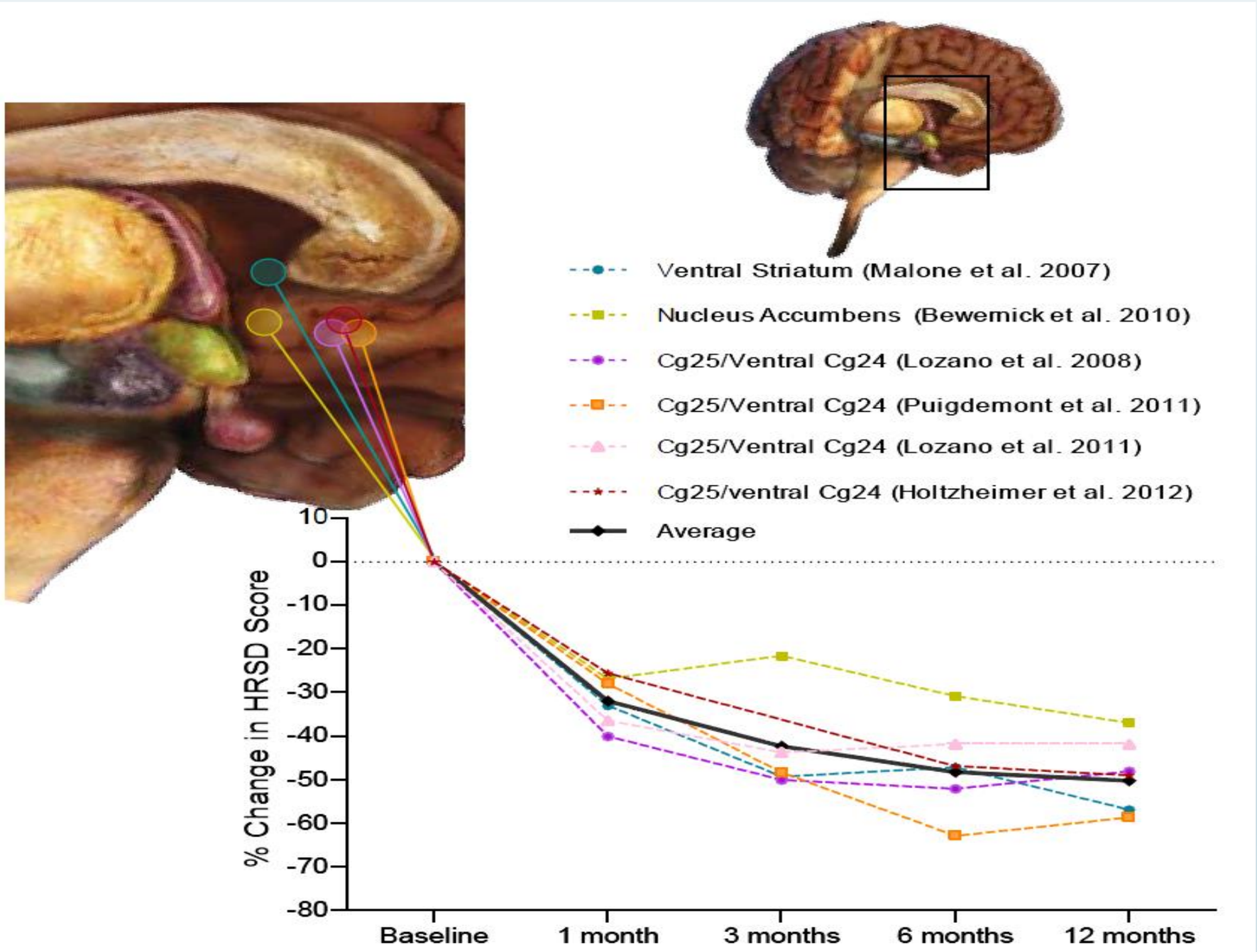


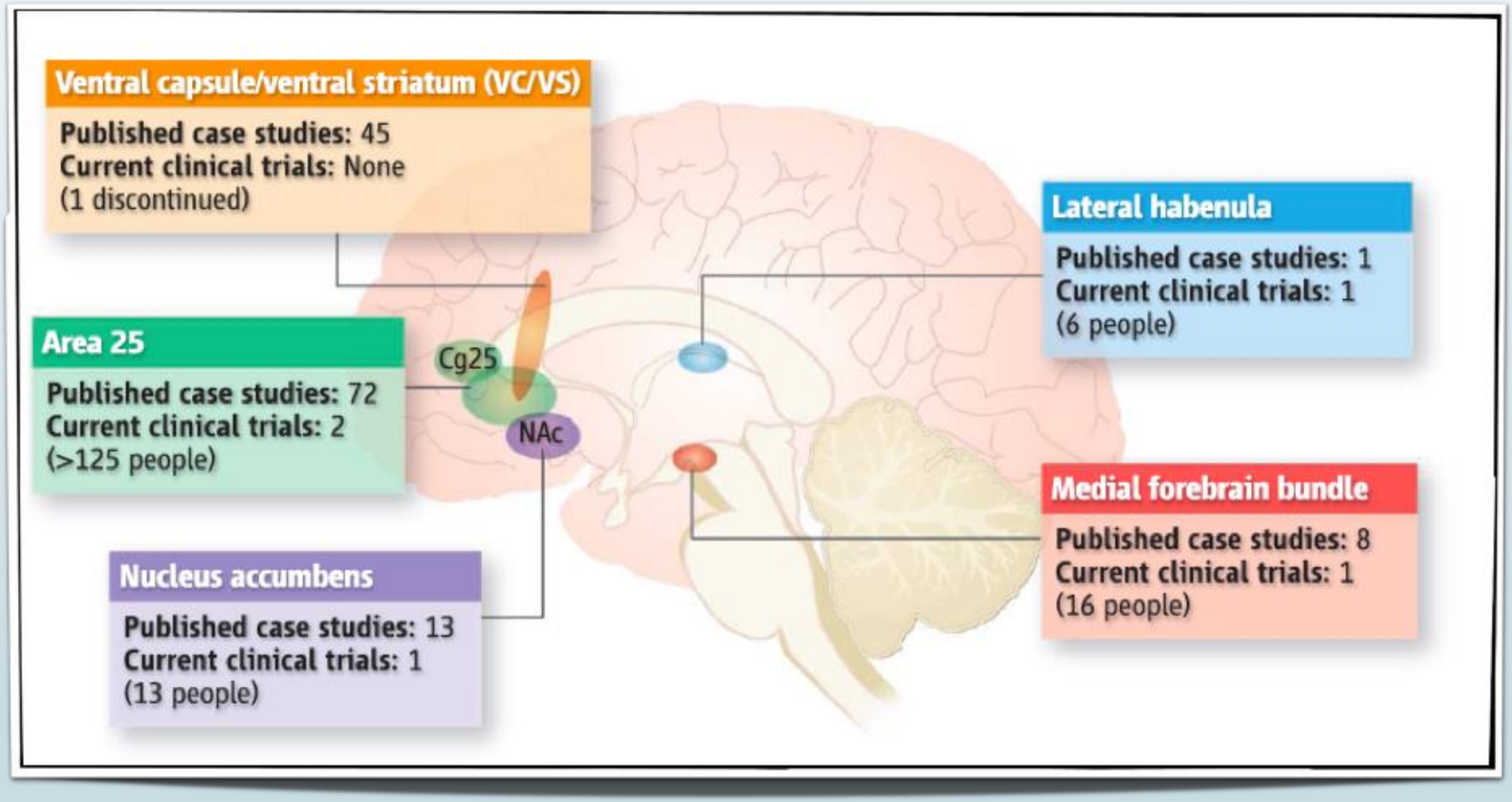
Fig. 3. Location of the electrode contacts on a sagittal view of the cingulate gyrus. Circles are schematic representations of the electrode contacts in patients responding (green circles) and not responding (red circles) to DBS of the SCG. Numbers correspond to every patient. More detailed information is given in Table 4.



DEEP BRAIN STIMULATION IN TREATMENT-RESISTANT DEPRESSIVE DISORDERS

Maria J. Portella*, Dolors Puigdemont, Enric Álvarez, Víctor Pérez





New focus. Science, Nov-2013

Deep Brain Stimulation for Treatment-Resistant Depression: Follow-Up After 3 to 6 Years

Sidney H. Kennedy, M.D.

Peter Giacobbe, M.D., M.Sc.

Sakina J. Rizvi, B.Sc.

Franca M. Placenza, Ph.D.

Yasunori Nishikawa, B.Sc.

Helen S. Mayberg, M.D.

Andres M. Lozano, M.D., Ph.D.

Objective: A prevalence of at least 30% for treatment-resistant depression has prompted the investigation of alternative treatment strategies. Deep brain stimulation (DBS) is a promising targeted approach involving the bilateral placement of electrodes at specific neuroanatomical sites. Given the invasive and experimental nature of DBS for treatment-resistant depression, it is important to obtain both short-term and long-term effectiveness and safety data. This report represents an extended follow-up of 20 patients with treatment-resistant depression who received DBS to the subcallosal cingulate gyrus (Brodmann's area 25).

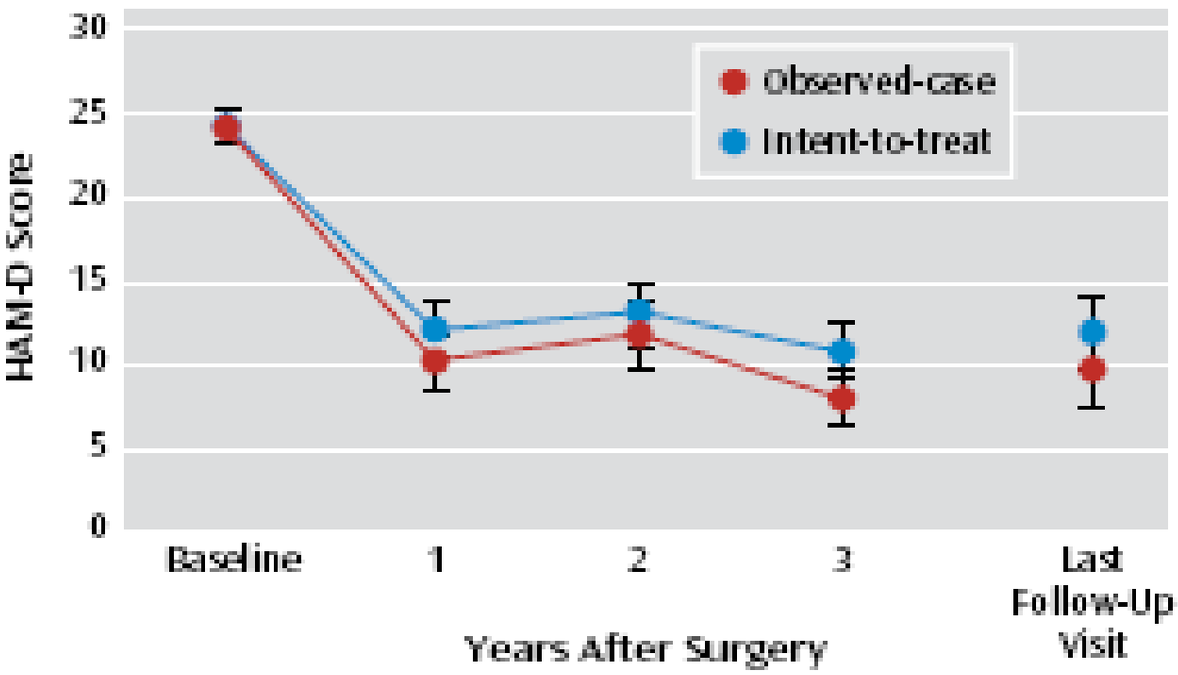
Method: After an initial 12-month study of DBS, patients were seen annually and at a last follow-up visit to assess depression severity, functional outcomes, and adverse events.

Results: The average response rates 1, 2, and 3 years after DBS implantation were 62.5%, 46.2%, and 75%, respectively. At the last follow-up visit (range=3–6 years), the average response rate was 64.3%. Functional impairment in the areas of physical health and social functioning progressively improved up to the last follow-up visit. No significant adverse events were reported during this follow-up, although two patients died by suicide during depressive relapses.

Conclusions: These data suggest that in the long term, DBS remains a safe and effective treatment for treatment-resistant depression. Additional trials with larger samples are needed to confirm these findings.

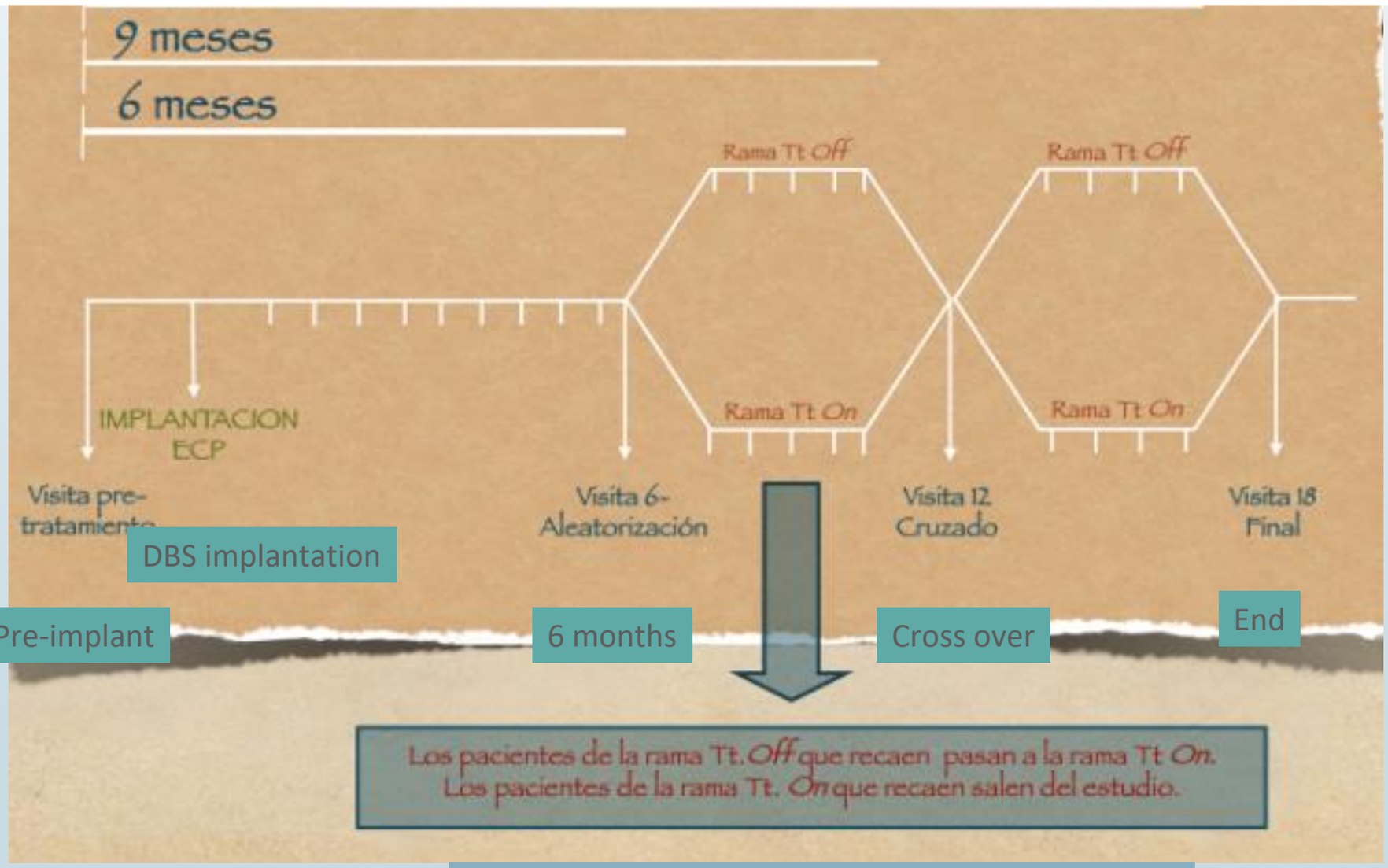
(Am J Psychiatry Kennedy et al.; AiA:1–9)

FIGURE 3. Hamilton Depression Rating Scale (HAM-D) Scores for Patients With Treatment-Resistant Depression (N=20) at Baseline, at 1, 2, and 3 Years After Surgery for Deep Brain Stimulation, and at Last Follow-Up Visit*



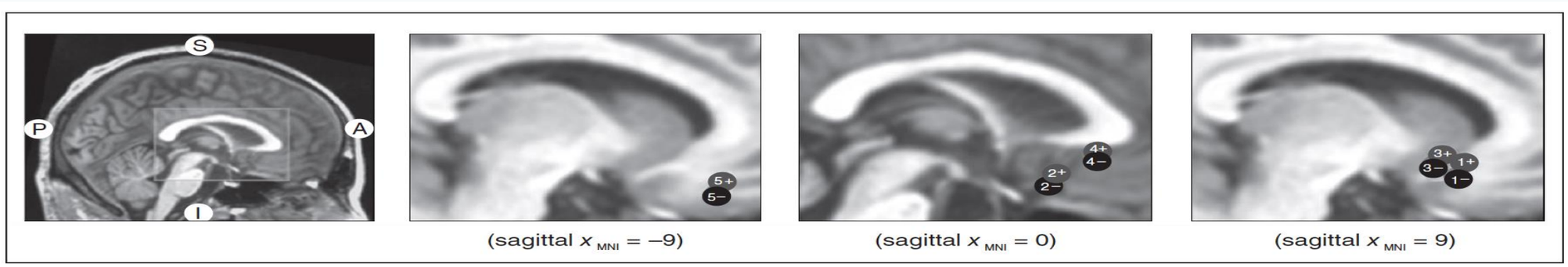
A randomized double-blind crossover trial of deep brain stimulation of the subcallosal cingulate gyrus in patients with treatment-resistant depression: a pilot study of relapse prevention

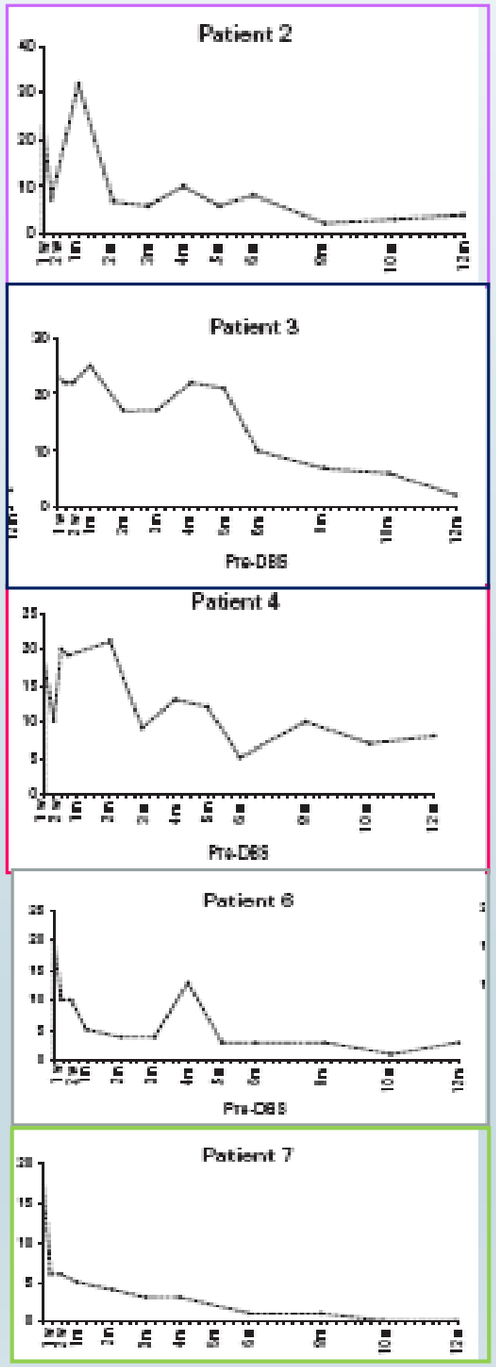
Dolors Puigdemont, MD; Maria J. Portella, PhD; Rosario Pérez-Egea, MD; Joan Molet, MD, PhD; Alexandre Gironell, MD, PhD; Javier de Diego-Adeliño, MD, PhD; Anna Martín, MD; Rodrigo Rodríguez, MD; Enric Àlvarez, MD PhD; Francesc Artigas, PhD; Víctor Pérez, MD PhD

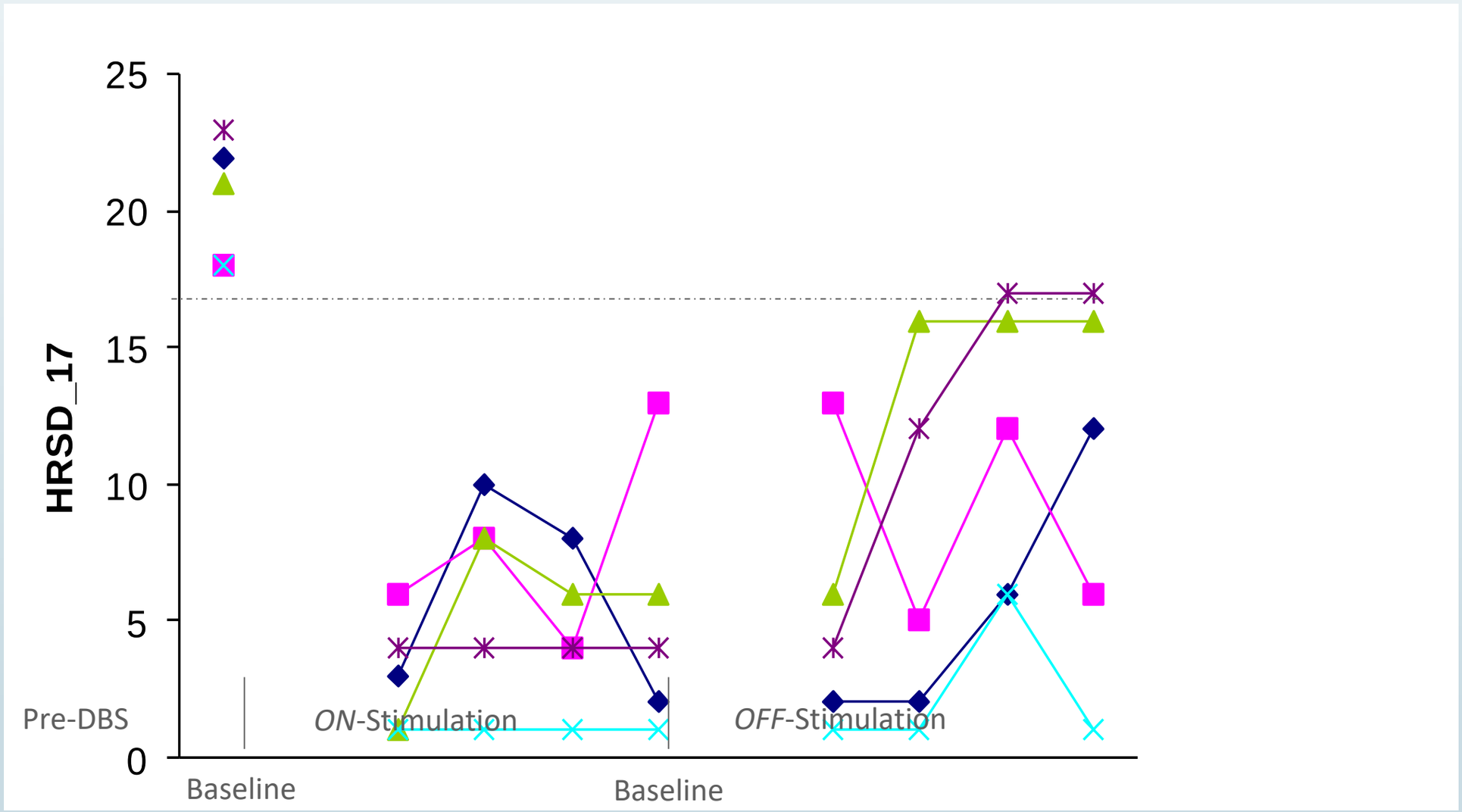


A. One patient OFF-ON relapse at the end OFF phase
B. One patient ON-OFF relapse at the beginning OFF phase

J Psychiatry Neurosci 2015







two patients relapsed during the *off*-stimulation arm

Behavioural Brain Research 359 (2019) 266–273

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journal homepage: www.elsevier.com/locate/bbr

Review

Deep brain stimulation targets for treating depression

Dominik Drobisz[a,1], Alena Damborská[a,b,c,*,1]

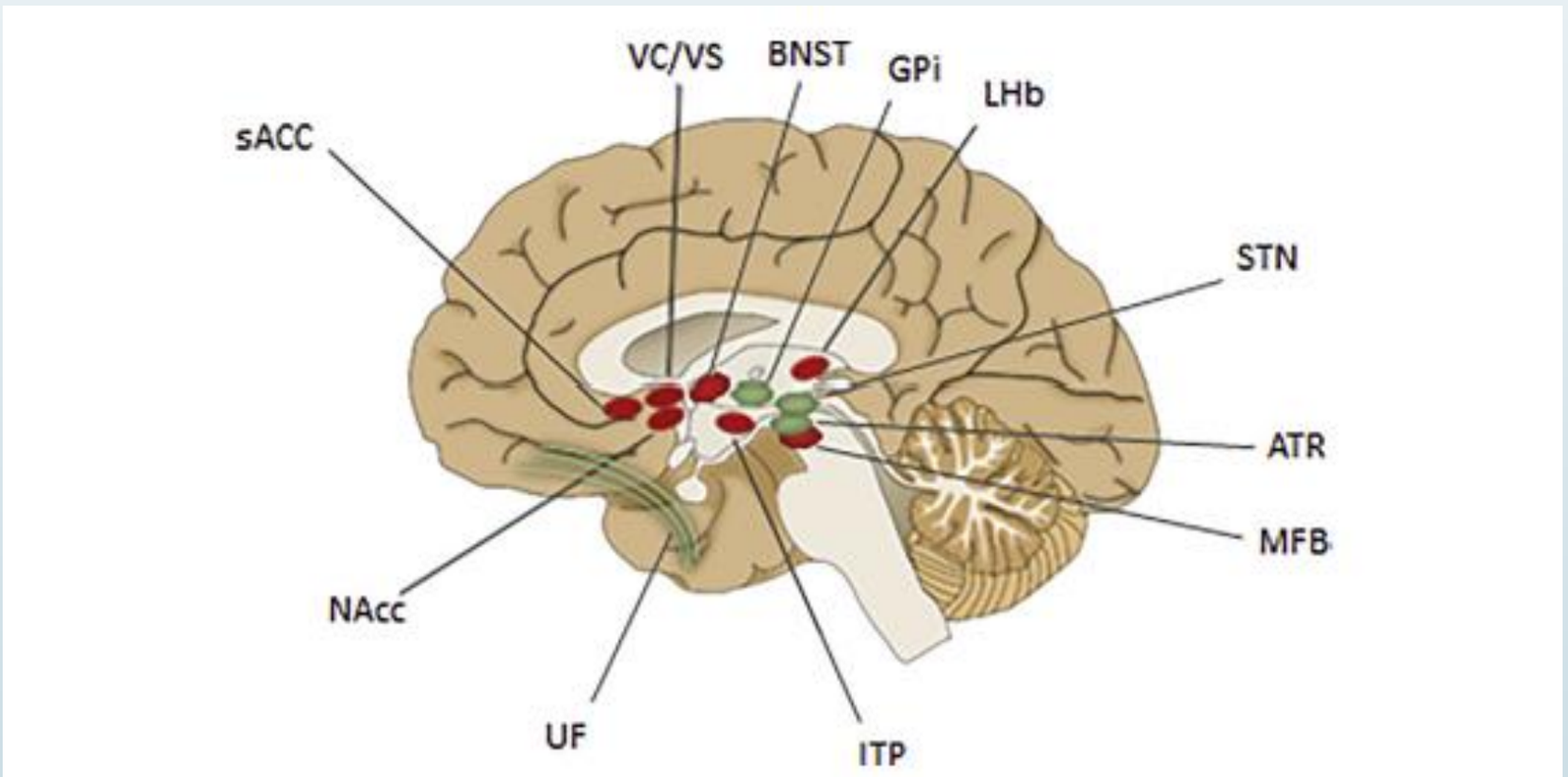

Fig. 1. Current (red) and candidate (green) deep brain stimulation targets for treatment-resistant depression. sACC – subgenual anterior cingulate cortex, VC/VS – ventral capsule/ventral striatum, BNST – bed nucleus of the stria terminalis, GPi – globus pallidus pars interna, LHb – lateral habenula, STN – subthalamic nucleus, ATR – anterior thalamic radiation, MFB –medial forebrain bundle, ITP – inferior thalamic peduncle, UF – uncinate fasciculus, NAcc – nucleus accumbens. Adopted and modified with permission from Anderson et al. [16].

Behavioural Brain Research 359 (2019) 266–273

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Review

Deep brain stimulation targets for treating depression

Dominik Drobisz[a,1], Alena Damborská[a,b,c,*,1]

Table 1
Outcomes of deep brain stimulation studies for depression using different brain targets.

Target and study	N	Follow-up period (months)	Mean age at surgery (years)	Mean age of MDD onset (years)	Response rate (%)	Remission rate (%)	Primary measure
Subgenual cingulate gyrus							
Mayberg [39]	6	6	47	29.5	67	33	$HDRS_{17}$
Lozano [40]	20	12	47.4	27.1	55	35	$HDRS_{17}$
Lozano [41]	21	12	47.3	27.3	29	–	$HDRS_{17}$
Kennedy [42]	20	39	47.3	27.1	64	43	$HDRS_{17}$
Neimat [21]	1	30	55	9	100	100	$HDRS_{17}$
Puigdemont [101]	8	12	47.4	24.9	63	50	$HDRS_{17}$
Merkl [99]	6	6	50.67	23.67	50	33	$HDRS_{24}$
Puigdemont [102]	8	12	–	–	63	50	$HDRS_{17}$
Ramasubbu [44]	4	9	50.25	–	50	0	$HDRS_{17}$
Sun [100]	20	4 - 76	45.35	–	60	40	$HDRS_{17}$
Hilimire [103]	7	6	–	–	86	29	$HDRS_{17}$
McNeely [98]	6	12	46	29.5	66	33	$HDRS_{17}$
Kibleur [104]	5	9 - 72	52	–	100	60	$HDRS_{17}$
Riva-Posse [43]	11	12	–	–	82	55	HDRS
Guinjoan [22]	1	18	60	39	100	100	$HDRS_{17}$
Holtzheimer [105]	10	24	40	20.3	92	58	$HDRS_{17}$
Ventral capsule/ventral striatum							
Strong [53]	1	48	43	–	100	100	MADRS
Malone [50]	15	23	46.3	25.3	53	40	$HDRS_{24}$
Malone [51]	17	37	46.3	25.3	71	35	MADRS
Dougherty [52]	30	12	47.7	22.8	20	13	MADRS
Bergfeld [54]	25	13	53.2	28.5	40	20	$HDRS_{17}$
Nucleus accumbens							
Schlaepfer [59]	3	0.5 - 2	46.7	–	33	–	$HDRS_{24}$
Bewernick [57]	10	12 - 36	48.6	31.7	50	30	$HDRS_{28}$
Bewernick [58]	11	12 - 48	48.4	32.6	45	9	$HDRS_{28}$
Millet [60]	4	15	52	–	75	25	$HDRS_{17}$
Inferior thalamic peduncle							
Jiménez [73]	1	24	49	29	–	–	HDRS
Raymaekers [20]	1	96	52	47	100	100	$HDRS_{17}$
Lateral habenula							
Sartorius [67]	1	15	64	18	100	100	$HDRS_{21}$
Medial forebrain bundle							
Schlaepfer [18]	7	3-8	42.6	30	86	57	$HDRS_{24}$
Fenoy [82]	3	6.5	46.3	16.5	67	33	$HDRS_{29}$
Bed nucleus of the stria terminalis							
Raymaekers [20]	7	36	50	35.3	71	29	$HDRS_{17}$
Blomstedt [19]	1	12	60	–	100	100	HDRS

N = Number of participants; $HDRS_n$ = Hamilton Depression Rating Scale with indicated number 'n' of questionnaire items; MADRS = Montgomery-Asberg

A systematic review and meta-analysis of deep brain stimulation for depression

Steve Kisely[1,2,3,4] | Amy Li[1] | Nicola Warren[1,2] | Dan Siskind[1,2]

Background: Deep brain stimulation is increasingly being used for treatment-resistant depression. Blinded, randomized controlled trials of active versus sham treatment have been limited to small numbers.

Method: We performed a systematic review and meta-analysis on the effectiveness of deep brain stimulation (DBS) in depression. Cochrane Central Register of Controlled Trials, PubMed/Medline, Embase and PsycINFO, Chinese Biomedical Literature Service System, and China Knowledge Resource Integrated Database were searched for single- or double placebo-controlled, crossover, and parallel-group trials in which DBS was compared with sham treatment using validated scales.

Results: Ten papers from nine studies met inclusion criteria, all but two of which were double-blinded RCTs. The main outcome was a reduction in depressive symptoms. It was possible to combine data for 190 participants. Patients on active, as opposed to sham, treatment had a significantly higher response (OR = 5.50; 95% CI = 2.79, 10.85; $p < .0001$) and reductions in mean depression score (SMD = −0.42; 95% CI = −0.72, -0.12; $p = .006$). However, the effect was attenuated on some of the subgroup and sensitivity analyses, and there were no differences for most other outcomes. In addition, 84 participants experienced a total of 131 serious adverse effects, although not all could be directly associated with the device or surgery. Finally, publication bias was possible.

Conclusions: DBS may show promise for treatment-resistant depression but remains an experimental treatment until further data are available.

KEYWORDS

depression, mood disorders, treatment, brain stimulation/TMS/DBS/VNS, clinical trials, systematic review

A systematic review and meta-analysis of deep brain stimulation for depression

Steve Kisely[1,2,3,4] | Amy Li[1] | Nicola Warren[1,2] | Dan Siskind[1,2]

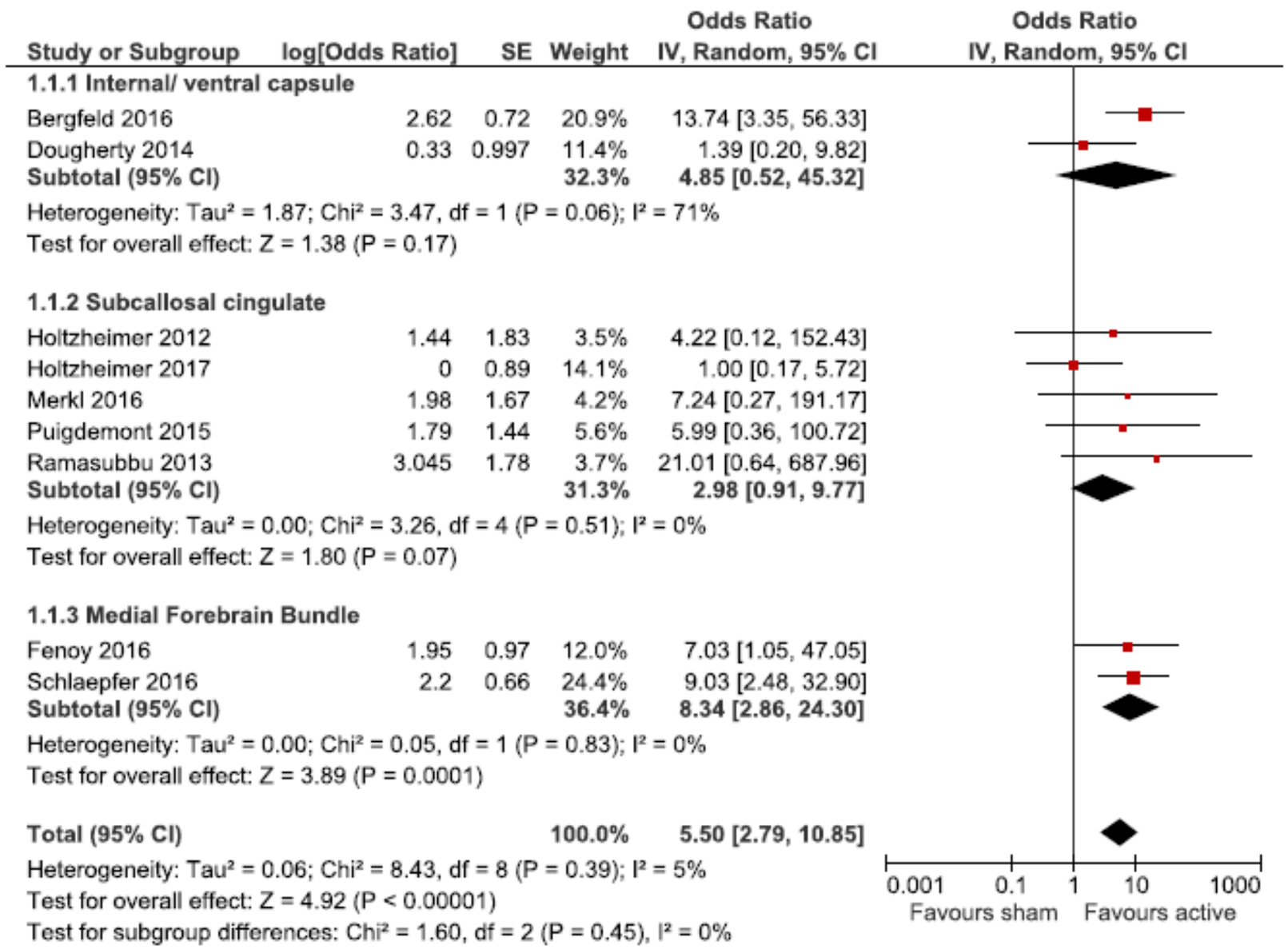
TABLE 3 Risk of bias table

	Random sequence generation (selection bias) (high, low, or unclear)	Allocation concealment (selection bias) (high, low, or unclear)	Blinding of participants, personnel (performance bias) (high, low, or unclear)	Blinding of outcome assessment (detection bias) (high, low, or unclear)	Incomplete outcome data (attrition bias) (high, low, or unclear)	Selective outcome reporting (reporting bias) (high, low, or unclear)	Other sources of bias (high, low, or unclear)
Bergfeld et al. (2006)	Low	Unclear	Low	Low	High	Low	High (a) (b) (c)
Dougherty 2015	Unclear	Unclear	Low	Low	Low	Low	High (a)
Holtzheimer et al. (2012)	High	High	High	High	High	Unclear	High (a) (b)
Holtzheimer et al. (2017)	Low	Low	Low	Low	Low	High (d)	High (a) (d)
Merkl 2016	Unclear	Unclear	Low	Low	Low	Unclear	High (a) (b)
Puigdemont et al. (2015)	Low	Low	Low	Low	Low (ITT plus LOCF)	Low	High (b) (e)
Ramasubbu et al. (2013)	Unclear	Unclear	Low	Low	Low	Unclear	High (a) (b)
Schlaepfer et al. (2016)	Unclear	Unclear	Unclear	Low	Unclear	Unclear	High (a)
Fenoy 2016	High	High	High	High	Low	Unclear	High (b)

ITT, Intention to treat; LOCF, last observation carried forward.
(a) Material/ financial support from Medtronic or Abbott (formerly St Jude).
(b) Crossover trial.
(c) ITT data were presented for all 25 patients who participated in the optimization phase. However, only 16 participated in the randomized crossover stage although all 16 patients completed this phase.
(d) Study details were redacted on the clinical trial registry.
(e) All patients had been in stable remission for 12 weeks prior to the study.

A systematic review and meta-analysis of deep brain stimulation for depression

Steve Kisely[1,2,3,4] | Amy Li[1] | Nicola Warren[1,2] | Dan Siskind[1,2]



Depress Anxiety. 2018;35:468–480.

DBS en Esquizofrenia

Prevalencia 1%

30% Resistente a tratamiento actual

Esperanza de vida < en 15-20 años

10 % de los pacientes se suicidan

NIH U.S. National Library of Medicine

ClinicalTrials.gov

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Recruiting	**Deep Brain Stimulation** in Treatment Resistant **Schizophrenia**	• Refractory **Schizophrenia**	• Device: On-Stimulation • Device: Off-Stimulation	• FIDMAG Germanes Hospitalàries Research Foundation Sant Boi de Llobregat, Barcelona Spain • Department of Psychiatry. Hospital Santa Creu i Sant Pau Barcelona Spain
2	☐	Recruiting	**Deep Brain Stimulation** in Treatment Resistant **Schizophrenia**	• Treatment-resistant **Schizophrenia**	• Device: Medtronic Activa Deep Brain Stimulation System	• The Johns Hopkins Hospital Baltimore, Maryland United States

Estudio tolerancia y eficacia ECP en Esquizofrenia resistente (PI12/00042)

Centro coordinador: Hospital de Sant Pau

Psiquiatría: Dra. I. Corripio, Dra A. Roldán, M. Rabella, A. Alonso, Dr. E. Álvarez
Neurocirugía: Dr Rodrigo Rodríguez; Dr Joan Molet

Centro coordinado: FIDMAG

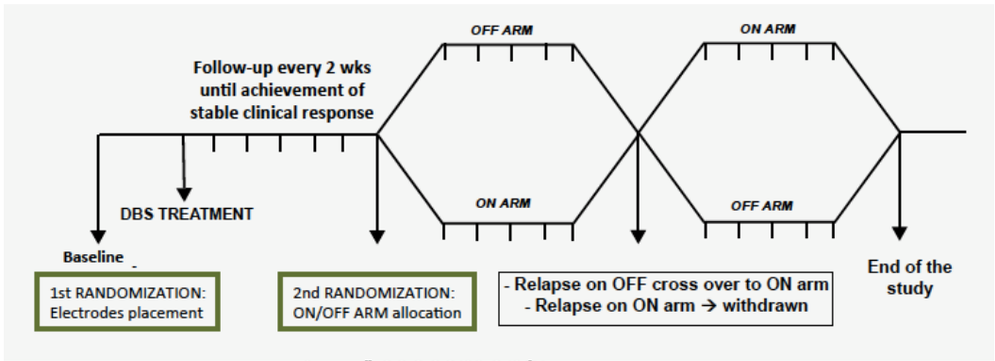
Peter Mackennan, Edith Pomarol, Salvador Sarró

Diseño

- **8 patients** with DSM-IV-TR diagnosis of **schizophrenia** that are:

  - RESISTANT to at least two different atypical antipsychotics
  - Non-responders to CLOZAPINE in monotherapy/combination
  - Non responders to electroconvulsive therapy

- Study design:



- Assessment:
  - Positive and Negative Symptom Scale (PANSS)
  - The Clinical Global Impression Scale (CGI)
  - Personal and Social Performance (*PSP*) Scale
  - Global Assessment of Functioning (GAF)
  - Neuropsychological battery
  - Stimulation parameters

- **Symptomatic response** to DBS is defined as having an improvement ≥25% on PANSS total score.

Clinical Improvement in a Treatment-Resistant Patient With Schizophrenia Treated With Deep Brain Stimulation

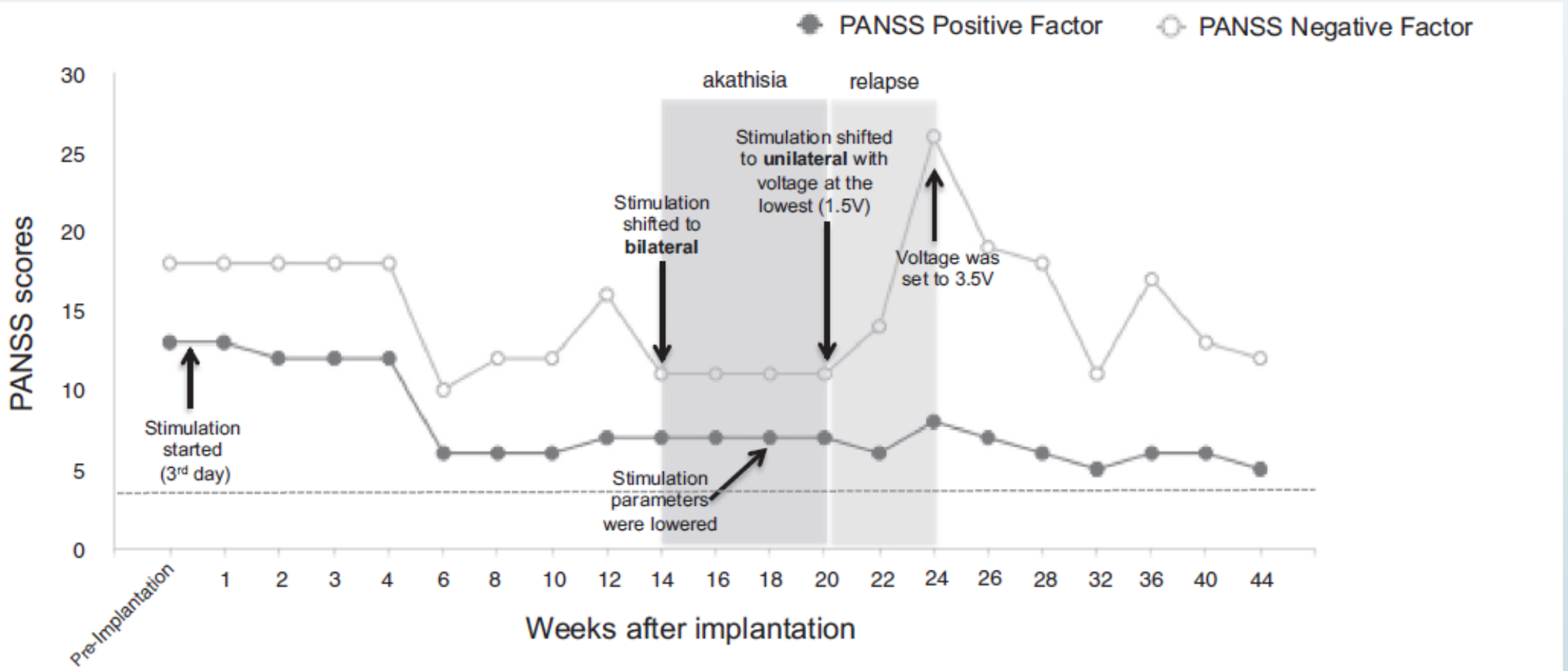


Figure 1. Scores on Positive and Negative Syndrome Scale (PANSS) Positive and Negative factors (13) in the patient over 11 months with deep brain stimulation (dotted line indicates absence of all positive symptoms).

Biological Psychiatry October 15, 2016; 80:e69–e70

Corripio et. al.

DBS en Anorexia Nerviosa

0-7 % de la población

40% se cronifican

TRATAMIENTO QUIRÚRGICO ANOREXIA NERVIOSA

1950 — 1970 — 2011

Leucotomias y lobotomias prefontales

17 pacientes

Procedimientos ablativos
Extereotaxia

Comites ética

6 pacientes (4 publicaciones)

. Talamolomía dorsomediales
. Capsulotomía anterior
. Leucotomía limbica (cingulo anterior)

DBS

24 pacientes (6 publicaciones)

Subcallosal cingulate deep brain stimulation for treatment-refractory anorexia nervosa: a phase 1 pilot trial

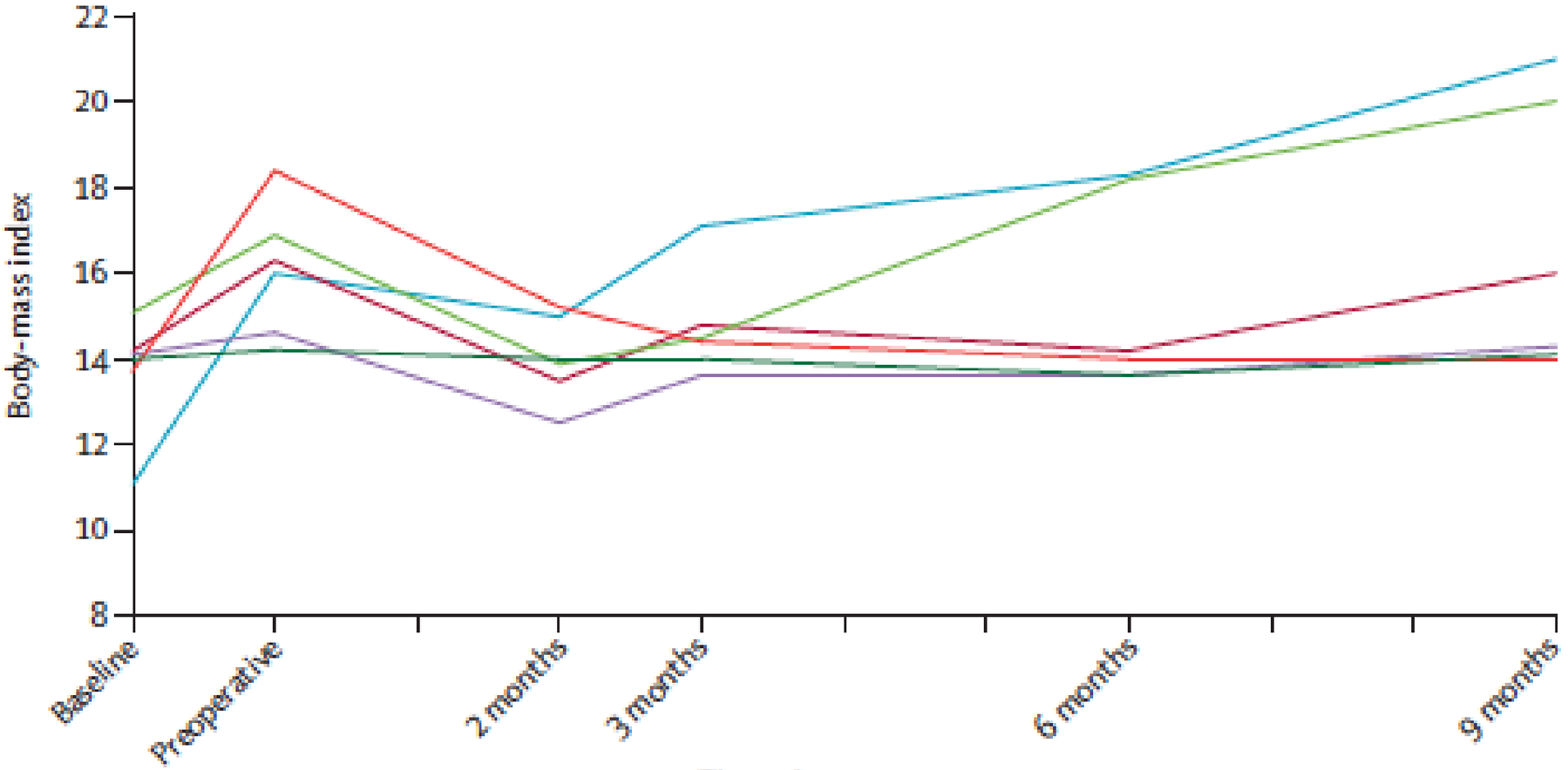
Nir Lipsman, D Blake Woodside, Peter Giacobbe, Clement Hamani, Jacqueline C Carter, Sarah Jane Norwood, Kalam Sutandar, Randy Staab, Gavin Elias, Christopher H Lyman, Gwenn S Smith, Andres M Lozano

Lancet 2013; 381: 1361–70

	Sex	Age at disease onset (years)	Age at surgery (years)	Duration of illness (years)	Anorexia subtype	BMI (historical low)	Psychiatric comorbidities	Psychiatric drugs at surgery	Number of acute inpatient admissions	Medical complications
Patient 1	Female	11	24	13	Purge	11·0	MDD, OCD	Quetiapine, lorazepam, sertraline	>10	Cardiac, endocrine, gastrointestinal, metabolic
Patient 2	Female	16	39	23	Binge–purge	11·9	MDD, OCD, SUD,* PTSD	Quetiapine, clonazepam, sertraline	>10	Cardiac, endocrine, gastrointestinal, metabolic
Patient 3	Female	17	35	18	Restriction	12·4	OCD	Citalopram	>10	Endocrine, cardiac, metabolic
Patient 4	Female	36	40	4	Restriction	13·1	MDD	Quetiapine fluoxetine, seroquel	3	Endocrine, metabolic
Patient 5	Female	20	35	15	Restriction	13·5	MDD, OCD, PTSD	Fluoxetine, quetiapine	>10	Cardiac, musculoskeletal, gastrointestinal, endocrine, metabolic
Patient 6	Female	20	57	37	Restriction	13·0	None	None	0†	Musculoskeletal, cardiac

BMI=body-mass index. MDD=major depressive disorder. OCD=obsessive–compulsive disorder. SUD=substance use disorder. PTSD=post-traumatic stress disorder. *Substance use disorder in remission for 6 months before study enrolment. †Remote inpatient admission as a teenager for chronic treatment, not medical stabilisation.

Table 1: **Demographic characteristics**



	Baseline	Preoperative	2 months	3 months	6 months	9 months
Patient 1	11·1	16·0	15·0	17·1	18·3	21·0
Patient 2	14·2	16·3	13·5	14·8	14·2	16·0
Patient 3	14·1	14·6	12·5	13·6	13·6	14·3
Patient 4	13·7	18·4	15·2	14·4	14·0	14·0
Patient 5	15·1	16·9	13·9	14·5	18·2	20·0
Patient 6	14·0	14·2	14·0	14·0	13·6	14·1
Mean	13·7 (1·4)	16·1 (1·5)	14·0 (1·0)	14·7 (1·2)	15·3 (2·3)	16·6 (3·2)

Deep-Brain Stimulation for Anorexia Nervosa

Hemmings Wu[1], Pieter Jan Van Dyck-Lippens[1], Remco Santegoeds[1,2], Kris van Kuyck[1], Loes Gabriëls[3], Guozhen Lin[4], Guihua Pan[5], Yongchao Li[6], Dianyou Li[7], Shikun Zhan[7], Bomin Sun[7], Bart Nuttin[1,2]

WORLD NEUROSURGERY 80 [3/4]: 529.e1-529.e10, SEPTEMBER/OCTOBER 2013

Table 1. Patient Demographics

Patient	Sex	Age of Onset, Years	BMI	Duration of Disease, Months	Duration of Amenorrhea, Months	Comorbidities	Treatment	Suspend from Schooling, Months
1	F	14	12.2	28	11	OCD	SSRI, olanzapine	5
2	F	15	13.3	18	15	OCD	SSRI, olanzapine	3
3	F	16	12	15	9	Generalized Anxiety Disorder	SSRI, olanzapine	10
4	F	15	10	13	9	OCD	SSRI	6

BMI, body mass index; F, female; OCD, obsessive-compulsive disorder; SSRI, selective serotonin reuptake inhibitors.

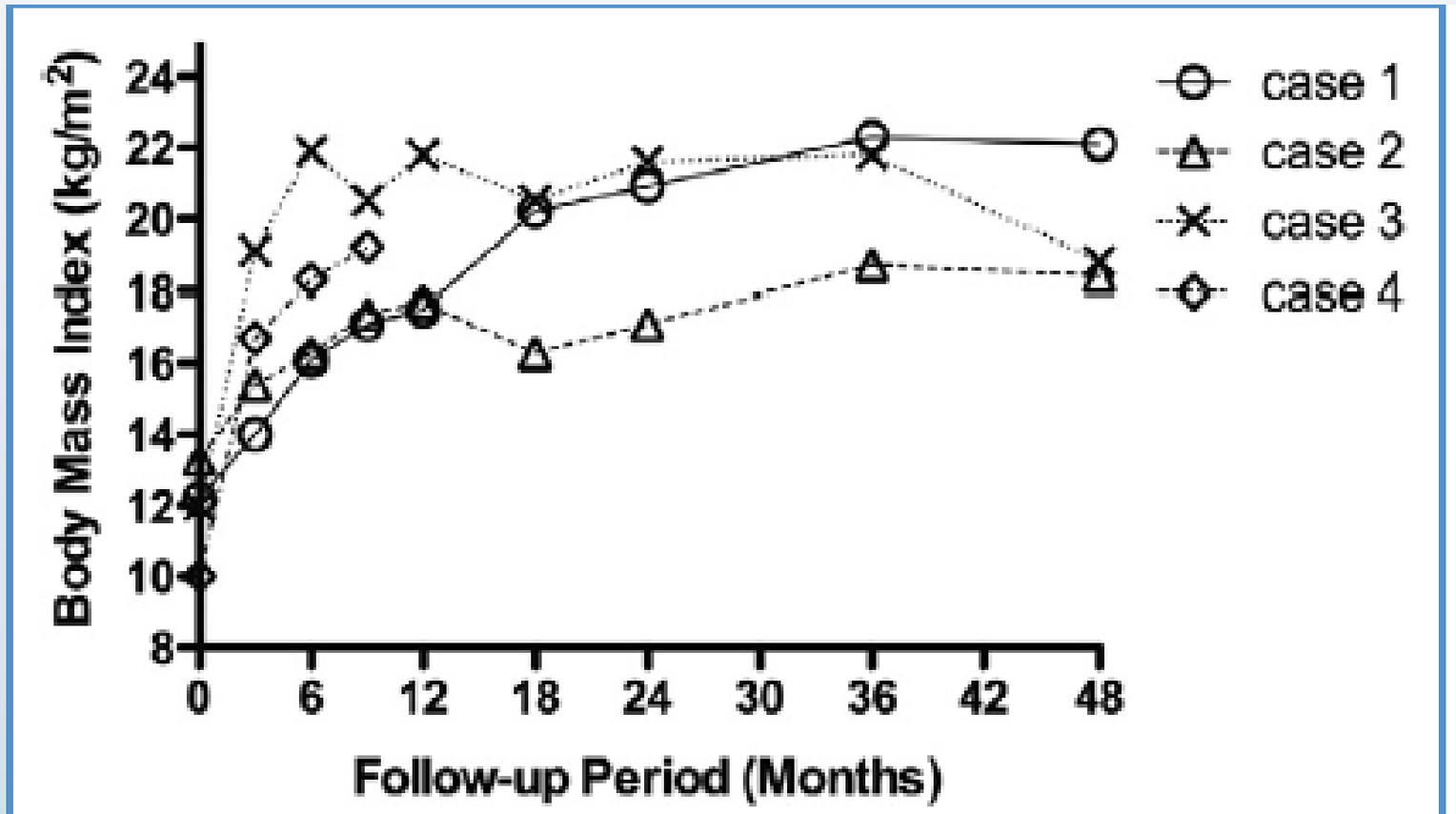


Figure 1. Changes in body mass index (BMI) over time. This figure shows BMI measurements (n = 4) at 0 (baseline), 3, 6, 9, 12, 18, 24, 36, and 48 months during follow-up (up to 9 months in case 4, who as of this writing underwent the procedure less than a year ago).

Deep brain stimulation of the subcallosal cingulate for treatment-refractory anorexia nervosa: 1 year follow-up of an open-label trial

Nir Lipsman, Eileen Lam, Matthew Volpini, Kalam Sutandar, Richelle Twose, Peter Giacobbe, Devin J Sodums, Gwenn S Smith, D Blake Woodside, Andres M Lozano

Summary

Background Anorexia nervosa is a life-threatening illness. Brain circuits believed to drive anorexia nervosa symptoms can be accessed with surgical techniques such as deep brain stimulation (DBS). Initial results suggest that DBS of the subcallosal cingulate is safe and associated with improvements in mood and anxiety. Here, we investigated the safety, clinical, and neuroimaging outcomes of DBS of the subcallosal cingulate in a group of patients during 12 months of active stimulation.

Methods We did this prospective open-label trial at the Department of Surgery of the University of Toronto (Toronto, ON, Canada). Patients were eligible to participate if they were aged 20–60 years and had a diagnosis of anorexia nervosa (restricting or binge–purging subtype) and a demonstrated history of chronicity or treatment resistance. Following a period of medical stabilisation, patients underwent surgery for DBS and received open-label continuous stimulation for the entire 1 year study duration. The primary outcome was safety and acceptability of the procedure. The secondary outcomes were body-mass index (BMI), mood, anxiety, affective regulation, and anorexia nervosa-specific behaviours at 12 months after surgery, as well as changes in neural circuitry (measured with PET imaging of cerebral glucose metabolism at baseline and at 6 and 12 months after surgery). This trial was registered with ClinicalTrials.gov, number NCT01476540.

Findings 16 patients with treatment-refractory anorexia nervosa were enrolled between September, 2011, and January, 2014, and underwent DBS of the subcallosal cingulate between November, 2011, and April, 2014. Patients had a mean age of 34 years (SD 8) and average illness duration of 18 years (SD 6). Two patients requested that their devices be removed or deactivated during the study, although their reasons for doing so were poorly defined. The most common adverse event was pain related to surgical incision or positioning that required oral analgesics for longer than 3–4 days after surgery (five [31%] of 16 patients). Seven (44%) of 16 patients had serious adverse events, most of which were related to the underlying illness, including electrolyte disturbances. Average BMI at surgery was 13·83 (SD 1·49) and 14 (88%) of the 16 patients had comorbid mood disorders, anxiety disorders, or both. Mean BMI after 12 months of stimulation was 17·34 (SD 3·40; p=0·0009 *vs* baseline). DBS was associated with significant improvements in measures of depression (mean Hamilton Depression Rating Scale scores 19·40 [SD 6·76] at baseline *vs* 8·79 [7·64] at 12 months; p=0·00015), anxiety (mean Beck Anxiety Inventory score 38·00 [15·55] *vs* 27·14 [18·39]; p=0·035), and affective regulation (mean Dysfunction in Emotional Regulation Scale score 131·80 [22·04] *vs* 104·36 [31·27]; p=0·019). We detected significant changes in cerebral glucose metabolism in key anorexia nervosa-related structures at both 6 months and 12 months of ongoing brain stimulation.

Interpretation In patients with chronic treatment-refractory anorexia nervosa, DBS is well tolerated and is associated with significant and sustained improvements in affective symptoms, BMI, and changes in neural circuitry at 12 months after surgery.

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has now been extended to other circuit-based neuropsychiatric disorders, such as major depression, obsessive–compulsive disorder, Tourette's syndrome, and Alzheimer's disease.[21–25] DBS is a non-lesional and

***Panel 1:* Inclusion and exclusion criteria**

Inclusion criteria

- Female or male patients aged 20–60 years
- Diagnosis of anorexia nervosa, restricting or binge–purging subtype, as defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)[35]
- Chronicity or treatment resistance shown by some or all of:
  - A pattern of 3 years' duration of relentless unresponsiveness to repeated voluntary hospital admissions, characterised by failure to complete treatment or immediate weight relapse after treatment
  - A pattern of increasing medical instability, accompanied by refusal to participate in or a pattern of poor response to intensive expert treatment and increasing medical acuity, lasting at least 2 years and including at least two episodes of involuntary feeding
  - A pattern of chronic stable anorexia nervosa that has lasted at least 10 years
- Able to provide informed consent
- Able to comply with all testing, follow-ups, and study appointments and protocols

Exclusion criteria

- Any past or present evidence of psychosis
- Active neurological disease such as epilepsy
- Alcohol or substance dependence or abuse in the previous 6 months, excluding caffeine and nicotine
- Any contraindication to MRI or PET scanning
- Likely to relocate or move during the study's 1-year duration
- Body-mass index less than 13
- Presence of cardiac arrhythmias or other cardiac, respiratory, renal or endocrine disorders, as a result of anorexia nervosa or not, that will result in substantial risk from a surgical procedure
- Pregnancy

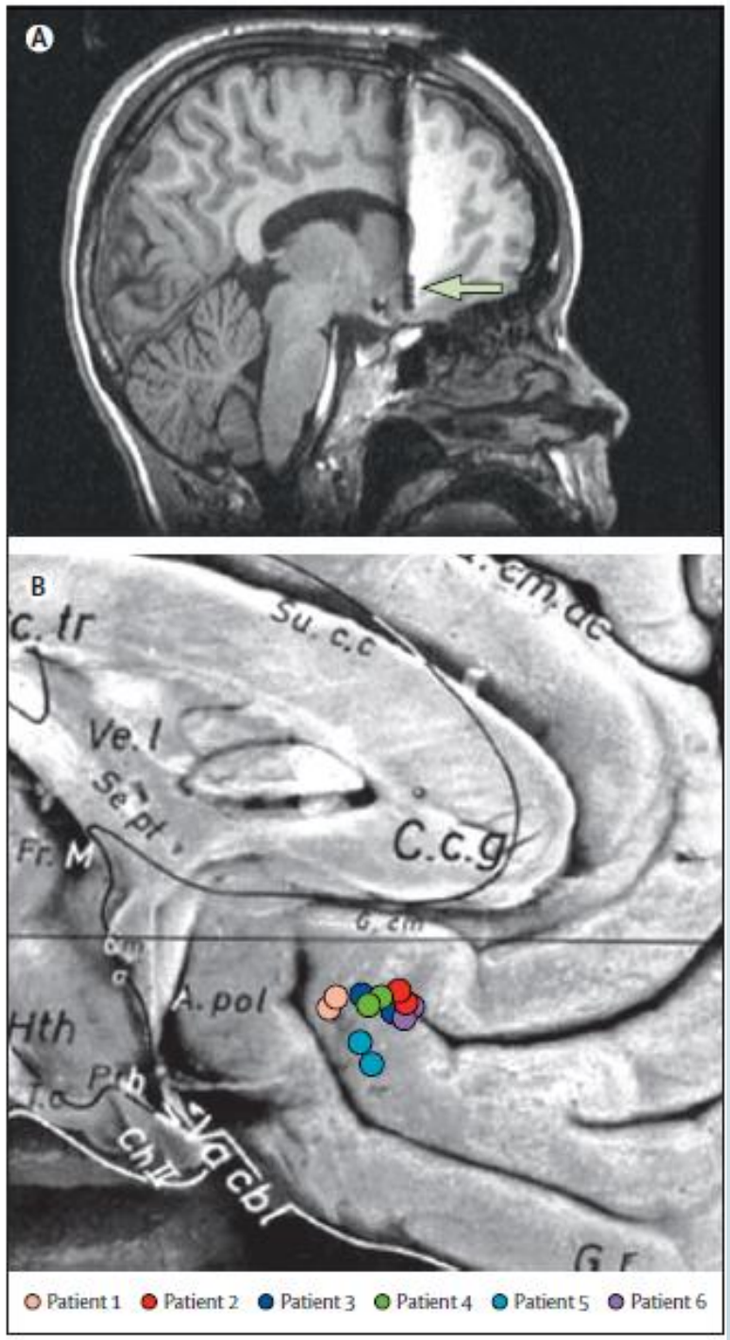

***Figure 1:* Positioning of deep brain stimulation electrodes**
(A) T1-weighted sagittal MRI shows deep brain stimulation electrode (arrow) in subcallosal cingulate area in patient 1. (B) Positions of active contacts in all six patients (two labels for each patient show the positions of bilateral active contacts). The background image for figure 1B is reproduced from reference 42, by permission of Thieme Medical Publishers.

Deep brain stimulation of the subcallosal cingulate for treatment-refractory anorexia nervosa: 1 year follow-up of an open-label trial

Nir Lipsman, Eileen Lam, Matthew Volpini, Kalam Sutandar, Richelle Twose, Peter Giacobbe, Devin J Sodums, Gwenn S Smith, D Blake Woodside, Andres M Lozano

Summary

Background Anor
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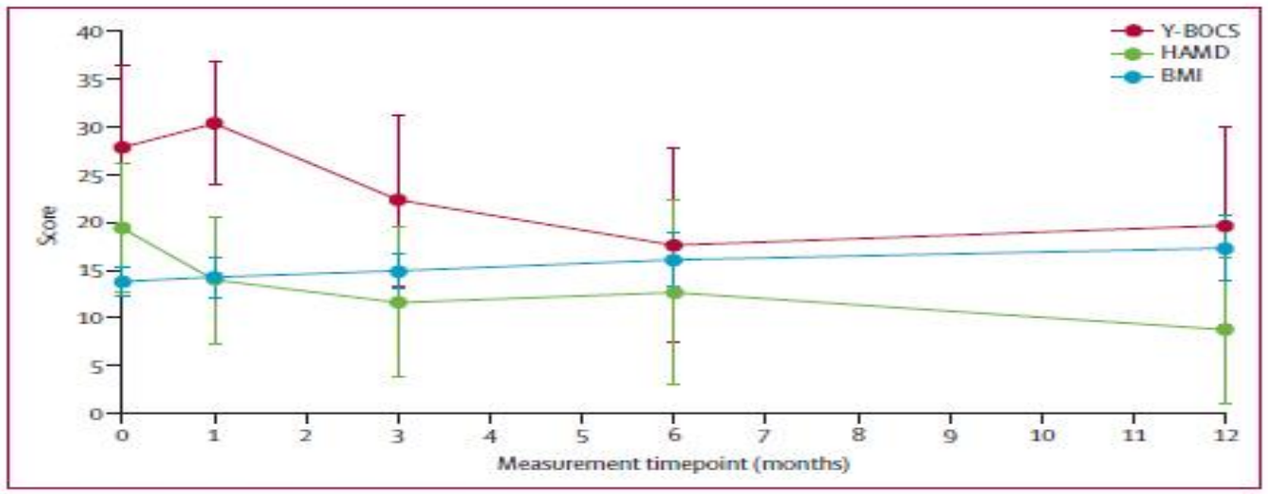
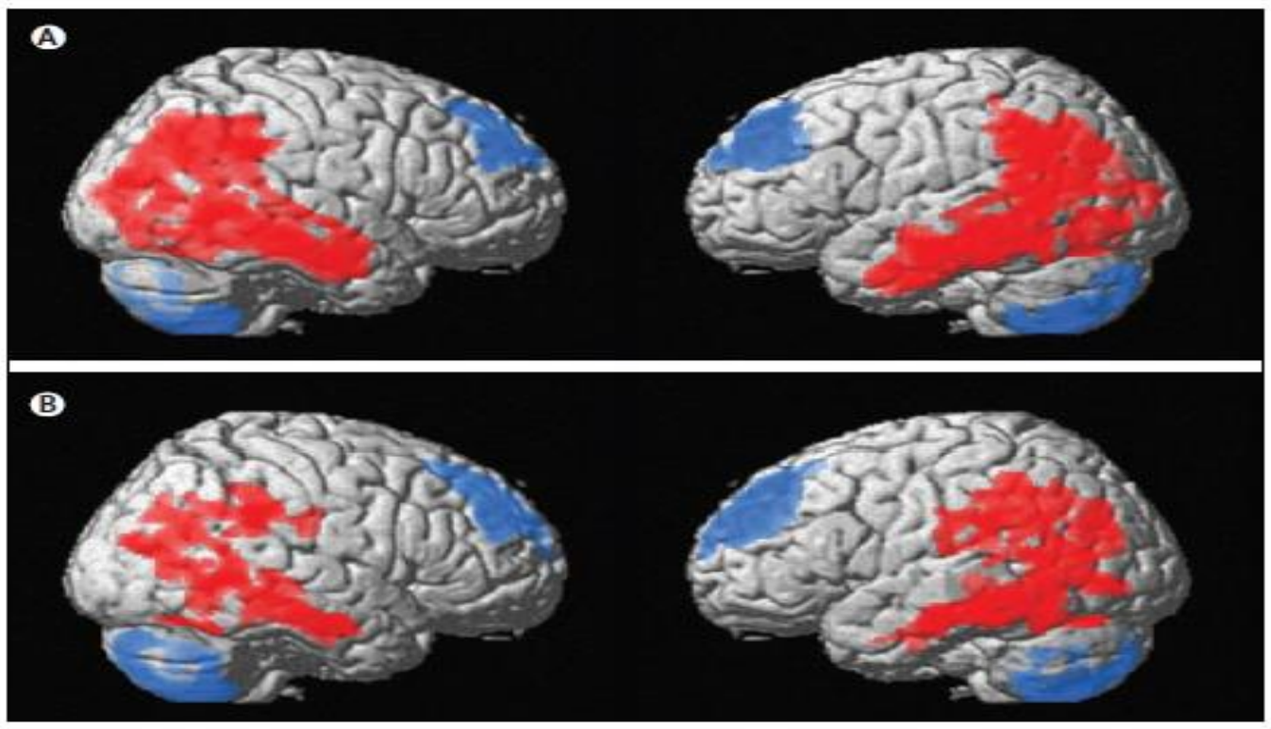


Figure 1: **Clinical and psychometric parameters**
Parameters were investigated at baseline and 1 month, 3 months, 6 months, and 12 months after device activation. Datapoints are means and error bars are 95% CIs. BMI=body-mass index. Y-BOCS=Yale-Brown Obsessive Compulsive Scale. HAMD=Hamilton Depression Rating Scale.



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22·04] *vs* 104·36 [31·27];
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tolerated and is associated
ges in neural circuitry at

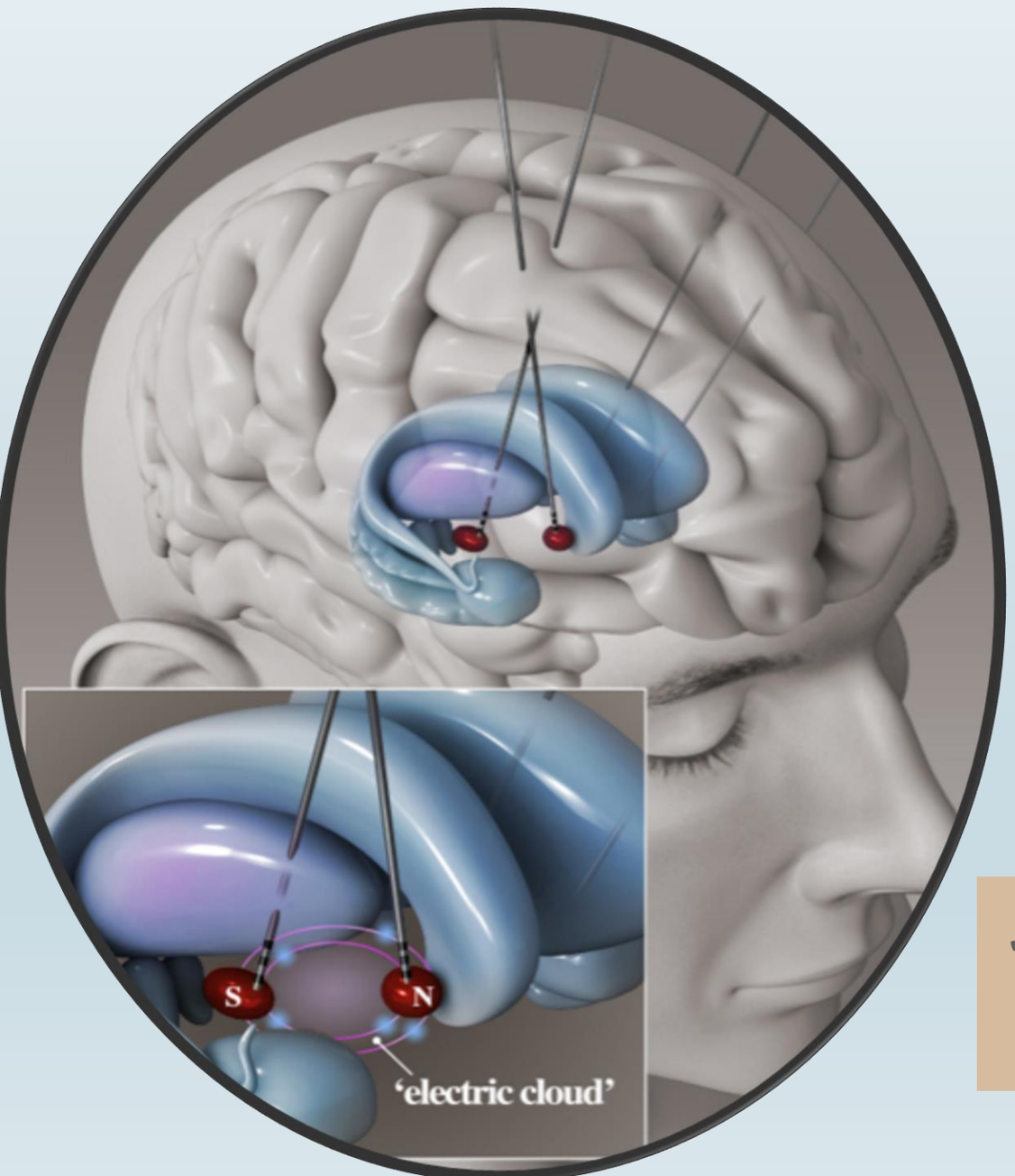
Deep brain stimulation for appetite disorders: a review

Alexander C. Whiting, MD,[1] Michael Y. Oh, MD,[2] and Donald M. Whiting, MD[2]

TABLE 2. Published trials or reports of deep brain stimulation for the treatment of anorexia nervosa in humans

Authors & Year	Pts	No. of Pts	Study Design	Target	Stimulation Parameters	Findings
Israël et al., 2010	Adult w/ restrictive AN	1	Case report	Subgenual cingulate	Rt-sided intermittent, 2 mins on, 1 min off, 5 μA, 91 μsec, 130 Hz	Maintained BMI greater than 19.1 for 2 yrs & required no further interventions for AN
Lipsman et al., 2013	Adults w/ treatment-refractory AN	6	Open-label trial	Subcallosal cingulate	Bilat, 5–7 V, 90 μsec, 130 Hz	Acceptable safety profile, 3/6 pts maintained BMI greater than baseline at 9 mos, 3/6 pts reported improved quality of life, 1 adverse event (seizure)
Wang et al., 2013	Adults w/ intractable AN	2	Case series	Nucleus accumbens	Bilat, 2.5–3.8 V, 120–210 μsec, 135–185 Hz	Improved BMI at 1 yr postop, no adverse effects reported
Wu et al., 2013	Adolescents w/ treatment-refractory AN	4	Open-label trial	Nucleus accumbens	Bilat, 6 V, 90 μsec, 180 Hz	Significant increase in BMI in all 4 pts, w/ average of 65% increase in body weight
Lipsman et al., 2017	Adults w/ treatment-refractory AN	16	Open-label trial	Subcallosal cingulate	Bilat, 5–6.5 V, 90 μsec, 130 Hz	Significant improvement in mean BMI, depression, anxiety, affective regulation; long-term changes in cerebral glucose metabolism

Nuestra Experiencia
Servicio Psiquiatría Parc de Salut Mar
Servicio Neurocirugía Parc de Salut Mar
ITA



Beca Instituto Carlos III (FIS2016):

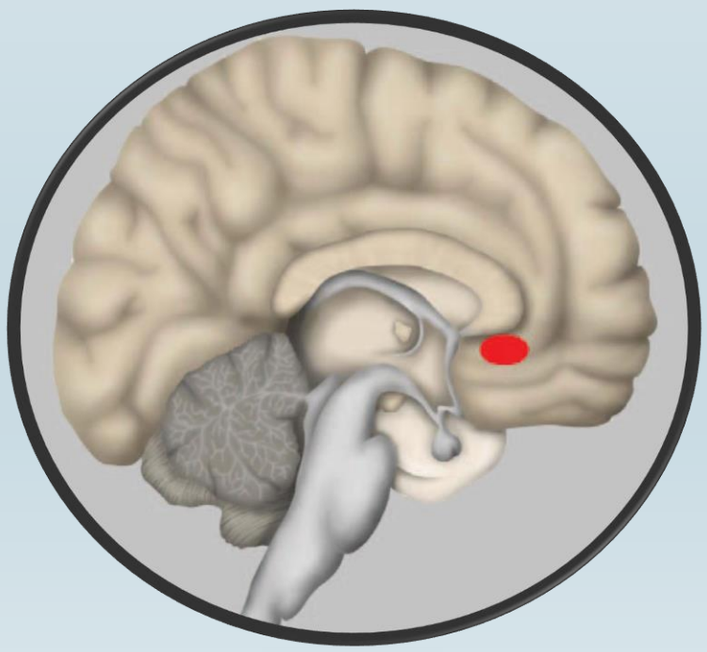
" Estimulación cerebral profunda en el cíngulo subgeniculado y en el núcleo accumbens como tratamiento en pacientes con anorexia nerviosa cronica, severa y refractaria"

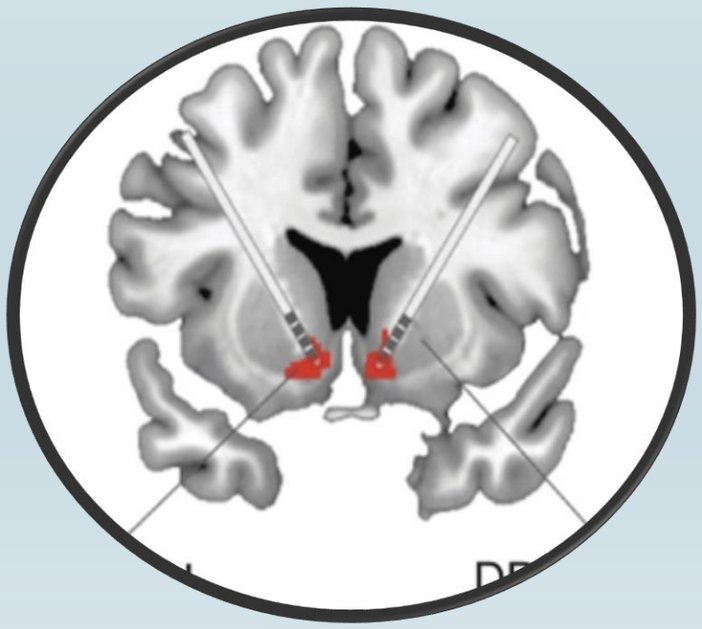
Complejidad AN:

. Hetereogeneidad enfermedad, cormobilidades asociadas
. Subtipos
. Varias etiologías

. Cíngulo subgeniculado: AN restristiva, DM, patrón afectivo

. Núcleo accumbens: AN atracón/purga, TOC





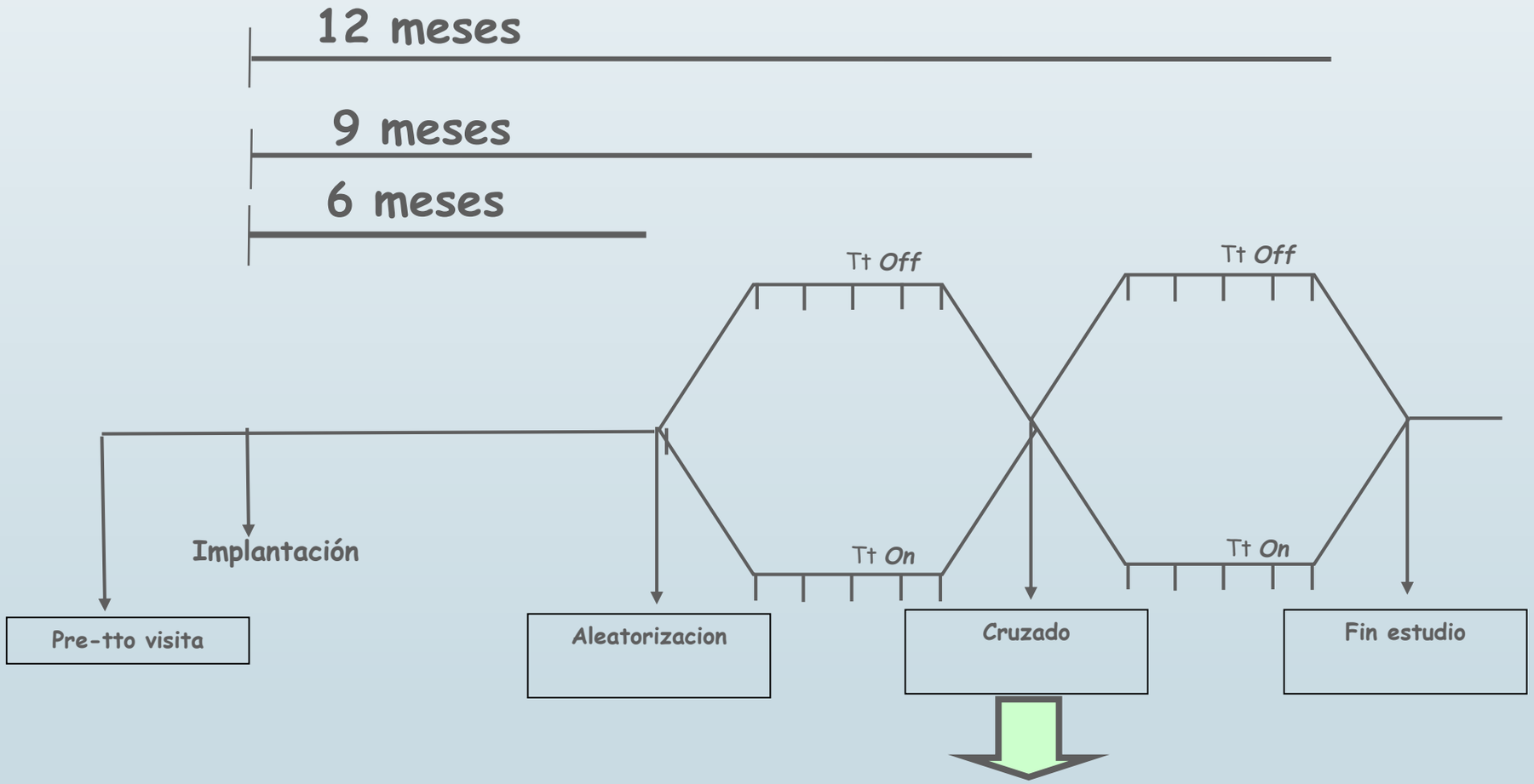
Criterios de inclusión

1. Edad entre 18-60 años
2. Diagnóstico de AN, tanto del tipo restrictivo como del tipo compulsión/purga definido por el DSM-V-TR
3. Cronicidad : mínimo de 10 años de enfermedad.
4. Resistencia al tratamiento, mostrado por uno o ambas de las siguientes situaciones:
   . Mínimo de un periodo de 7 años en los que haya aceptado voluntariamente más de un programa de tratamiento hospitalario pero que no haya sido capaz de finalizar o que si que haya finalizado pero haya mostrado recaíal alta.
   .SIituación clínica de inestabilidad médica, acompañado por el rechazo a participar en ningún programa de tratamiento, o poca respuesta a una ayuda medica intensiva, en un período mínimo de 2 años e incluyendo como mínimo 2 episodios de ingreso para alimentación involuntaria.
5. De gravedad extrema (IMC inferior a 15), o grave (IMC entre 15-15,99)
6. Capacidad para firmar el consentimiento informado
7. Capacidad para poder someterse a todas las pruebas y seguimientos del estudio

Criterios de exclusión

1. IMC inferior a 13 en el momento de reclutamiento para el estudio.
2. Psicosis en el momento actual o en el pasado.
3. Enfermedad neurológica actual.
4. Abuso y dependencia de sustancias o alcohol en el último año.
5. Contraindicaciones para realizar una RM cerebral
6. Presencia de arritmias cardíacas u otras afectaciones cardíacas, respiratorias, renales o endocrinas, como resultado de la AN o no, que comporte riesgo para el procedimiento quirúrgico.
7. Embarazo

8 PACIENTES, seguimiento de estudio mínimo de 1 año
Fase doble ciego
Resultado: peso y cormobilidades asociadas



Los pacientes en off que recaigan saldran de estudio y pasaran a fase on, los pacientes que recaigan en fase on saldran del estudio y se ajustaran los parametros

Reflexiones


Ethics

Antecedentes de la Psicocirugía

Walter Freeman, psiquiatra nortemericano, demostrando su técnica (**lobotomía transorbital**).

En 1960 ya se habían hecho (sólo en Estados Unidos) **100.000**, incluída la hermana de John F. Kennedy.

Probing and Regulating Dysfunctional Circuits Using Deep Brain Stimulation

Table 4. Ethical Considerations in DBS Practice and Research

Considerations	Example Questions
Patient selection	How should "treatment resistance" for DBS-eligible conditions be defined (Schermer, 2011; Lipsman et al., 2010b)?
	Should DBS be considered a treatment of "last resort" (Juckel et al., 2009)?
	What are the criteria for the development of DBS trials for novel indications, and how can these be empirically defined (Lipsman et al., 2010a)?
Informed consent	Do patients understand the difference between research trials and treatment (therapeutic misconception) (Fisher et al., 2012)?
	Do patients with refractory neuropsychiatric conditions have the capacity to consent and, if not, is proxy consent by a caregiver or guardian sufficient (Lipsman et al., 2012)?
Governance	What measures need to be in place for oversight and regulation of individuals and centers performing DBS?
Resource allocation	Does the availability of DBS only in high-volume, expert centers violate the ethical principle of justice, and how can access to experimental procedures and treatment be optimized (Bell et al., 2011)?
Defining outcomes	What is the impact of DBS on personality and personhood (Schermer, 2011; Lipsman and Glannon, 2012; Gilbert, 2012)?
Special populations	What considerations need to be in place to manage vulnerable or desperate patients, as well as children with DBS (Rabins et al., 2009)?
Responsible publishing	How should results of DBS trials in novel and established indications best be communicated to the public (Gilbert and Ovadia, 2011)?
	Do case reports have a place in the DBS literature and should these, along with results of larger trials, be submitted to a formal registry (Schlaepfer and Fins, 2010)?
Conflicts of interest	What is the best way to manage the relationship between clinician researchers and the DBS industry (Fins and Schiff, 2010; Fins et al., 2011b)?
Enhancement	Should DBS, or other forms of neuromodulation technology, be used in otherwise healthy individuals to enhance "normal" function (Mendelsohn et al., 2010; Lipsman et al., 2011)?

Table 4. Ethical Considerations in DBS Practice and Research

Lozano&Lipsman, Neuron 2013

Deep Brain Stimulation in Anorexia Nervosa: Hope for the Hopeless or Exploitation of the Vulnerable? The Oxford Neuroethics Gold Standard Framework

Rebecca J. Park[1], Ilina Singh[2,3], Alexandra C. Pike[1] and Jacinta O. A. Tan[4]*

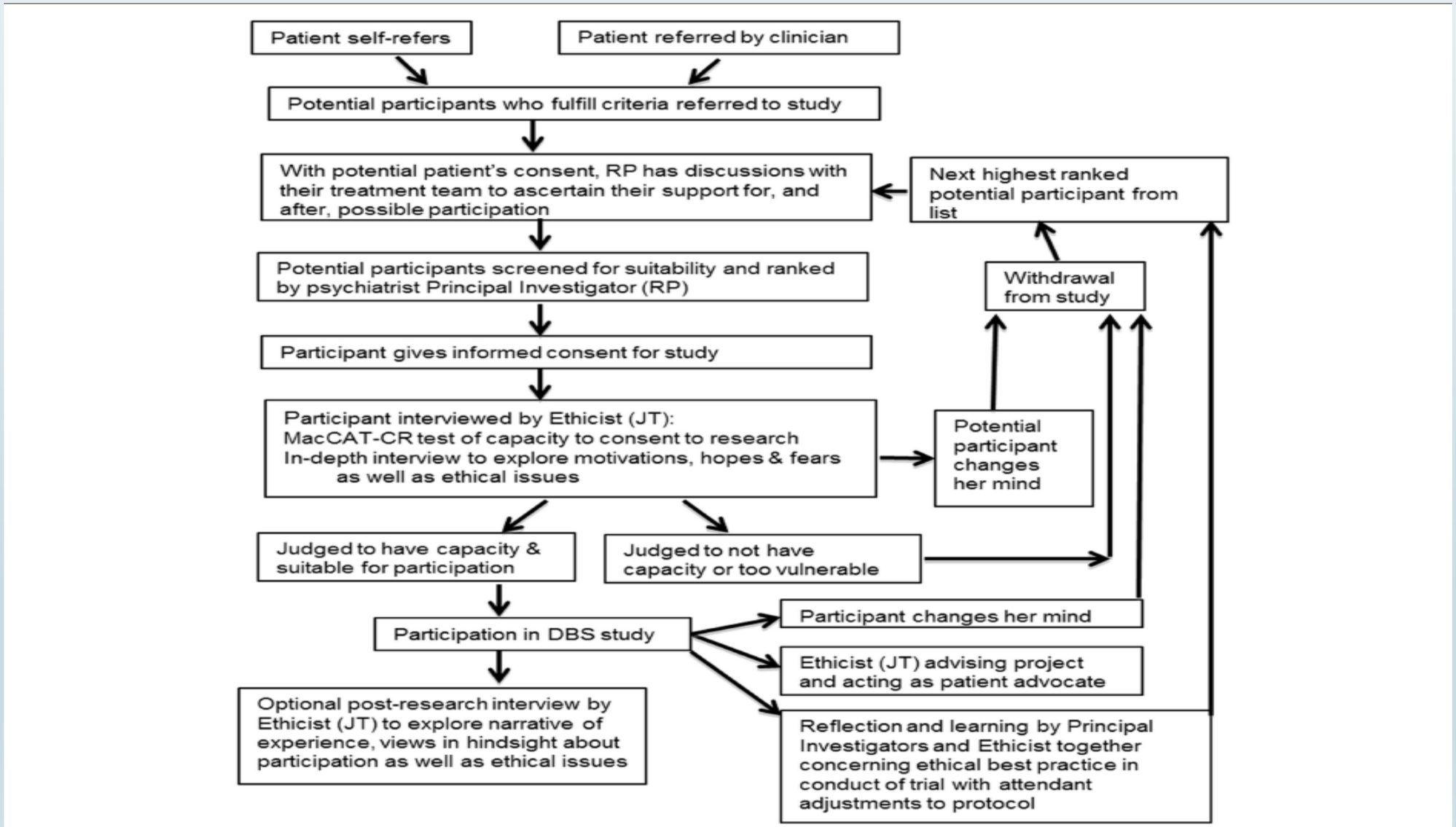


FIGURE 1 | Diagram of deep brain stimulation (DBS) clinical trial for severe and enduring anorexia nervosa, focusing on the ethical components of this study. This includes both the ethics sub-study and the checks and balances in the overall protocol.

Probing and Regulating Dysfunctional Circuits Using Deep Brain Stimulation

Phase I

93 Trials

37 Parkinson's Disease
8 PD+
7 Major Depression
6 Obsess. Comp. Diso.
5 Alzheimer's Disease
4 Dystonia
3 Epilepsy
2 Addiction
2 Cluster headache
2 Essential tremor
1 Anorexia nervosa
1 Bipolar Disorder
1 Chronic pai
1 DLB
1 Huntington's Disease
1 Tourette's Syndrome
1 Traumatic Brain Injury
1 Obesity
1 MS Tremor
1 Urinary Function
1 "Movement disorders"

Phase II

7 Trials

3 PD
1 OCD
1 MDD
1 Dystonia
1 Alzheimer's

Phase III

10 Trials

4 PD
2 OCD
3 Dystonia
1 Tourette's

Phase II/III

6 Trials

2 Dystonia
1 Bipolar
1 Epilepsy
1 ET
1 PD/ET/ Dystonia

Phase III

15 Trials

5 PD
4 MDD
2 Dystonia
2 Epilepsy
1 OCD
1 TS

Figure 2. Registered Phase I to Phase III DBS Trials that Are Ongoing and Enrolling Patients, as of September 2012

A phase I trial tests a new drug or treatment for the first time in humans and is primarily a safety and feasibility study. A phase II trial expands the phase I trial to a larger group of patients to test for possible efficacy. A phase III trial tests a new treatment against a placebo and/or a currently accepted "gold-standard" treatment, in order to establish the efficacy of the new treatment and to make recommendations on its use. All data were obtained from the United States National Institutes of Health (http://www.clinicaltrials.gov). PD+, Parkinson's disease plus an additional disorder (tremor, depression, dystonia); DLB, dementia Lewy body; MDD, major depressive disorder; TS, Tourette's syndrome; MS, multiple sclerosis; PD, Parkinson's disease; OCD, obsessive-compulsive disorder; ET, essential tremor.

Lozano&Lipsman, Neuron 2013

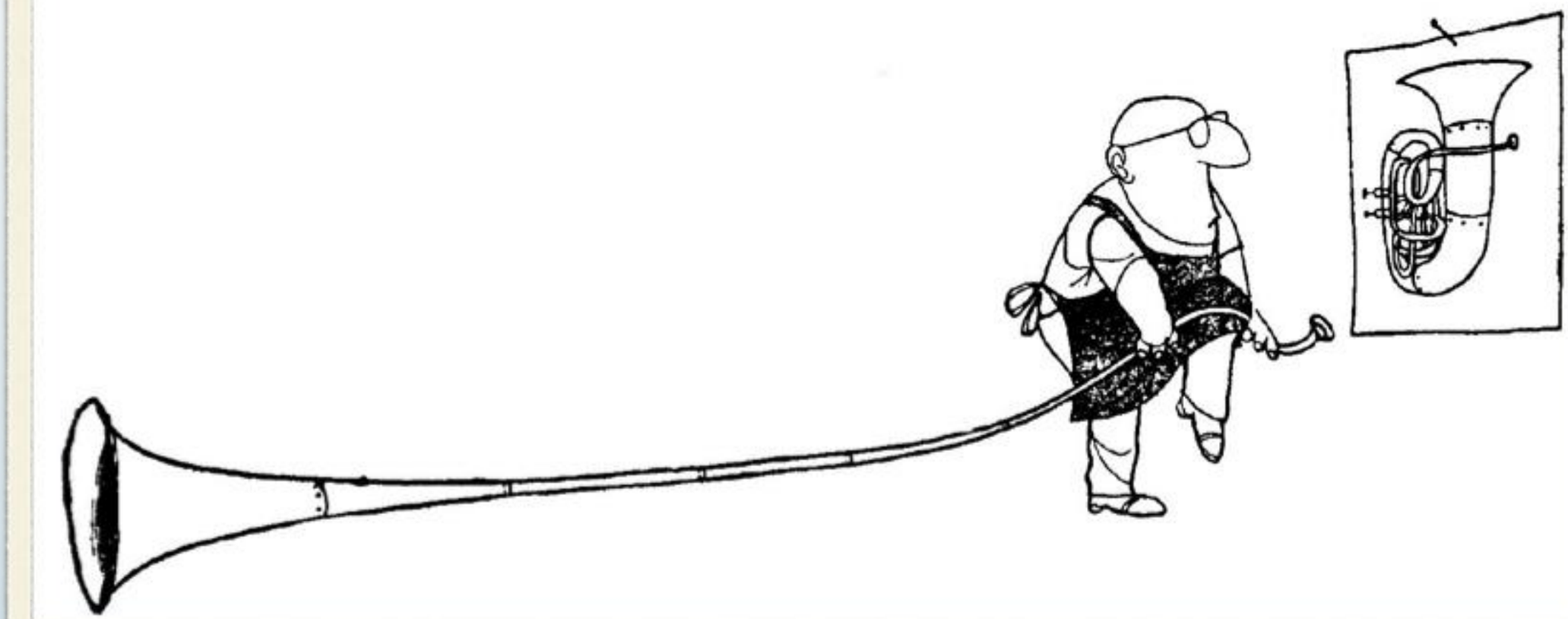
The burden of normality: from 'chronically ill' to 'symptom free'. New ethical challenges for deep brain stimulation postoperative treatment

Frederic Gilbert

Table 1 BoN's features observed within epilepsy patient treated by an ATL[6–12]

Type of change	BoN within epilepsy patients, ATL treatment
Psychological	Changes in Self-concept: A sense of 'cure'; increased expectations on self; grieving for the illness; etc
Behavioural	Changes in activities: Excessive activity such as physical, vocational, social; Increased sexual life; etc
Affective	Changes in mood: Cases of hypomania
Sociological	Changes in socio-familial dynamics and expectations: High rates of family restructuring.

F. Gilbert, J Med Ethics 2012



Aun faltan muchas respuestas....