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MECHANISMS OF DRUG ACTION

Deep brain stimulation for treatment-resistant depression: an integrative review of preclinical and clinical findings and translational implications

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Although deep brain stimulation (DBS) is an established treatment choice for Parkinson's disease (PD), essential tremor and movement disorders, its effectiveness for the management of treatment-resistant depression (TRD) remains unclear. Herein, we conducted an integrative review on major neuroanatomical targets of DBS pursued for the treatment of intractable TRD. The aim of this review article is to provide a critical discussion of possible underlying mechanisms for DBS-generated antidepressant effects identified in preclinical studies and clinical trials, and to determine which brain target(s) elicited the most promising outcomes considering acute and maintenance treatment of TRD. Major electronic databases were searched to identify preclinical and clinical studies that have investigated the effects of DBS on depression-related outcomes. Overall, 92 references met inclusion criteria, and have evaluated six unique DBS targets namely the subcallosal cingulate gyrus (SCG), nucleus accumbens (NAc), ventral capsule/ventral striatum or anterior limb of internal capsule (ALIC), medial forebrain bundle (MFB), lateral habenula (LHb) and inferior thalamic peduncle for the treatment of unrelenting TRD. Electrical stimulation of these pertinent brain regions displayed differential effects on mood transition in patients with TRD. In addition, 47 unique references provided preclinical evidence for putative neurobiological mechanisms underlying antidepressant effects of DBS applied to the ventromedial prefrontal cortex, NAc, MFB, LHb and subthalamic nucleus. Preclinical studies suggest that stimulation parameters and neuroanatomical locations could influence DBS-related antidepressant effects, and also pointed that modulatory effects on monoamine neurotransmitters in target regions or interconnected brain networks following DBS could have a role in the antidepressant effects of DBS. Among several neuromodulatory targets that have been investigated, DBS in the neuroanatomical framework of the SCG, ALIC and MFB yielded more consistent antidepressant response rates in samples with TRD. Nevertheless, more well-designed randomized double-blind, controlled trials are warranted to further assess the efficacy, safety and tolerability of these more promising DBS targets for the management of TRD as therapeutic effects have been inconsistent across some controlled studies.

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INTRODUCTION

Major depressive disorder (MDD) is a chronic and disabling condition associated with significant morbidity, with an estimated lifetime prevalence of 14.6 and 11.1% in high- and low-to-middle-income countries, respectively.[1,2] Standard antidepressant drugs are thought to primarily act inhibiting or otherwise modulating monoamine neurotransmission.[3,4] Only approximately a third of patients with MDD achieve remission after an adequate trial with a first-line antidepressant agent.[5,6] The failure to respond to one or more adequate antidepressant trials (that is, with adequate doses and duration) indicates the presence of treatment-resistant depression (TRD), although the definition for TRD has varied across trials.[7–9] Moreover, the use of first-line antidepressants is associated with safety and tolerability concerns.[10] TRD is associated with elevated health-care costs, morbidity, reduced quality of life and work productivity, and thus meaningfully contributes to the overall burden of MDD.[11] Therefore, the search for mechanistically novel therapeutic options for TRD is currently a research priority.[12] In last decade, accumulating evidence indicates that ketamine is efficacious and may provide rapid antidepressant effects for patients with TRD.[13,14] Nevertheless, its long-term efficacy remains unclear, and benefits should be weighed against untoward effects including but not limited to dissociative effects, potential for abuse and deleterious cognitive side effects at higher or repeated doses.[15] Given the significant public health impact of TRD, and the limited effectiveness of available psychological and pharmacological treatments for chronic TRD patients, the field has witnessed an increasing interest in exploring the therapeutic potential of non-pharmacological interventions like repetitive transcranial magnetic stimulation,

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transcranial direct current stimulation, vagus nerve stimulation, epidural cortical stimulation, electroconvulsive therapy (ECT) and deep brain stimulation (DBS) as therapeutic options for TRD.[16–20] Herein, we provide an integrative review of preclinical and clinical studies that have assessed DBS, a relatively recent neuromodulatory treatment modality, within different neuroanatomical targets as a putative treatment for TRD. Details of the search strategy and criteria for selection of references are provided in the supporting online material.

DEEP BRAIN STIMULATION

In DBS surgery, the electrode is stereotactically implanted into specific neuroanatomical targets where stimulation is provided via a pacemaker-like stimulator device that delivers continuous electrical stimulation.[21] A schematic representation of the apparatus is provided in Figure 1. Benabid and Pollak pioneered modern DBS over ablative surgery for the treatment of movement disorders by targeting the thalamic nucleus ventralis intermedius, globus pallidus internus and subthalamic nucleus (STN).[22,23] Because of the tremendous clinical success of DBS as a treatment for movement disorders and reported concurrent beneficial effects on neuropsychiatric manifestations, this neuromodulatory approach has also been explored as a possible treatment for many mental disorders including obsessive–compulsive disorder and intractable depression.[24–26] Interestingly, ketamine's rapid antidepressant and anti-anhedonic effects are associated with alterations in glucose metabolism in brain structures, that are also serving as potential targets for DBS, like the habenula, insula, prefrontal cortex (PFC) and anterior cingulate cortex in patients with TRD.[27,28] Despite the incomplete understanding of the underlying mechanisms of action (MOA) involved in the therapeutic response to DBS among patients with TRD,[29] several brain targets have been tested, and thus DBS has evolved to become a promising strategy for the management of TRD.[3,24,30–39]

CLINICAL AND PRECLINICAL OUTCOMES

Clinical studies have assessed putative therapeutic effects of DBS in participants with TRD across several major brain targets namely Brodmann area 25 or subcallosal cingulate gyrus (SCG), nucleus accumbens (NAc), ventral capsule/ventral striatum (VC/VS) or ventral part of anterior limb of the internal capsule (vALIC), medial forebrain bundle (MFB), lateral habenular complex (LHb), and

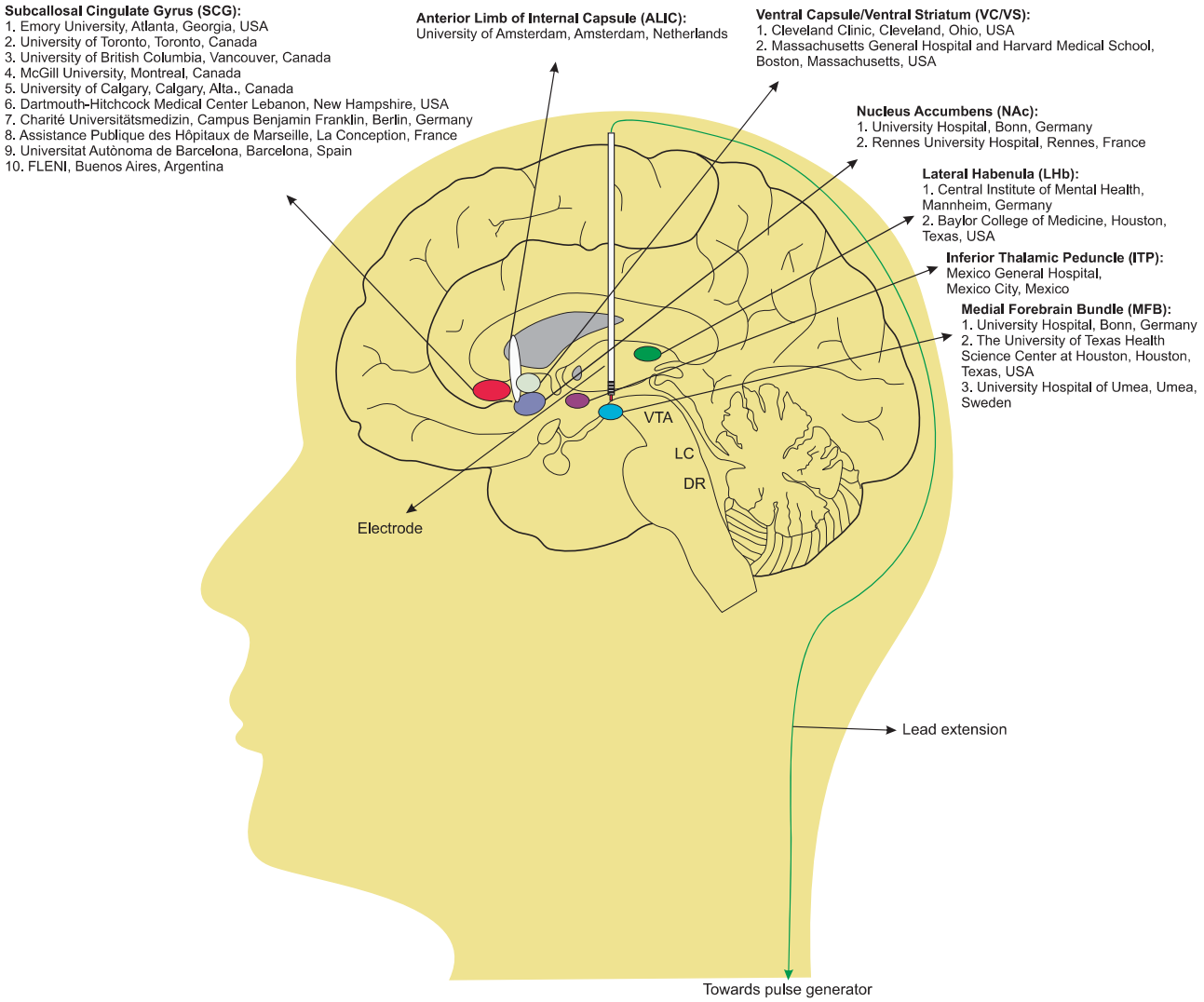

Figure 1. Schematic representation of six DBS targets tested for the management of TRD. A quadripolar DBS electrode is implanted into the selected brain targets, which is connected with long connecting lead extension wires to the pacemaker-like device (pulse generator) that is mounted under the skin of the chest. The name of pioneering academic or research institutions that have tested each brain target are provided. DSB, deep brain stimulation; DR, dorsal raphe; LC, locus coeruleus; TRD, treatment-resistant depression; VTA, ventral tegmental area.

Table 1. Summary of clinical trials and case reports of DBS applied to various brain targets for the management of TRD

Target structure	*Reference*	*N*	*Design*	*Follow-up (months)*	*Stimulation parameters*				*Response/remission rates*		*Comments*
					Electrode type	*Amplitude (V)*	*Frequency (Hz)*	*Pulse width (μs)*	*% Response*	*% Remission*	
SCG	Mayberg *et al.* (2005)[24]	6	OLS	6	BL, MP	4	130	60	66	50	Reduction in local CBF and changes in downstream limbic and cortical sites; 35% improvement in CGI
	Neimat *et al.* (2008)[49]	1	CR	30	MP	4.5	130	60	NA	NA	Case report: cingulotomy prior to DBS
	McNeely *et al.* (2008)[71]	6	OLS	12	MP	3.0–4.5	130	60	66	NA	Improves cognitive functions with time without producing positive effects on mood behavior
	Lozano *et al.* (2008)[47]	20	OLS	12	BL, MP	3.5–5.0	130	90	55	33	Mood improvements within 1 month and last for at least 1 year in TRD patients
	Hamani *et al.* (2009)[192]	20	OLS	12	BL, MP	3.0–5.0	130	90	55	NA	Identified a method to locate target point of this SCG
	Puigdemont *et al.* (2009) [48]	1	CR	12	BL, BP	3.6	135	90	100	0	Case report: decreases the relapse rate and maintenance therapy of ECT
	Guinjoan *et al.* (2010)[200]	1	CR	18	UL, MP	4.5	120	90	NA	NA	Suggests the pre-eminence of right hemisphere in regulation of depression
	Holtzheimer and Mayberg (2010)[52]	1	CR	6	BL, MP	6.0 mA	130	91	NA	NA	Report a marked and sustained antidepressant response
	Kennedy *et al.* (2011)[53]	20	OLS	36-72	BL, MP	3.5–5	130	90	64.3	42.9-50	Follow-up for long run DBS remains a safe and effective treatment for TRD
	Holtzheimer *et al.* (2012)[54]	17	OLS	24	BL, MP	4-8 mA	130	91	92	58	No patient achieving remission experienced a spontaneous depressive relapse and supported the long-term safety
	Broadway *et al.* (2012)[114]	12	OLS	4-24 weeks	BL, MP	6.0–8.0	130	90	67.8	NA	FTC can serve as early biomarker for screening DBS effect on depression severity
	Puigdemont *et al.* (2012)[55]	8	OLS	12	BL, BP	3.6	135	90	62.5	50	Suggests potential utility of this target to treat patients with TRD
	Hamani *et al.* (2012a)[81]	1	CR	6	BL, MP	2.5	130	90	NA	NA	MAOI potentiates the effects of DBS
	Lozano *et al.* (2012)[62]	21	OLS	12	BL, MP	3.5–5.0	110–140	65–182	29	NA	Reduction in depressive symptomatology and disease severity in patients
	Merkl *et al.* (2013)[60]	6	OLS	24–36 Weeks	BL, MP	2.5–10	130	90	33.3	33.3	Exerts moderate acute and chronic antidepressant effects
	Ramasubbu *et al.* (2013)[61]	4	OLS	36 Weeks	BL, MP	0–10.5	2–185	60–450	50	50	Demonstrate association between longer pulse widths (270–450 μs) and reductions in HAMD scores
	Torres *et al.* (2013)[50]	1	CR	9	BL, MP	6 mA	130	91	100	NA	Reverses the manic episodes in bipolar depressive patient
	Perez-Caballero *et al.* (2014)[85]	8	OLS	1	BL, MP	3.5–5	135	120–210	NA	NA	Use of anti-inflammatory drugs after electrode implantation attenuate the early antidepressive response in patients who were subjected to DBS
	Hilimire *et al.* (2015)[68]	7	OLS	1 Month after 6 months DBS	BL, MP	4-8 mA	130	91	92	NA	Reduction in negative words endorsed as self-descriptive associated with a reduction in depression severity
		7	OLS	9	BL, MP	3.5–5.0	135		NA	NA	

Table 1. (Continued)

Target structure	*Reference*	*N*	*Design*	*Follow-up (months)*	*Stimulation parameters*				*Response/remission rates*		*Comments*
					Electrode type	*Amplitude (V)*	*Frequency (Hz)*	*Pulse width (μs)*	*% Response*	*% Remission*	
	Martin-Blanco *et al.* (2015)[56]							120–210			Inactive stimulation decreases metabolism in BA24, BA6 and putamen with respect to active stimulation
	Puigdemont *et al.* (2015)[57]	5	RCT	6	BL, MP	3.5–5	130–135	120–240	NA	NA	Continuous electrical stimulation is required to maintain therapeutic effects in TRD patients
	Serra-Blasco *et al.* (2015)[69]	8	OLS	12	BL, BP	3.6	135	90	NA	NA	Improvement in memory performance without worsening of cognitive function after chronic stimulation
	Accolla *et al.* (2016)[77]	5	OLS	24	BL, MP	5	130	90	79	20	DBS of the bilateral posterior gyrus rectus found effective in one patient as compared with SCG-DBS
	Richieri *et al.* (2016)[74]	1	CR	6	BL, BP	4.2	130	90	NA	NA	DBS targeting the limbic system may increase the risk of seizure in depressive patient
	Funayama *et al.* (2016)[51]	1	CR	NA	NA	NA	NA	NA	NA	NA	Lesion to OFC and SCG shows alleviation of TRD symptoms
	McInerney *et al.* (2017)[70]	20	OLS	12	BL, MP	2.5–9	130	90	NA	NA	No deleterious effects on cognition
	Riva-Posse *et al.* (2017)[45]	11	OLS	12	BL, MP	6-8 mA	130	91	81.8	54	Tractography-based surgical targeting to reduce variability and increases number of responders
	Holtzheimer *et al.* (2017)[75]	90	RCT	24	BL, MP	4-8 mA	130	91	20% (Active) 17% (Control)	5% (Active) 7% (Control)	No statistically significant antidepressant effects after 6 months of active versus sham stimulation in randomized, double-blind, sham-controlled trial
	Merkl *et al.* (2017)[76]	8	RCT	28	BL, MP	2.5–10	130	90	33.3	33	Double-blind assessment fails to show significant antidepressant effect between sham and active
	Eitan *et al.* (2018)[58]	9	RCT	13	BL, MP	4–8 mA	20 or 130	91	23.1	NA	HFS exhibits superior antidepressant effects in long-term study
NAc	Schlaepfer *et al.* (2008)[34]	3	OLS	1 Week	BL, MP	4	145	90	NA	NA	Shows immediate decrease in depression scale
	Bewernick *et al.* (2010)[118]	10	OLS	12	BL, MP	1.5–10.0	100–150	60–210	50	30	Antidepressant and antianhedonic effects in TRD patients
	Grubert *et al.* (2011)[119]	10	OLS	12	BL, MP	1.5–10	100–150	60–210	NA	NA	Significant improvement in attention, learning and memory, visual perception and executive functions
	Bewernick *et al.* (2012)[36]	11	OLS	12.0–48.0	BL, MP	5.0–8.0	130	90	45.5	9	Sustain antidepressant effects up to 4 years (five patients) and improvement in QoL; one non-responder committed suicide
NAc/ caudate nucleus	Millet *et al.* (2014)[120]	6	OLS	6	BL, MP	4.0–8.0	130	60	NA	NA	NAc as a key structure within the corticostriatal loop in the pathophysiology of TRD
VC/VS	Malone *et al.* (2009)[32]	15	OLS	12	BL, MP	6.7	127	113	53.3	40	Significant improvements in depressive symptoms
		17	OLS	14–67	BL, MP	2.5–8	100–130	NA	71	35	

Table 1. (Continued)

Target structure	*Reference*	*N*	*Design*	*Follow-up (months)*	*Stimulation parameters*				*Response/remission rates*		*Comments*
					Electrode type	*Amplitude (V)*	*Frequency (Hz)*	*Pulse width (μs)*	*% Response*	*% Remission*	
	Malone *et al.* (2010)[135]										Sustain improvements across multiple scales of depression, anxiety and global function in TRD patients
	Strong *et al.* (2012)[136]	1	CR	48	MP	6	130	120	NA	NA	DBS might compensate for reward deficits and reduce smoking
	Dougherty *et al.* (2015)[137]	30	RCT	16 Weeks	BL, MP	8	NA	90-210	23.3 (Active) 20 (Control)	200	As per double-blind RCT VC/VS-DBS is not an efficacious therapy for TRD
	Kubu *et al.* (2017)[139]	25	RCT	16 Weeks	BL, MP	8	NA	90–210	NA	NA	Patients with TRD does not significantly affect neuropsychological function
vALIC	Bergfeld *et al.* (2016)[140]	25	RCT	52 Weeks	BL	2.5–6.0	130–180	90	40.0	20.0	Double-blind RCT, a significant decrease of depressive symptoms in 10 of 25 patients
	Bergfeld *et al.* (2017)[141]	25	RCT	52 Weeks	BL	2.5–6.0	130–180	90	40.0	20.0	No lasting positive or negative impact on cognition in TRD patients
ALIC/BNST and ITP	Raymaekers *et al.* (2017)[176]	7	OLS	3–8 years	BL, QP	NA	NA	NA	71.4	28.5	Stimulation of both targets decreases depressive symptoms, but six out of seven patients preferred ALIC/BNST stimulation versus ITP-DBS
MFB	Schlaepfer *et al.* (2013)[33]	7	OLS	12–33 Weeks	BL, BP	2.0–3.0	130	60	86	57.1	Rapid onset of antidepressant efficacy and a higher proportion of the population responded
	Fenoy *et al.* (2016)[39]	4	OLS	26 Weeks	BL, BP	3.0–3.5	125	75	75	75	Rapid antidepressant effects within the first week of stimulation and striking motivational effects (hedonic effects)
	Bewernick *et al.* (2017)[35]	8	OLS	12–48	BL, BP	2.0–3.0	130	60	75	50	Long-term results suggest acute and sustained antidepressant effect
	Blomstedt *et al.* (2017)[146]	1	CR	24	BL, BP	2.8–3.0	130	60	NA	NA	Blurred vision problem occurred after 10 months of DBS; therefore, patient re-operated for other brain region after 2 years
LHb	Sartorius *et al.* (2010)[163]	1	CR	15	NA	10.5	NA	NA	NA	NA	Shows a sustained full remission of depressive symptoms in patient with TRD
ITP	Jimenez *et al.* (2005);[173] Jimenez *et al.* (2007)[174]	1	CR	18	BP	3.0–5.0	130	450	NA	100	Produces antidepressant response as reflected by decrease in HAMD scores, without any potential side effects
	Jimenez *et al.* (2013)[175]	1	CR	3 Years	BP	3.0–5.0	130	450	85.71	100	HAMD scale score changes from 42 to 6

Abbreviations: BA24/6, Brodmann area 24/6; BL, bilateral; BNST, bed nucleus of the stria terminalis; BP, bipolar; CBF, cerebral blood flow; CGI, clinical global impressions scale; CR, case report; DBS, deep brain stimulation; FTC, frontal theta cordance; HAMD, Hamilton depression rating scale; HFS, high-frequency stimulation; ITP, inferior thalamic peduncle; LHb, lateral habenula; MADRS, Montgomery–Asberg depression rating scale; MAOI, monoamine oxidase inhibitor; MFB, medial forebrain bundle; MP, monopolar; NA, not applicable; NAc, nucleus accumbens; OFC, orbital prefrontal cortex; OLS, open-label study; QoL, quality of life; QP, quadripolar; RCT, randomized controlled trial; SCG, subcallosal cingulate gyrus; TRD, treatment-resistant depression; vALIC, ventral part of the anterior limb of the internal capsule; VC/VS, ventral capsule/ventral striatum. Summary of key clinical DBS studies in depression.

Table 2. Application of DBS in the various neuroanatomical targets using *in vivo* preclinical models

Target structure	*Reference*	*Stimulation settings*					*Comments*
		Electrode type	*Amplitude (μA)*	*Frequency (Hz)*	*Pulse width (μs)*	*DBS duration*	
vmPFC	Hamani and Nobrega (2010);[42] Hamani *et al.* (2010a, b)[79,80]	BL/UL, MP	100–300	130	90	8 h/day up to 14 days	SD rats: observe strongest response with a current intensity of 200 μA, followed by 100 μA, and 300 μA and frequency 130 Hz; left unilateral stimulation was equally effective as bilateral DBS; reverses DLP in the CUS model; reduces latency to eat in the NSF; increases cortical zif268 expression
	Gersner *et al.* (2010)[93]	UL, MP	400	20	200	10 min/day for 10 days	SD rats: the antidepressant effect of repeated SCES of the vPLC or NAc is comparable to that of ECT, without induction of its associated cognitive deficits
	Hamani *et al.* (2012b)[82]	BL, MP	100–300	130	90	8 h/day up to 14 days	SD rats: partially restores the reduced hippocampal BDNF in CUS animal model
	Rea *et al.* (2013)[90]	BL, MP	300	130	100	30 min/day up to 14 days	FSL rats: reverses DLP
	Laver *et al.* (2014)[105]	BL, MP	100	130	90	4 h on day 1 and 2 h on day 2	SD rats: reverses passivity in the FST; co-administration of buspirone, risperidone and orpindolol did not potentiate DBS response
	Veerakumar *et al.* (2014)[94]	UL, BP	150	160	60	5 h/day for 7 days	Pet1-tdTomato transgenic mice: reverses CSDS-induced social avoidance; neuroplastic adaptation in 5-HT system in DRN
	Parthoens *et al.* (2014)[99]	UL, BP	150	60-130	200	1 h	SD rats: 60 Hz PL mPFC DBS or its human analog the dlPFC useful for the treatment of disorders associated with prefrontal hypofunction
	Bambico *et al.* (2015)[101]	BL	100	130	90	8 h/day, for 3 consecutive weeks	Fisher rats: chronic DBS induces anxiolytic-, antidepressant- and antianhedonic-like effects in stressed rats; increases BDNF level in the PFC and hippocampus
	Edemann–Callesen *et al.* (2015)[92]	BL, MP	170–560	20-200	100	ICSS protocol	FSL rats: antagonizes the depressive-like symptoms, anhedonia and despair but not affect helplessness; no response on reward-seeking behavior
	Lim *et al.* (2015a, b)[86,87]	BL	100	10, 100	100	~15 min before each behavioral task and continued during testing	SD rats: profound antidepressant effects (decreases immobility time) with enhanced hedonia, reduces anxiety; HFS modulates a brain circuit linked to the DRN
	Bruchim–Samuel *et al.* (2016)[106]	BL, MP	400	20	200	15 min/day, for 10 consecutive days	FSL rats: significantly decreases immobility time in FST; a significant correlation between BDNF protein levels and improvement in DLP after PFC stimulation
	Chakravarty *et al.* (2016)[102]	BL, MP	50	130	90	6 h/day for 5 days	C57Bl/6 mice: increases in whole hippocampus and the left thalamus volume, also enhances blood vessel size and synaptic density in hippocampus
	Bregman *et al.* (2018)[103]	BL, MP	100	130	90	4 h	SERT homozygous KO/WT mice: WT and SERT KO mice displays similar antidepressant-like response and serotonin release
	Torres-Sanchez *et al.* (2017)[107]	BL, MP	100	130	90	4 h on day 1 and 2 h on day 2	WH rats: antidepressant-like effects accompanies with increase in tonic and evoked activity of LC-noradrenergic neurons

Table 2. (Continued)

Target structure	*Reference*	*Stimulation settings*					*Comments*
		Electrode type	*Amplitude (μA)*	*Frequency (Hz)*	*Pulse width (μs)*	*DBS duration*	
IL-PFC	Perez-Caballero *et al.* (2014)[85]	BL, BP	100	130	90	4 h on day 1 and 2 h on day 2	WH rats: DBS of the prelimbic and infralimbic cortex exerts an antidepressant-like effect in the FST; inflammatory response following surgery might displayed early insertional antidepressive effect
	Etievant *et al.* (2015)[96]	UL, BP	150	130	60	4 h on day 1 and 2 h on day 2	SD rats: decreases immobility duration; promote hippocampal mitosis and reverses the effects of stress on hippocampal synaptic metaplasticity; increases DRN 5-HT firing activity and synaptogenesis
	Insel *et al.* (2015)[97]	BL, UP	100	130	90	8 h/day for 10 days	SD rats: therapeutic effects of DBS is independent of 5-HT levels, DBS disrupts communication between regions important for expectation-based control of emotion like infralimbic cortex and VH
	Srejic *et al.* (2015)[104]	UL, BP	60	100	200	5 min	SD rats: DRN cells significantly decreases firing rate (82%) during HFS
	Jimenez–Sanchez *et al.* (2016a)[88]	BL, BP	200	130	90	1 h	WH rats: reverses hyperlocomotion, hyperemotionality and anhedonia, and increases social interaction in the OBX rats; increases synthesis of BDNF and GluA1 AMPA receptor, and stimulates mTOR, CREB
	Jimenez–Sanchez *et al.* (2016b)[89]	BL, BP	200	130	90	1 h	WH rats: shows antidepressant-like effects in FST and NSF test; increases prefrontal efflux of glutamate and activate AMPA receptor
	Bezchlibnyk *et al.* (2017)[98]	BL, BP	2.5 V	130	90	1 h	WH rats: increases the complexity of apical dendrites and the length of basal dendritic trees of pyramidal neurons located in the CA1 region of hippocampus
Prelimbic	Moshe *et al.* (2016)[95]	UL	400	20	0.2 ms	10 min per session for 10 consecutive days	DRL and SD rats: reverses the depressive-like behaviors and increases the reduced BDNF levels
vmPFC/NAc/ WMF	Hamani *et al.* (2014)[126]	UL, MP	100	130	90	4 h on day 1 and 2 h on day 2	SD rats: shows similar antidepressant-like effects at all three sites despite distinct impact in regional brain activity
	Winter *et al.* (2015)[130]	BL, MP	100–300	130	90	1 h	SD rats: neither vmPFC nor NAc DBS increases hippocampal neurogenesis
Cingulate cortex	Dournes *et al.* (2013)[100]	BL	2.5 V	80, 120	90	1 h/day for 2 weeks	BALB/c ByJ mice: normalizes the motivated-like responses, anxiety-related behaviors, hyperactivity and aggressiveness
NAc	Gersner *et al.* (2010)[93]	UL, MP	400	20	200	10 min/day for 10 days	SD rats: reverses anhedonic-like behavior in CUS model, but no effect in FST assay
	Sesia *et al.* (2010)[121]	BL, BP	3, 30, 150	130	60	7 Days	Lewis rats: increases levels of DA and 5-HT in the NAc, but not in mPFC; DBS of the NAc core has beneficial behavioral effects
	Falowski *et al.* (2011)[129]	UL, BP	2 V	130	200 ms	3 h/day for 14 day continuous	WH rats: reduces anxiety, increases exploratory behavior and DA and NA in PFC

Table 2. (Continued)

Target structure	*Reference*	*Stimulation settings*					*Comments*
		Electrode type	*Amplitude (μA)*	*Frequency (Hz)*	*Pulse width (μs)*	*DBS duration*	
	van Dijk *et al.* (2011)[122]	UL, BP	300–400	120	80	5 h	WH rats: no significant effect on monoaminergic neurotransmitters or their metabolites in the stimulated region, that is, NAc core
	van Dijk *et al.* (2012)[123]	BL, BP	300	120	80	1.45 h/day for 2 consecutive days and 2 h in the NAc core	WH rats: increases the DA, NA and 5-HT in the mPFC and OFC after onset of stimulation in the NAc core
	van der Plasse *et al.* (2012)[125]	BL	10, 50, 100	NA	NA	1 h	WH rats: NAc shell-DBS profoundly and selectively increases the chow intake; the intake of chow and motivation to work for palatable food can independently be modulated by DBS of subregions of the NAc shell
	Schmuckermair *et al.* (2013)[91]	UL, BP	100	130	60	1 h/day for 7 days	HAB mice: antagonize the depressive- and anxiolytic-like phenotypes
	Hamani *et al.* (2014)[126]	BL, MP	100	130	90	4 h on day 1; 2 h on day 2	SD rats: shows antidepressant-like effects in the FST; increases zif268 expression in subcortical structures and piriform cortex
	Lim *et al.* (2015b)[87]	BL	100	10, 100	100	~15 min before behavioral task and continued during testing	SD rats: reduces anxiety (decreased escape latency in the home-cage emergence test) and increases motivation for food intake
	Winter *et al.* (2015)[130]	BL, MP	100, 300	130	90	1 h	SD rats: no change in hippocampal neurogenesis
	Huguet *et al.* (2017)[131]	BL, BP	100	100	100	~15 min before behavioral task and continued during testing	SD rats: reduces CUS-induced increased c-Fos expression in the medial vestibular nucleus
	Kim *et al.* (2016b)[165]	BL, BP	100	130	90	7 Days uninterrupted stimulation	WH rats: reduces immobility time (76%) in ACTH-treated animals; increases RCR in ACTH-treated rats
	Rummel *et al.* (2016)[127]	BL, MP	150	130	100	16 Days continuously	FSL and congenitally LH rats: antidepressant response is associated with an increase in 5-HT turnover alongside site-specific reductions in 5-HT contents
MFB	Bregman *et al.* (2015)[150]	BL	100	20, 130	90	4 h on day 1; 2 h on day 2	SD rats: shows antidepressant-like effect; increases zif268 expressions in the piriform cortex, prelimbic cortex, NAc-Shell, caudate/putamen and VTA
	Edemann–Callesen *et al.* (2015)[92]	BL, MP	170–560	20–200	100	ICSS	FSL rats: increases swimming time (antidepressant effects); consume more sucrose solution (hedonic activity)
	Furlanetti *et al.* (2015a)[148]	BL, BP	250	130	288	Continuously for 3–6 weeks	SD rats: unilateral DA depletion do not preclude MFB-DBS in reversing depressive-like and anhedonic-like behavior
	Furlanetti *et al.* (2015b)[149]	BL, BP	288	130	100	Continuously for 3–6 weeks	SD rats: increases and long-lasting c-fos expression in target regions of the mesolimbic/mesocortical system
	Furlanetti *et al.* (2016)[147]	BL, BP	250	130	100	Continuously for 3 weeks	SD rats: rescues DLP; work through both DA dependent and independent mechanisms; activates distant structures involved in the neurocircuitry of depression
	Dandekar *et al.* (2017)[152]	UL, BP	200	130	90	4 h on day 1; 2 h on day 2	Decreases passivity in the FST and increases expression DA D2 receptors in the PFC

Table 2. (Continued)

Target structure	*Reference*	*Stimulation settings*					*Comments*
		Electrode type	*Amplitude (μA)*	*Frequency (Hz)*	*Pulse width (μs)*	*DBS duration*	
LHb	Friedman *et al.* (2011)[164]	BP	200	10–100	0.5 ms	15 min DBS and then ICSS	SD rats: attenuates processes of positive reward-associated reinforcement
	Meng *et al.* (2011)[84]	UL, BP	80–100	150	300	7–28 Days continuously	WH rats: reduces DLP in CUS model; increases DA/NA/5-HT in blood serum and hippocampus
	Li *et al.* (2011)[83]	UL, BP	150, 300	130	40 ms	FST: 1 h after and 1 h before swimming sessions LH: 1 h after baseline testing and 1 h before LH sessions	Congenital LH rats: antidepressant-like effects in the FST and LH
	Lim *et al.* (2015b)[87]	BL	100	10, 100	100	~15 min before behavioral task and continued for the entire duration of testing	SD rats: HFS reduces anxiety in the home-cage emergence test and immobility time in the FST; also improves motivational behavior in food intake study
	Kim *et al.* (2016a)[128]	BL, BP	200	130	90	3 Days prior to the FST	WH rats: reduces immobility in ACTH-treated animals and phosphorylation of CaMKIIα/β and GSK3α/β in the LHb together with the downregulation of CaMKIIαβ/b, GSK3α/β and AMPK in the lL cortex
STN	Temel *et al.* (2007)[184]	BL, BP	3–150	10–130	60	3 min	SD rats: inhibits DRN 5-HT activity and precipitates DLP
	Creed *et al.* (2013)[178]	BP, MP	100	130	90	4 h/day for 21 days	SD rats: induces and potentiates DLP; repeated DBS causes decreased levels of BDNF and trkB mRNA in hippocampus
	Faggiani *et al.* (2015)[177]	BL, BP	170	130	60	10 min before starting the session and maintained during behavioral testing	SD rats: acute DBS improves DLP with bilateral depletion of DA, NA and 5-HT

Abbreviations: 5-HT, serotonin; ACTH, adrenocorticotropic hormone; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AMPK, AMP-activated protein kinase; BDNF, brain-derived neurotrophic factor; BL, bilateral; BP, bipolar; CaMKIIα/β, Ca2+/calmodulin-dependent protein kinase; CREB, c-AMP response element binding; CSDS, chronic social defeat stress; CUS, chronic unpredictable mild stress; DA, dopamine; DLP, depression-like phenotype; dlPFC, dorsolateral prefrontal cortex; DRL, depressive rat line; DRN, dorsal raphe nucleus; ECT, electroconvulsive therapy; fMRI, functional magnetic resonance imaging; FSL, Flinders sensitive line; FST, forced swim test; GSK3α/β, glycogen synthase kinase 3; h, hour; HAB, high-anxiety behavior; HFS, high-frequency stimulation; IL-PFC, infralimbic prefrontal cortex; ICSS, intracranial self-stimulation; KO, knockout; LC, locus coeruleus; LFP, local field potential; LH, learned helplessness; LHb, lateral habenula; MFB, medial forebrain bundle; Min, minute; MP, monopolar; mPFC, medial prefrontal cortex; mTOR, mammalian target of rapamycin; NA, noradrenaline; NAc, nucleus accumbens; NET, novelty exploration test; NSF, novelty suppressed feeding; OBX, olfactory bulbectomy; OFC, orbitofrontal cortex; PFC, prefrontal cortex; PL, prelimbic; RCR, respiratory control ratio; SCES, subconvulsive electrical stimulation; SCG, subcallosal cingulate gyrus; SD, Sprague–Dawley; SERT, serotonin transporter; SI, social interaction; STN, subthalamic nucleus; trkB, tropomyosin receptor kinase B; UL, unilateral; VH, ventral hippocampus; vmPFC, ventromedial prefrontal cortex; vPLC, ventral prelimbic cortex; VTA, ventral tegmental area; WMF, white matter fibers of the frontal region; WH, Wistar rats; WT, wild type. Summary of key preclinical DBS studies in depression.

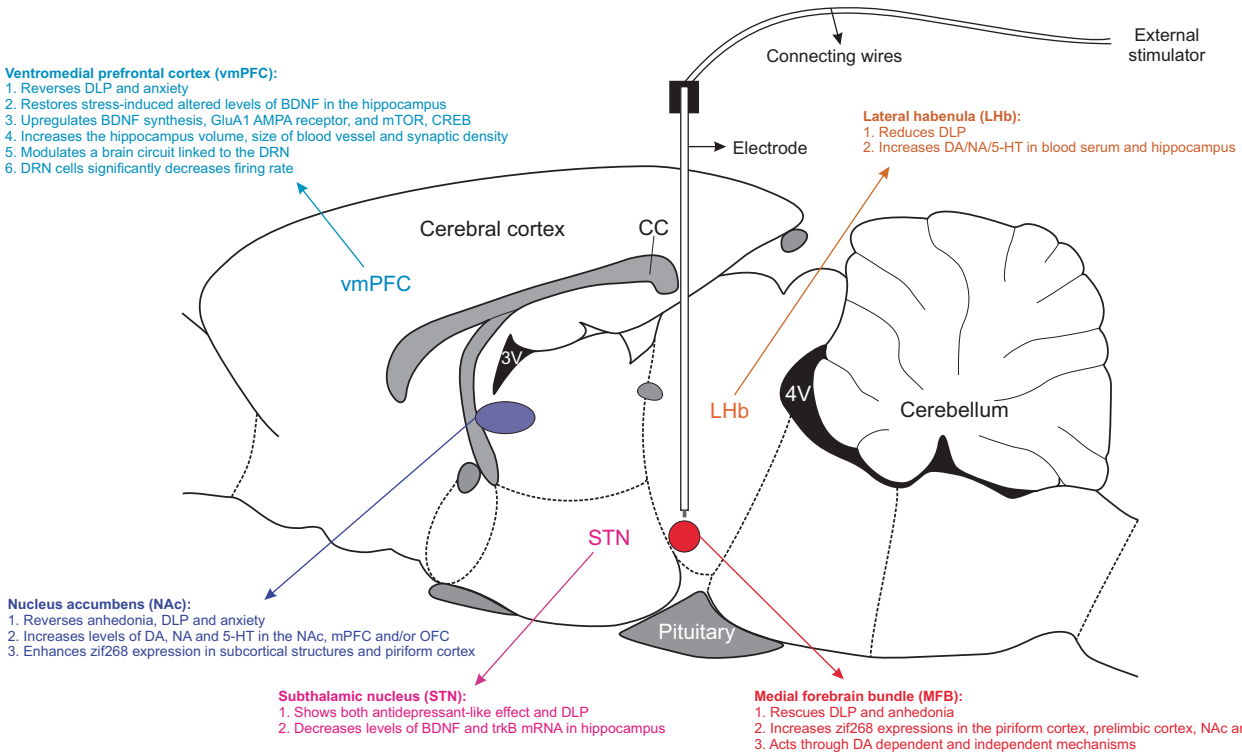

Figure 2. Diagrammatic representation of DBS brain targets that have been tested in preclinical investigations. The outline of the sagittal diagram through the rat brain indicates the vmPFC, NAc, STN, MFB and LHb, which are not in scale. As denoted, monopolar or bipolar electrodes are stereotactically implanted in any one of the brain targets. At the time of stimulation, implanted electrodes are connected with long connecting wires to external stimulators, which delivers electric current as per protocol. Important functional and biochemical changes following DBS applied to each brain target are highlighted. 3V, third ventricle; 4V, fourth ventricle; 5-HT, 5-Hydroxytryptamine; AMPA, α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BDNF, brain-derived neurotrophic factor; CC, corpus callosum; CREB, c-AMP-response element-binding; DA, dopamine; DBS, deep brain stimulation; DLP, depression-like phenotype; DRN, dorsal raphe nucleus; LHb, lateral habenula; MFB, medial forebrain bundle; mPFC, medial prefrontal cortex; mTOR, mammalian target of rapamycin; NA, noradrenaline; NAc, nucleus accumbens; OFC, orbitofrontal cortex; STN, subthalamic nucleus; trkB, tropomyosin receptor kinase B.

inferior thalamic peduncle (ITP). The names of the respective pioneering institutions that conducted DBS manipulations across these brain targets for the treatment of TRD are presented in Figure 1. The ideal settings for achieving optimum antidepressant effects in humans remain unclear, although it is worthy to note that therapeutic effects may vary as a function of respective DBS targets and stimulation parameters, and also according to clinical characteristics of individual patients.[40] The exploratory meta-analysis conducted by Smith[41] suggests that active DBS applied to some of the above brain targets could be 71% more efficacious than sham treatment (summary effect size: 1.71; 95% confidence interval: 1.47–1.96) for TRD. However, only eight studies were available, and effect sizes could not be separated according to specific brain targets. Detailed information pertaining to clinical and preclinical central nervous system targets chosen for DBS as a treatment for depression is provided in the following sections, and is briefly summarized in Tables 1 and 2.

Details of neuroanatomical substrates tested across preclinical DBS studies for depression-like phenotypes are diagrammatically depicted in Figure 2. As presented in Table 2, stimulation parameters markedly varied across preclinical investigations. Yet, settings between 60 and 130 Hz for frequency, 60 and 200 μs for pulse width and 50 and 300 μA for amplitude exhibited promising antidepressant-like effects across various DBS targets. Preclinical studies have also pointed that different stimulation parameters and neuroanatomical locations may influence antidepressant-related effects. However, at least in part because of the complex and multifactorial pathophysiology of human depression, currently no animal model meets all validity criteria (including predictive validities),[42,43] and hence limitations of preclinical models should be considered when inferences pertaining to depression in humans are made.

DBS of the SCG

Clinical studies. The SCG may have a pivotal role in the regulation of sadness and negative emotions occurring in both depressed and healthy subjects.[24,44–46] Clinical outcomes for this DBS target are summarized in Table 1. Mayberg and coworkers[24] initially reported that four out of six patients with TRD achieved antidepressant response after 6 months of open-label SCG-DBS. Afterwards, Lozano *et al.*[47] reported that 40% of participants with TRD ($n = 20$) achieved response after 1 week of stimulation, whereas 60 and 55% of patients met response criteria at 6 and 12 months, respectively, in an open-label trial that tested SCG-DBS. A few case reports also demonstrated efficacy for this target in the TRD patients.[48–52] Long-term outcomes of SCG-DBS for the aforementioned open-label trial were subsequently reported, with 55–60 and 64.3% response rates after 1–3 and 3-6 years' follow-up visits, respectively,[53] and four participants either committed or attempted suicide over the course of study, although because of uncontrolled design of this study it could not be established whether this serious adverse effect was related to DBS or to illness evolution *per se*. Holtzheimer *et al.*[54] replicated those findings in an uncontrolled study involving 17 participants with TRD after SCG-DBS. This trial reported 43.6–70.1% response rates (assessed with the Hamilton depression rating scale) following 24-week, 1-year and 2-year follow-up visits. Although this study was uncontrolled, it should be noted that the blinded discontinuation

of SCG-DBS resulted in the full relapse of depressive episodes in all three patients in which this was attempted, whereas depressive symptoms improved once stimulation was reinstated.[54] Furthermore, these robust therapeutic benefits and brain metabolic changes have been further replicated in a preliminary uncontrolled observation;[55,56] seven out of eight TRD patients achieved antidepressant response after SCG-DBS at a 6-month follow-up visit. In a more recent randomized, double-blind, sham-controlled crossover trial Puigdemont *et al.*[57] reported reversal of depressive scores after active SCG-DBS application in five participants with TRD,[57] and long-term high frequency stimulation (HFS) exhibited better antidepressant response.[58]

Berlim *et al.*[59] conducted an exploratory meta-analysis of four observational studies, and verified that response and remission rates following SCG-DBS were 36.6 and 16.7%, 53.9 and 24.1%, and 39.9 and 26.3% at 3-, 6- and 12-month follow-up periods, respectively. Moreover, open-label studies reported remission rates ranging from 29 to 58% after chronic stimulation of the SCG for up to 12–36 months,[60–62] although evidence suggests that longer pulse durations could influence pathways farther from the SCG, and activation of the SCG–NAc network may contribute to antidepressant response after SCG-DBS.[31] Patient-specific tractography modeling provided relevant insights for the identification of electrode location and critical neuronal tracts that could mediate antidepressant responses to SCG-DBS, and may also mitigate inter-individual variability in the direct effects of stimulation on brain circuitry.[45,63,64] Using tractography-based surgical targeting, Riva-Posse *et al.*[45] demonstrated 72.7% (8 of 11 participants) and 81.8% (9 of 11 participants) response rates at 6 months and 1 year after SCG-DBS, respectively, whereas six patients were in remission at both time points.

SCG-DBS may also improve memory as well as executive and motor functioning in participants with TRD, without meaningful adverse effects upon cognitive measures.[65–71] Moreover, patients with TRD may exhibit transient emotional hypersensitivity and a predictable worsening of depressive symptom scores at the initial phases of SCG-DBS,[55] thus long-term treatment could be critical for central nervous system remodeling and neuroplasticity, and hence to therapeutic benefits.[72] In SCG-DBS-operated participants with TRD, the most frequently observed surgery-associated adverse events were hardware-related (11.4%), suicidality (9.3%)[73] and risk of partial seizures.[74] In addition, a multicenter, randomized controlled trial (RCT) of SCG-DBS for TRD (BROADEN study) was prematurely interrupted based on results of an interim futility analysis (St Jude Medical Clinical Study).[38,75] Recently, Holtzheimer *et al.*[75] published results of multisite, randomized, double-blind, sham-controlled SCG-DBS study in 90 TRD participants. They did not observe statistically significant effects in the primary efficacy outcome between the stimulation (20%) and control group (17%), similarly in a double-blind study of eight participants Merkl *et al.*[76] reported no difference between active versus sham group. However, 33–48% participants displayed an antidepressant response and 25% achieved remission with up to 2 years of open-label SCG-DBS.[75,76] Nevertheless, the lack of therapeutic response in TRD patients after SCG-DBS may be due to the wrong placement of electrodes or misleading points of stimulation.[45] Preliminary evidence for site-specific clinical responses following SCG-DBS was provided in the small open-label trial conducted by Accolla *et al.*[77] that enrolled five participants with TRD; noticeable antidepressant responses following stimulation of the posterior gyrus rectus region in one patient with TRD was observed, although none of the participants in whom DBS was applied to the originally planned Brodmann area 25 were considered responders.

Preclinical studies. The infralimbic cortex, which is part of the rodent ventromedial PFC (vmPFC) is thought to represent the rodent homologous of the human SCG (Brodmann area 25).[78] Preclinical studies indicate that DBS applied to the vmPFC may lead to antidepressant-like effects across several preclinical models including the forced swimming test (FST), sucrose preference test and novelty suppressed feeding (Table 2).[79–90] Electrical stimulation of this neuroanatomical target has also been shown to increase hedonic and motivational states in animal models of depression,[91,92] and to reverse depressive-like phenotypes induced by chronic unpredictable stress (CUS), chronic social defeat stress, olfactory bulbectomy and in a putative therapy-refractory depressive-like rat line.[82,87–89,93–95]

Hamani *et al.*[79] characterized the optimal brain stimulation settings for DBS applied to the vmPFC in rats. DBS targeted to the infralimbic cortex also resulted in antidepressant-like effects, may be through a reversal of synaptic metaplasticity and increments in mitosis.[85,96–98] In another study, DBS applied to prelimbic mPFC led to different functional brain alterations.[99] Moreover, chronic DBS applied to the vmPFC may reverse stress-induced behavioral deficits in the sucrose preference test, FST, novelty suppressed feeding and elevated plus maze models, and may also increase brain-derived neurotrophic factor levels, blood vessel size, synaptic density and astrocyte size in the hippocampus.[82,100–102] Altogether, these data suggest that stimulation parameters need to be precisely set for achieving meaningful responses after prelimbic or infralimbic PFC-DBS.

Hamani and colleagues[80,82,103] provided preclinical data to support a putative role for the serotonergic system as a mediator of the antidepressant-like effects of vmPFC-DBS. Moreover, vmPFC stimulation was found to produce antidepressant, anxiolytic and hedonic effects through the modulation of dorsal raphe nucleus (DRN) circuitry in the CUS animal model of depression.[86,87,94,104] Furthermore, adjuvant treatment with monoamine oxidase inhibitors was reported to potentiate behavioral effects of vmPFC-DBS in the FST.[81] However, co-administration of buspirone, pindolol or risperidone did not significantly alter antidepressant-like effects of DBS.[105] This further suggests that vmPFC-DBS might involve the modulation of prefrontal projections to the DRN, which is a brain region involved in serotonin (5-HT) synthesis and release. Apart from the DRN, neurostimulation of the vmPFC may also remotely affect activity of the ventral tegmental area (VTA) and locus coeruleus.[106,107]

Possible MOA. Depression has been associated with increased activity of the SCG and dysregulated corticolimbic networks.[30,96,108–111] Furthermore, SCG neurons are preferentially more responsive to negative (unpleasant) emotions.[112] SCG-DBS may ameliorate depressive symptoms or more specifically anhedonia in patients with TRD.[113] Antidepressant response to SCG-DBS in participants with TRD has been associated with frontal asymmetry, higher frontal theta cordance (θ) and local field potential broad α-band activity.[114–116] Suppression of gamma oscillations and increased θ-gamma coupling by active SCG-DBS stimulation may also enhance gamma-aminobutyric acid neurotransmission.[117] Therefore, it seems that SCG-DBS stimulation may have a key role in normalizing spectral rhythms in brain networks related to depression neurobiology.

DBS applied to the NAc

Clinical studies. Anhedonia was one of the first manifestations to improve during NAc stimulation in participants with TRD, which also reported a heightened perception of pleasurable activities.[34,36,113,118] The ideal parameters of electrical stimulation that could provide adequate antidepressant responses are summarized in Table 1. Schlaepfer *et al.*[34] reported short-term outcomes in three patients with TRD who underwent NAc-DBS. Twelve months of chronic, open-label NAc-DBS led to a decrease in the metabolism of the SCG, amygdala and prefrontal regions with 45 and 9% response and remission rates, respectively, in 10

participants with TRD.[118] The long-term open-label trial conducted by Bewernick *et al.*[36] reported a sustained antidepressant effect for NAc-DBS in 11 participants with TRD (45.5% response rate at 48-month follow-up). Yet, only five participants completed this 4-year trial.[36] Moreover, there was no evidence of cognitive deterioration in agreement with data from the same research group.[36,119] An open-label trial with six participants reported 50% responders, and did not show signs of cognitive deterioration.[120] Altogether, these data suggest that NAc-DBS could be efficacious for the management of TRD.

Preclinical studies. Application of DBS to the NAc-shell triggered impulsive behaviors accompanied by significant increases in dopamine and 5-HT levels in the NAc. However, DBS applied to the NAc core led to antidepressant-like effects without significantly altering levels of 5-HT and dopamine,[121,122] although 2 consecutive days of bilateral stimulation elicited a rapid increase in dopamine and 5-HT release in the orbital PFC.[123] HFS or low frequency stimulation of the NAc-DBS also produced distinct region-specific and frequency band-specific changes in local field potential oscillations,[124] therefore, suggesting that different stimulation parameters may engage distinct brain areas, which could then influence antidepressant responses to NAc-DBS. Furthermore, a recent study reported that DBS applied to the lateral NAc-shell reduced motivation for sucrose, whereas stimulation of the medial NAc–shell selectively increased the intake of chow.[125] These findings suggest that subdivisions of the NAc–shell may influence motivational eating behavior, and may point to dissociable effects of NAc-DBS in alleviating anhedonia in depression. Yet, the field awaits further investigations. Recently, Lim *et al.*[87] observed reduced anxiety-like behaviors and increase in motivation for chow intake in the CUS depression model after HFS of the NAc–core as compared to that in the NAc–shell.

Accumulating evidence indicates that NAc-DBS may decrease depressive-like behavior in CUS-induced animal model of depression.[86,87,93,126,127] Similar results were documented in the high anxiety-related behavior mouse model and in a chronic adrenocorticotropic hormone model of TRD after NAc stimulation.[91,128] Hamani *et al.*[126] observed comparable antidepressant-like effects after stimulation either the vmPFC or the NAc in the FST. Nevertheless, only NAc-DBS influenced different subcortical relay centers in the brain reward circuitry. In contrast, in another study vmPFC-DBS outperformed NAc-DBS.[127] Antidepressant-like effects were significantly higher after interrupted stimulation of the NAc compared with intermittent stimulation,[128,129] which was associated with decreased levels of tyrosine hydroxylase, dopamine and norepinephrine in the PFC. Although acute DBS-NAc did not significantly alter hippocampal neurogenesis,[130] DBS-NAc–core lowered CUS-induced increase in c-Fos expression in the magnocellular part of the medial vestibular nucleus compared with CUS sham.[131]

Possible MOA. Consistent with imaging studies in humans, a significant increase in blood oxygenation level-dependent signal in the insula, thalamus and parahippocampal cortex and a decrease in the SCG and PFC during stimulation of the NAc functional magnetic resonance imaging was reported in a pig model.[132] Moreover, modulation of the NAc may normalize disease-related hypermetabolism in the SCG and in prefrontal regions including the orbitofrontal cortex, with possible procognitive effects,[118] which are similar metabolic decreases observed in patients undergoing SCG-DBS.[47] Thus, it has been hypothesized that effects on the SCG could also mediate antidepressant effects of NAc-DBS.[118] In addition, as reviewed in the section above, site-specific effects on monoamine neurotransmission have been implicated as a putative antidepressant mechanism of NAc-DBS.

DBS applied to the VC/VS or vALIC

Clinical studies. Application of DBS to the VC/VS (also referred as vALIC in some studies) significantly decreased anxiety and depressive symptoms in participants with obsessive–compulsive disorder, thus providing a rationale for testing its efficacy in samples with TRD.[65,133,134] Obsessive–compulsive disorder patients who underwent DBS of the VC/VS showed a reduction of cerebral blood flow in the SCG, which appears to be metabolically hyperactive in patients with MDD.[30] An open-label pilot trial conducted by Malone *et al.*[32,135] assessed the efficacy of VC/VS-DBS in 17 patients with TRD. Response rates of 53 and 71% at 12 month and last (14–67 months) follow-up visits, respectively, and a 40% remission rate at last follow-up (6–51 months) were observed. A case report described smoking cessation in a single responder after VC/VS-DBS.[136] However, double-blind, randomized, sham-controlled trials of VC/VS-DBS for MDD have thus far provided inconsistent findings.[137,138] In a 16-week sham-controlled randomized trial followed by an open-label continuation phase, Dougherty *et al.*[137] did not observe significant differences in treatment response rates in the active DBS group. The same research group subsequently reported that vALIC-DBS did not influence cognitive function compared with sham.[139] In addition, adverse events were more severe for vALIC-DBS compared with the sham group (Table 3). Nevertheless, 25 participants underwent 52-week open-label vALIC-DBS (optimization phase), and 10 participants out of 25 with TRD were classified as responders (40%).[140,141] Sixteen participants were subsequently randomized to active-sham or sham-active groups in a cross-over design, and participants scored significantly lower during active rather than during sham DBS.[140] Therefore, the antidepressant efficacy of DBS primarily applied to the VC/VS (or vALIC, a brain structure slightly anterior and ventral to the VC/VS) remains to be established.

Preclinical studies. As ALIC is not well developed in rodents, Hamani *et al.*[126] had chosen white matter fibers of the frontal region for electrical stimulation as this neuroanatomical structure resemble the ALIC in human. Application of DBS in white matter fiber influenced the large brain regions of the cortical and subcortical structures, without producing a significant antidepressant-like effect in FST.[126]

Possible MOA. Neuroimaging studies conducted in participants with obsessive–compulsive disorder who underwent DBS in this target demonstrated modulation of different nodes of the cortico–striatal–thalamic–cortical circuitry, including the orbitofrontal cortex, basal ganglia, along with a reduction in metabolic hyperactivity of the SCG, observed particularly in participants with co-occurring MDD.[142,143] In addition, the VS encompasses structures like the bed nucleus of the stria terminalis (BNST) and the NAc, which are regions putatively involved in the regulation of stress and reward-motivational pathways in individuals with depression.[144,145] Nevertheless, the antidepressant efficacy as well as possible MOA of VC/VS-DBS remains unclear.

DBS of the MFB

Clinical studies. Three different academic institutions have assessed the efficacy of MFB-DBS in samples with TRD (Figure 1 and Table 1). However, evidence for putative antidepressant effects of MFB-DBS remains relatively unexplored as only data from 11 participants with TRD were provided from two uncontrolled studies.[33,35,39] Despite these limitations, findings suggest that MFB-DBS could confer rapid and long-lasting antidepressant effects. Short-term bilateral stimulation of the superolateral-MFB showed a rapid reduction in the severity of depressive symptoms in six out of seven participants within 2 days of stimulation, and four out of seven patients met criteria for

Table 3. Summary of most common observed adverse effects after DBS of various brain targets

Target structure	*Reference*	*Adverse effects*
SCG-DBS	Mayberg *et al.* (2005)[24]	Infections with hardware removal (33%) and skin erosion (17%)
	Lozano *et al.* (2008)[47]	Infections (25%), seizure, perioperative headaches (20%), pain at pulse generator site and worsening of mood/irritability (10%)
	Guinjoan *et al.* (2010)[200]	Sign of orthostatic hypotension when stimulated adjacent to subcallosal cingulate gray matter
	Kennedy *et al.* (2011)[53]	Patients suffer from nonpsychotic unipolar major depression; two of the 20 patients committed suicide and two others made suicide attempts
	Lozano *et al.* (2012)[62]	One patient committed suicide out of 21, and another patient attempted suicide, and presented tremor, spasms, muscle stiffness, nausea, vomiting, dizziness, headache, polyuria, superficial skin erosion, buzzing in ears, insomnia and agitation mainly after increase of amplitude
	Holtzheimer *et al.* (2012)[54]	Infection, anxiety, worsening depression, suicidal ideation, suicide attempt
	Puigdemont *et al.* (2012)[55]	Cephalalgia in two patients; three out of eight participants reported pain in the neck at the site of the subdermal cable and one patient attempted suicide
	Merkl *et al.* (2013)[60]	Headaches, pain and scalp tingling at the surgical site, dizziness, sore throat, feeling of tenseness in the neck region (hardware-related)
	Ramasubbu *et al.* (2013)[61]	The long pulse width (450 μs) stimulation induced insomnia, anxiety, confusion and drowsiness, decreases battery life of the pulse generator and risk of tissue damage due to higher electrical charge density
	Puigdemont *et al.* (2015)[57]	Headache, dizziness, gastrointestinal disturbances, paresthesias
	Holtzheimer *et al.* (2017)[75]	Twenty-eight participants experienced 40 serious adverse events. Study device or surgery-related: six infections (five patients), one skin erosion and one postoperative seizure, and other were primary mood disorder-related like anxiety, suicidal ideation, suicide attempt, seizure, headache
	Merkl *et al.* (2017)[76]	Headaches, pain and scalp tingling at the surgical site, dizziness and sore throat due to anesthesia, three out of eight participants removed macroelectrodes and internal pulse generator due to either inconvenience at movement or lack of effect
	Eitan *et al.* (2018)[58]	Twenty-eight of forty adverse events related to the device/procedure; only one of these events was serious adverse event
NAc-DBS	Bewernick *et al.* (2010)[118]	Surgical procedure (swollen eye, dysphagia and pain), to parameter change (erythema, transient increase in anxiety or tension and sweating)
	Bewernick *et al.* (2012)[36]	One patient out of eleven committed suicide and one patient attempted suicide during first year
	Millet *et al.* (2014)[120]	Each of the following in 25% patients: suicide attempt, suicidal thoughts, worsening effects on mood/anxiety and sleep, memory problems, excessive food intake, increases appetite for sweets, slightly increases libido, headache or pain near the device, paresthesia
	Richieri *et al.* (2016)[74]	DBS targeting the limbic system may increase the risk of seizure in depressive patient
VC/VS-DBS or vALIC-DBS	Malone *et al.* (2009)[32]	VC/VS-DBS: pain at incision site (6.7%), lead fracture (6.7%), hypomania (6.7%)
	Malone (2010)[135]	VC/VS-DBS: infection at lead or battery implantation site, paresthesias, anxiety, mood changes and autonomic effects
	Dougherty *et al.* (2015)[137]	VC/VS-DBS: electrical stimulated subjects versus control subjects—worsening depression (5 versus 3), insomnia (4 versus 3), irritability (3 versus 0), suicidal ideation (2 versus 0), hypomania (2 versus 0), disinhibition (2 versus 0) and mania (1 versus 0), early-morning awakening and purging (0 versus 1). Out of thirty participants, eight showed worsening depression, followed by suicidal ideation in 5 subjects, suicide attempt (four participants) implant site infection (five participants)
	Richardson *et al.* (2015)[138]	VC/VS-DBS: worsening depression, insomnia, irritability, suicidal ideation, hypomania, disinhibition and mania
	Bergfeld *et al.* (2016)[140]	vALIC-DBS out of total 25 patients : severe nausea during surgery (one patient), suicide attempt (four patients), suicidal ideation (two patients) and hypomania
ALIC/BNST and ITP	Raymaekers *et al.* (2017)[176]	Seventy-five adverse events and eleven serious adverse events (for example, conversely labeled leads, infections around neurostimulator site, damage of electrode), psychiatric (increase in depressive symptoms, sleep disturbances), suicide (two participants)
MFB-DBS	Schlaepfer *et al.* (2013)[33]	Blurred vision and strabismus at higher amplitudes (as MFB target site is in close proximity to the oculomotor nerve fibers), dizziness and increased sweating
	Fenoy *et al.* (2016)[39]	Vertical diplopia, transient headache postoperatively
	Bewernick *et al.* (2017)[35]	Blurred vision, and double vision, a small strabism, small Intracranial bleeding (one patient)
	Blomstedt *et al.* (2017)[146]	Blurred vision following 10 months of DBS treatment
Overall DBS	Saleh and Fontaine (2015)[73]	Hardware-related adverse effects 11.4% and suicidality 9.3%

Abbreviations: BNST, bed nucleus of the stria terminalis; DBS, deep brain stimulation; ITP, inferior thalamic peduncle; MFB, medial forebrain bundle; NAc, nucleus accumbens; SCG, subcallosal cingulate gyrus; vALIC, ventral part of anterior limb of the internal capsule; VC/VS, ventral capsule/ventral striatum.

treatment response after 1-week stimulation,[33] whereas at the last observation (after 12–33 weeks) six participants (85.7%) were treatment responders. Fenoy *et al.*[39] also reported in their interim analysis a robust and rapid antidepressant response in an open-label trial of bilateral MFB-DBS, in which three out of four participants with TRD were responders after 1 week of DBS initiation, and two of four participants displayed >80% decrease in MADRS scores after 26 weeks of stimulation. Recently, Bewernick *et al.*[35] provided long-term data for their open-label trial.[33] At the time of analysis, six out of eight participants (75%)

were treatment responders at 12-month follow-up; these antidepressant effects remained stable for up to 4 years. Furthermore, no evidence of cognitive impairments were noted even after several months of stimulation in this target.[35,39] The most frequently reported adverse effect associated with MFB-DBS were oculomotor disturbances (Table 3), which in most cases diminished over time. In a recent case study, a 58-year-old patient perceived marked mood improvement effect after 1 week of MFB-DBS.[146] However, this patient experienced oculomotor side effects that failed to remit over time. The patient was re-operated after 2 years, and responded to DBS applied to the BNST without troublesome oculomotor side effects. These data provide further evidence that in selected clinical situations this adverse effect could be a reason for discontinuing MFB-DBS.[39] Taken together, these preliminary data suggest that MFB-DBS could be efficacious for the management of TRD. Thus, the design of a randomized, sham-controlled trial is warranted to confirm those promising findings.

Preclinical studies. Similarly to the NAc, the MFB has a critical role in the regulation of motivation, and thus may contribute to anhedonia.[147] In preclinical studies, the MFB-HFS generated antidepressant-like effects was associated long-lasting neural adaptation in target regions of the mesolimbic–mesocortical circuitry (Table 2).[92,148,149] When Flinders sensitive line rats received bilateral HFS to the MFB, antidepressant-like effects in the FST were observed.[92] Similar antidepressant-like effects were reported following bilateral HFS in rats accompanied by an increase in expression of the immediate early gene, zif268, in the piriform cortex, prelimbic cortex, NAc shell, anterior regions of the caudate/putamen and the VTA.[150] However, no significant changes in the release of either dopamine or serotonin at the level of the NAc were observed. Although MFB-DBS was reported to mitigate depressive-like behaviors and increase pleasurable or rewarding experiences after mild VTA lesion in rats, it was unable to reverse a despair phenotype after severe VTA lesions in rats.[151] Recently, rapid antidepressant-like effects and increased expression of dopamine D2 receptors in the PFC have been reported following acute stimulation of MFB in rats.[152]

Possible MOA. The MFB is a central component of the mesolimbic–mesocortical dopamine reward system,[153–155] and it is interconnected with several other DBS targets.[24,34,156,157] MFB-DBS may activate the mesocorticolimbic system by increasing neuronal activity within these regions through the modulation of dopaminergic and glutamatergic neurotransmission.[33,39,158,159] Recently, optogenetic activation of VTA dopaminergic neurons led to increased functional magnetic resonance imaging blood oxygenation level-dependent signals in the NAc concomitantly with an increase in motivational behavior in rats.[160] It is thought that modulation of the MFB via DBS may recruit descending glutamatergic fibers from the mPFC to the VTA, and may thus indirectly modulate dopaminergic firing at the VTA.[161] MFB-DBS may also modulate upstream cortical regions.[33] Yet, the precise MOA underlying putative antidepressant effects of MFB-DBS remain to be elucidated.

DBS of the LHb

Clinical studies. Hyperactivity of neurons at the LHb has been suggested to have a pathophysiological role in MDD.[83,162] Bilateral LHb-DBS may decrease activation within this neuroanatomical region.[163] Sartorius *et al*.[163] observed a sustained remission of depressive symptoms after 4 months of DBS in a patient with TRD. A marked re-emergence of depressive symptoms elapsed after the erroneous cessation of stimulation, further pointing to the potential therapeutic usefulness of LHb-DBS for TRD. As evidence from single case report is available, more studies would decide the relevance of this target for TRD.

Preclinical studies. LHb-DBS has been shown to reverse depressive-like behaviors in the CUS as well as in the chronic adrenocorticotropic hormone and learned helplessness models of TRD.[83,84,87,164,165] DBS applied at the LHb gradually increased peripheral and brain levels of norepinephrine, dopamine and 5-HT, which peaked after 28 days of treatment.[84] In a comparative study of vmPFC-DBS versus LHb-DBS, Lim *et al*.[87] showed that, although vmPFC-DBS produced a fourfold increase in hippocampal 5-HT release, LHb stimulation produced an ~55–70% increase in striatal 5-HT release. Moreover, HFS of the LHb was reported to counteract depressive-like behavior in the CUS animal model.[87]

Possible MOA. Electrical stimulation of the LHb was found to significantly inhibit the firing of dopaminergic neurons in the substantia nigra pars compacta and the VTA.[166,167] In a genetic animal model of TRD, a significant alteration of regional cerebral blood volume was observed within the LHb.[168] Furthermore, the antidepressant effects of LHb-DBS may involve monoamine pathways as there are strong interactions and direct efferents from the LHb to the DRN, locus coeruleus and the VTA.[169]

DBS of the ITP

The ITP encompasses a bundle of fibers connecting the dorsomedial thalamus to the orbitofrontal cortex,[170] which is dysregulated in participants with MDD.[171] Moreover, surgical lesions to the ITP may disrupt the inhibitory action of the thalamo–orbitofrontal system, and may also promote antidepressant-like effects in preclinical models.[172] Two case reports have described the results of ITP-DBS in a single patient with TRD.[173–175] A significant decrease in Hamilton depression rating scale scores (from 42 to 6) without side effects at high-frequency DBS settings of 3.5 V and 450 μs of pulse width was verified.[173] Recently, antidepressant efficacy of ITP and ALIC/BNST stimulation were compared in blinded crossover study.[176] Although no superiority of either targets were noticed, 6/7 patients preferred stimulation in ALIC/BNST.[176] Clearly, this brain target deserves further exploration in clinical trials.

DBS of the STN

Acute treatment with STN-DBS significantly improved depression-like behaviors in preclinical models (Table 2).[177,178] Similarly, *post hoc* clinical evidence suggested possible antidepressant effects following STN-DBS in samples with Parkinson's disease (PD).[179–183] In contrast, worsening of depressive-like behaviors in rats, and an increased risk of transient cognitive and psychiatric complications have been reported after STN-DBS for PD.[184–186] However, depressive symptoms were less frequent after pallidal-DBS compared with STN-DBS in PD patients.[187] In a case report, an increase in current frequency of STN-DBS from 60 to 185 Hz led to a significant improvement of depressive symptoms with complete resolution of his suicidal thoughts in a PD patient.[188] In sum, divergent findings in both the clinical and preclinical literature have diminished enthusiasm in the field for further testing this target in clinical trials involving participants with TRD.

CONCLUSION

Evidence indicates that DBS can be delivered to discrete brain targets and may directly modulate brain activity in a limited brain structure and also activity of interconnected (that is, more distant) brain networks. Furthermore, available evidence suggests that it could be a relatively safe and well-tolerated non-pharmacological therapeutic option for TRD.[24,39,47,189,190] Six prominent DBS targets have been tested for the management of TRD. Interestingly, in

most circumstances those targets have been tested in clinical trials prior to the conduction of preclinical studies. However, the underlying mechanisms of DBS-related antidepressant effects remain elusive, and may vary as a function of the primary brain target as well as with stimulation parameters. In addition, clinical trials to date have methodological shortcomings such as a lack of proper randomization, the lack of a control (that is, sham-stimulated) group, small sample sizes, heterogeneity of participants across trials (for example, different definitions of TRD) as well as a lack of consensus algorithms for DBS delivery.[40] Herein, the underlying mechanisms for putative antidepressant effects of DBS identified in clinical trials and preclinical studies are reviewed. We sought to determine which brain target(s) most consistently elicited antidepressant responses. Out of six DBS targets, only VC/VS and the SCG have been investigated in multicenter, randomized, sham-controlled trials. However, these trials failed to confirm the efficacy of those targets in participants with TRD.[57,75,137] On the other hand, open-label clinical studies verified high response rates (ranging from 60 to 78%) in participants with TRD after the application of DBS to several targets.[191] Furthermore, discrepant findings across these open-label trials may be ascribed to interpersonal anatomical differences (size and shape) of DBS targets, which could be rectified by mapping the internal neuroanatomical structure of individual patients.[35,39,45,77,192,193] Taken together, detailed characterization of the anatomical, physiological and neurochemical substrates underlying the effects of DBS may delineate suitable brain targets for the management of TRD.

CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

The use of DBS in the management of TRD remains at investigational stages. How research in this treatment modality for depression should continue and improve from this point represents a meaningful challenge for neuroclinicians.[38,40,194] As most neuroanatomical centers regulating affect and motivation are interconnected,[3,195–197] DBS could influence distant brain networks regardless of the initial target.[198] Tractography and other imaging techniques could provide valuable resources to guide surgical procedures, and also for post-surgery monitoring.[39,40,45,47,72,118] The identification of individual clinical characteristics as well as biomarkers of treatment response within the emerging framework of precision psychiatry also provides a relevant yet relatively unexplored research direction.[114,115,165,193,199] It should be noted that the effectiveness of unilateral versus bilateral DBS of brain targets warrant confirmation in randomized, double-blind, sham-controlled trials.[39,79,80,152,200] Importantly, it is yet debatable whether non-responders to one target might benefit from DBS delivered to an alternative target. Taken together, the selection of patients, target brain regions, parameters of stimulation and identification of early biomarkers are necessary steps to be taken to provide more consistent evidence for this promising treatment modality for intractable depression. It should be noted that RCTs of DBS applied to the SCG, VC/VS or vALIC have thus far provided inconsistent results. Therefore, adequately powered and well-designed double-blind RCTs are warranted to provide a more accurate assessment of the efficacy and safety for DBS delivered at different brain targets as a therapeutic option for TRD.

CONFLICT OF INTEREST

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REFERENCES

1 Bromet E, Andrade LH, Hwang I, Sampson NA, Alonso J, de Girolamo G *et al.* Cross-national epidemiology of DSM-IV major depressive episode. *BMC Med* 2011; **9**: 90.
2 Kessler RC, Bromet EJ. The epidemiology of depression across cultures. *Annu Rev Public Health* 2013; **34**: 119–138.
3 Anderson RJ, Frye MA, Abulseoud OA, Lee KH, McGillivray JA, Berk M *et al.* Deep brain stimulation for treatment-resistant depression: efficacy, safety and mechanisms of action. *Neurosci Biobehav Rev* 2012; **36**: 1920–1933.
4 Rosenblat JD, McIntyre RS, Alves GS, Fountoulakis KN, Carvalho AF. Beyond monoamines-novel targets for treatment-resistant depression: a comprehensive review. *Curr Neuropharmacol* 2015; **13**: 636–655.
5 Rush AJ, Trivedi MH, Wisniewski SR, Stewart JW, Nierenberg AA, Thase ME *et al.* Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. *N Engl J Med* 2006; **354**: 1231–1242.
6 Carvalho AF, Berk M, Hyphantis TN, McIntyre RS. The integrative management of treatment-resistant depression: a comprehensive review and perspectives. *Psychother Psychosom* 2014; **83**: 70–88.
7 Souery D, Papakostas GI, Trivedi MH. Treatment-resistant depression. *J Clin Psychiatry* 2006; **67**(Suppl 6): 16–22.
8 McIntyre RS, Filteau MJ, Martin L, Patry S, Carvalho A, Cha DS *et al.* Treatment-resistant depression: definitions, review of the evidence, and algorithmic approach. *J Affect Disord* 2014; **156**: 1–7.
9 Berlim MT, Turecki G. What is the meaning of treatment resistant/refractory major depression (TRD)? A systematic review of current randomized trials. *Eur Neuropsychopharmacol* 2007; **17**: 696–707.
10 Carvalho AF, Sharma MS, Brunoni AR, Vieta E, Fava GA. The safety, tolerability and risks associated with the use of newer generation antidepressant drugs: a critical review of the literature. *Psychother Psychosom* 2016; **85**: 270–288.
11 Mrazek DA, Hornberger JC, Altar CA, Degtiar I. A review of the clinical, economic, and societal burden of treatment-resistant depression: 1996-2013. *Psychiatr Serv* 2014; **65**: 977–987.
12 Papakostas GI, Ionescu DF. Towards new mechanisms: an update on therapeutics for treatment-resistant major depressive disorder. *Mol Psychiatry* 2015; **20**: 1142–1150.
13 Zarate CA Jr., Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA *et al.* A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry* 2006; **63**: 856–864.
14 Papadimitropoulou K, Vossen C, Karabis A, Donatti C, Kubitz N. Comparative efficacy and tolerability of pharmacological and somatic interventions in adult patients with treatment-resistant depression: a systematic review and network meta-analysis. *Curr Med Res Opin* 2017; **33**: 701–711.
15 Sanacora G, Frye MA, McDonald W, Mathew SJ, Turner MS, Schatzberg AF *et al.* A consensus statement on the use of ketamine in the treatment of mood disorders. *JAMA Psychiatry* 2017; **74**: 399–405.
16 Dumitriu D, Collins K, Alterman R, Mathew SJ. Neurostimulatory therapeutics in management of treatment-resistant depression with focus on deep brain stimulation. *Mount Sinai J Med* 2008; **75**: 263–275.
17 Mohr P, Rodriguez M, Slavickova A, Hanka J. The application of vagus nerve stimulation and deep brain stimulation in depression. *Neuropsychobiology* 2011; **64**: 170–181.
18 Rizvi SJ, Donovan M, Giacobbe P, Placenza F, Rotzinger S, Kennedy SH. Neurostimulation therapies for treatment resistant depression: a focus on vagus nerve stimulation and deep brain stimulation. *Int Rev Psychiatry* 2011; **23**: 424–436.
19 Blumberger DM, Mulsant BH, Daskalakis ZJ. What is the role of brain stimulation therapies in the treatment of depression? *Curr Psychiatr Rep* 2013; **15**: 368.
20 Kopell BH, Halverson J, Butson CR, Dickinson M, Bobholz J, Harsch H *et al.* Epidural cortical stimulation of the left dorsolateral prefrontal cortex for refractory major depressive disorder. *Neurosurgery* 2011; **69**: 1015–1029, discussion 1029.

21 Tye SJ, Frye MA, Lee KH. Disrupting disordered neurocircuitry: treating refractory psychiatric illness with neuromodulation. *Mayo Clin Proc* 2009; **84**: 522–532.
22 Benabid AL, Benazzouz A, Hoffmann D, Limousin P, Krack P, Pollak P. Long-term electrical inhibition of deep brain targets in movement disorders. *Mov Disord* 1998; **13**(Suppl 3): 119–125.
23 Benabid AL, Pollak P, Louveau A, Henry S, de Rougemont J. Combined (thalamotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson disease. *Applied Neurophysiol* 1987; **50**: 344–346.
24 Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C *et al.* Deep brain stimulation for treatment-resistant depression. *Neuron* 2005; **45**: 651–660.
25 Kuhn J, Huff W. Will deep brain stimulation be as successful in major depression as it has been in Parkinson's disease? *Exp Rev Neurother* 2010; **10**: 1363–1365.
26 Alonso P, Cuadras D, Gabriels L, Denys D, Goodman W, Greenberg BD *et al.* Deep brain stimulation for obsessive-compulsive disorder: a meta-analysis of treatment outcome and predictors of response. *PLoS ONE* 2015; **10**: e0133591.
27 Lally N, Nugent AC, Luckenbaugh DA, Ameli R, Roiser JP, Zarate CA. Anti-anhedonic effect of ketamine and its neural correlates in treatment-resistant bipolar depression. *Transl Psychiatry* 2014; **4**: e469.
28 Carlson PJ, Diazgranados N, Nugent AC, Ibrahim L, Luckenbaugh DA, Brutsche N *et al.* Neural correlates of rapid antidepressant response to ketamine in treatment-resistant unipolar depression: a preliminary positron emission tomography study. *Biol Psychiatry* 2013; **73**: 1213–1221.
29 McIntyre CC, Savasta M, Kerkerian-Le Goff L, Vitek JL. Uncovering the mechanism (s) of action of deep brain stimulation: activation, inhibition, or both. *Clin Neurophysiol* 2004; **115**: 1239–1248.
30 Mayberg HS, Liotti M, Brannan SK, McGinnis S, Mahurin RK, Jerabek PA *et al.* Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. *Am J Psychiatry* 1999; **156**: 675–682.
31 Johansen-Berg H, Gutman DA, Behrens TE, Matthews PM, Rushworth MF, Katz E *et al.* Anatomical connectivity of the subgenual cingulate region targeted with deep brain stimulation for treatment-resistant depression. *Cereb Cortex* 2008; **18**: 1374–1383.
32 Malone DA Jr., Dougherty DD, Rezai AR, Carpenter LL, Friehs GM, Eskandar EN *et al.* Deep brain stimulation of the ventral capsule/ventral striatum for treatment-resistant depression. *Biol Psychiatry* 2009; **65**: 267–275.
33 Schlaepfer TE, Bewernick BH, Kayser S, Madler B, Coenen VA. Rapid effects of deep brain stimulation for treatment-resistant major depression. *Biol Psychiatry* 2013; **73**: 1204–1212.
34 Schlaepfer TE, Cohen MX, Frick C, Kosel M, Brodesser D, Axmacher N *et al.* Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression. *Neuropsychopharmacology* 2008; **33**: 368–377.
35 Bewernick BH, Kayser S, Gippert SM, Switala C, Coenen VA, Schlaepfer TE. Deep brain stimulation to the medial forebrain bundle for depression- long-term outcomes and a novel data analysis strategy. *Brain Stimul* 2017; **10**: 664–671.
36 Bewernick BH, Kayser S, Sturm V, Schlaepfer TE. Long-term effects of nucleus accumbens deep brain stimulation in treatment-resistant depression: evidence for sustained efficacy. *Neuropsychopharmacology* 2012; **37**: 1975–1985.
37 Taghva AS, Malone DA, Rezai AR. Deep brain stimulation for treatment-resistant depression. *World Neurosurg* 2013; **80**: S27 e17-24.
38 Morishita T, Fayad SM, Higuchi MA, Nestor KA, Foote KD. Deep brain stimulation for treatment-resistant depression: systematic review of clinical outcomes. *Neurotherapeutics* 2014; **11**: 475–484.
39 Fenoy AJ, Schulz P, Selvaraj S, Burrows C, Spiker D, Cao B *et al.* Deep brain stimulation of the medial forebrain bundle: distinctive responses in resistant depression. *J Affect Disord* 2016; **203**: 143–151.
40 Mayberg HS, Riva-Posse P, Crowell AL. Deep brain stimulation for depression: keeping an eye on a moving target. *JAMA Psychiatry* 2016; **73**: 439–440.
41 Smith DF. Exploratory meta-analysis on deep brain stimulation in treatment-resistant depression. *Acta Neuropsychiatr* 2014; **26**: 382–384.
42 Hamani C, Nobrega JN. Deep brain stimulation in clinical trials and animal models of depression. *Eur J Neurosci* 2010; **32**: 1109–1117.
43 Nestler EJ, Hyman SE. Animal models of neuropsychiatric disorders. *Nat Neurosci* 2010; **13**: 1161–1169.
44 Drevets WC, Savitz J, Trimble M. The subgenual anterior cingulate cortex in mood disorders. *CNS Spectr* 2008; **13**: 663–681.
45 Riva-Posse P, Choi KS, Holtzheimer PE, Crowell AL, Garlow SJ, Rajendra JK *et al.* A connectomic approach for subcallosal cingulate deep brain stimulation surgery: prospective targeting in treatment-resistant depression. *Mol Psychiatry* 2017 article in press.
46 Riva-Posse P, Holtzheimer PE, Garlow SJ, Mayberg HS. Practical considerations in the development and refinement of subcallosal cingulate white matter deep brain stimulation for treatment-resistant depression. *World Neurosurg* 2013; **80**: S27 e25–S27 e34.
47 Lozano AM, Mayberg HS, Giacobbe P, Hamani C, Craddock RC, Kennedy SH. Subcallosal cingulate gyrus deep brain stimulation for treatment-resistant depression. *Biol Psychiatry* 2008; **64**: 461–467.
48 Puigdemont D, Portella MJ, Perez-Egea R, de Diego-Adelino J, Gironell A, Molet J *et al.* Depressive relapse after initial response to subcallosal cingulate gyrus-deep brain stimulation in a patient with a treatment-resistant depression: electroconvulsive therapy as a feasible strategy. *Biol Psychiatry* 2009; **66**: e11–e12.
49 Neimat JS, Hamani C, Giacobbe P, Merskey H, Kennedy SH, Mayberg HS *et al.* Neural stimulation successfully treats depression in patients with prior ablative cingulotomy. *Am J Psychiatry* 2008; **165**: 687–693.
50 Torres CV, Ezquiaga E, Navas M, de Sola RG. Deep brain stimulation of the subcallosal cingulate for medication-resistant type I bipolar depression: case report. *Bipolar Disord* 2013; **15**: 719–721.
51 Funayama M, Kato M, Mimura M. Disappearance of treatment-resistant depression after damage to the orbitofrontal cortex and subgenual cingulate area: a case study. *BMC Neurol* 2016; **16**: 198.
52 Holtzheimer PE 3rd, Mayberg HS. Deep brain stimulation for treatment-resistant depression. *Am J Psychiatry* 2010; **167**: 1437–1444.
53 Kennedy SH, Giacobbe P, Rizvi SJ, Placenza FM, Nishikawa Y, Mayberg HS *et al.* Deep brain stimulation for treatment-resistant depression: follow-up after 3 to 6 years. *Am J Psychiatry* 2011; **168**: 502–510.
54 Holtzheimer PE, Kelley ME, Gross RE, Filkowski MM, Garlow SJ, Barrocas A *et al.* Subcallosal cingulate deep brain stimulation for treatment-resistant unipolar and bipolar depression. *Arch Gen Psychiatry* 2012; **69**: 150–158.
55 Puigdemont D, Perez-Egea R, Portella MJ, Molet J, de Diego-Adelino J, Gironell A *et al.* Deep brain stimulation of the subcallosal cingulate gyrus: further evidence in treatment-resistant major depression. *Int J Neuropsychopharmacol* 2012; **15**: 121–133.
56 Martin-Blanco A, Serra-Blasco M, Perez-Egea R, de Diego-Adelino J, Carceller-Sindreu M, Puigdemont D *et al.* Immediate cerebral metabolic changes induced by discontinuation of deep brain stimulation of subcallosal cingulate gyrus in treatment-resistant depression. *J Affect Disord* 2015; **173**: 159–162.
57 Puigdemont D, Portella M, Perez-Egea R, Molet J, Gironell A, de Diego-Adelino J *et al.* 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. *J Psychiatr Neurosci* 2015; **40**: 224–231.
58 Eitan R, Fontaine D, Benoit M, Giordana C, Darmon N, Israel Z *et al.* One year double blind study of high vs low frequency subcallosal cingulate stimulation for depression. *J Psychiatr Res* 2018; **96**: 124–134.
59 Berlim MT, McGirr A, Van den Eynde F, Fleck MP, Giacobbe P. Effectiveness and acceptability of deep brain stimulation (DBS) of the subgenual cingulate cortex for treatment-resistant depression: a systematic review and exploratory meta-analysis. *J Affect Disord* 2014; **159**: 31–38.
60 Merkl A, Schneider GH, Schonecker T, Aust S, Kuhl KP, Kupsch A *et al.* Antidepressant effects after short-term and chronic stimulation of the subgenual cingulate gyrus in treatment-resistant depression. *Exp Neurol* 2013; **249**: 160–168.
61 Ramasubbu R, Anderson S, Haffenden A, Chavda S, Kiss ZH. Double-blind optimization of subcallosal cingulate deep brain stimulation for treatment-resistant depression: a pilot study. *J Psychiatr Neurosci* 2013; **38**: 325–332.
62 Lozano AM, Giacobbe P, Hamani C, Rizvi SJ, Kennedy SH, Kolivakis TT *et al.* A multicenter pilot study of subcallosal cingulate area deep brain stimulation for treatment-resistant depression. *J Neurosurg* 2012; **116**: 315–322.
63 Lujan JL, Chaturvedi A, Choi KS, Holtzheimer PE, Gross RE, Mayberg HS *et al.* Tractography-activation models applied to subcallosal cingulate deep brain stimulation. *Brain Stimul* 2013; **6**: 737–739.
64 Riva-Posse P, Choi KS, Holtzheimer PE, McIntyre CC, Gross RE, Chaturvedi A *et al.* Defining critical white matter pathways mediating successful subcallosal cingulate deep brain stimulation for treatment-resistant depression. *Biol Psychiatry* 2014; **76**: 963–969.
65 Holtzheimer PE, Mayberg HS. Deep brain stimulation for psychiatric disorders. *Annu Rev Neurosci* 2011; **34**: 289–307.
66 Moreines JL, McClintock SM, Kelley ME, Holtzheimer PE, Mayberg HS. Neuropsychological function before and after subcallosal cingulate deep brain stimulation in patients with treatment-resistant depression. *Depress Anxiety* 2014; **31**: 690–698.
67 Bogod NM, Sinden M, Woo C, Defreitas VG, Torres IJ, Howard AK *et al.* Long-term neuropsychological safety of subgenual cingulate gyrus deep brain stimulation for treatment-resistant depression. *J Neuropsychiatr Clin Neurosci* 2014; **26**: 126–133.
68 Hilimire MR, Mayberg HS, Holtzheimer PE, Broadway JM, Parks NA, DeVylder JE *et al.* Effects of subcallosal cingulate deep brain stimulation on negative self-bias in patients with treatment-resistant depression. *Brain Stimul* 2015; **8**: 185–191.
69 Serra-Blasco M, de Vita S, Rodriguez MR, de Diego-Adelino J, Puigdemont D, Martin-Blanco A *et al.* Cognitive functioning after deep brain stimulation in

subcallosal cingulate gyrus for treatment-resistant depression: an exploratory study. *Psychiatr Res* 2015; **225**: 341–346.
70 McInerney SJ, McNeely HE, Geraci J, Giacobbe P, Rizvi SJ, Ceniti AK *et al.* Neurocognitive predictors of response in treatment resistant depression to subcallosal cingulate gyrus deep brain stimulation. *Front Hum Neurosci* 2017; **11**: 74.
71 McNeely HE, Mayberg HS, Lozano AM, Kennedy SH. Neuropsychological impact of Cg25 deep brain stimulation for treatment-resistant depression: preliminary results over 12 months. *JNerv Ment Dis* 2008; **196**: 405–410.
72 Crowell AL, Garlow SJ, Riva-Posse P, Mayberg HS. Characterizing the therapeutic response to deep brain stimulation for treatment-resistant depression: a single center long-term perspective. *Front Integr Neurosci* 2015; **9**: 41.
73 Saleh C, Fontaine D. Deep brain stimulation for psychiatric diseases: what are the risks? *Curr Psychiatr Rep* 2015; **17**: 33.
74 Richieri R, Borius PY, Lagrange G, Faget-Agius C, Guedj E, Mc Gonigal A *et al.* Unmasking partial seizure after deep brain stimulation for treatment-resistant depression: a case report. *Brain Stimul* 2016; **9**: 636–638.
75 Holtzheimer PE, Husain MM, Lisanby SH, Taylor SF, Whitworth LA, McClintock S *et al.* Subcallosal cingulate deep brain stimulation for treatment-resistant depression: a multisite, randomised, sham-controlled trial. *Lancet Psychiatry* 2017; **4**: 839–849.
76 Merkl A, Aust S, Schneider GH, Visser-Vandewalle V, Horn A, Kuhn AA *et al.* Deep brain stimulation of the subcallosal cingulate gyrus in patients with treatment-resistant depression: a double-blinded randomized controlled study and long-term follow-up in eight patients. *J Affect Disord* 2017; **227**: 521–529.
77 Accolla EA, Aust S, Merkl A, Schneider GH, Kuhn AA, Bajbouj M *et al.* Deep brain stimulation of the posterior gyrus rectus region for treatment resistant depression. *J Affect Disord* 2016; **194**: 33–37.
78 Wallis JD. Cross-species studies of orbitofrontal cortex and value-based decision-making. *Nat Neurosci* 2011; **15**: 13–19.
79 Hamani C, Diwan M, Isabella S, Lozano AM, Nobrega JN. Effects of different stimulation parameters on the antidepressant-like response of medial prefrontal cortex deep brain stimulation in rats. *J Psychiatr Res* 2010a; **44**: 683–687.
80 Hamani C, Diwan M, Macedo CE, Brandao ML, Shumake J, Gonzalez-Lima F *et al.* Antidepressant-like effects of medial prefrontal cortex deep brain stimulation in rats. *Biol Psychiatry* 2010b; **67**: 117–124.
81 Hamani C, Giacobbe P, Diwan M, Balbino ES, Tong J, Bridgman A *et al.* Monoamine oxidase inhibitors potentiate the effects of deep brain stimulation. *Am J Psychiatry* 2012a; **169**: 1320–1321.
82 Hamani C, Machado DC, Hipolide DC, Dubiela FP, Suchecki D, Macedo CE *et al.* Deep brain stimulation reverses anhedonic-like behavior in a chronic model of depression: role of serotonin and brain derived neurotrophic factor. *Biol Psychiatry* 2012b; **71**: 30–35.
83 Li B, Piriz J, Mirrione M, Chung C, Proulx CD, Schulz D *et al.* Synaptic potentiation onto habenula neurons in the learned helplessness model of depression. *Nature* 2011; **470**: 535–539.
84 Meng H, Wang Y, Huang M, Lin W, Wang S, Zhang B. Chronic deep brain stimulation of the lateral habenula nucleus in a rat model of depression. *Brain Res* 2011; **1422**: 32–38.
85 Perez-Caballero L, Perez-Egea R, Romero-Grimaldi C, Puigdemont D, Molet J, Caso JR *et al.* Early responses to deep brain stimulation in depression are modulated by anti-inflammatory drugs. *Mol Psychiatry* 2014; **19**: 607–614.
86 Lim LW, Janssen ML, Kocabicak E, Temel Y. The antidepressant effects of ventromedial prefrontal cortex stimulation is associated with neural activation in the medial part of the subthalamic nucleus. *Behav Brain Res* 2015a; **279**: 17–21.
87 Lim LW, Prickaerts J, Huguet G, Kadar E, Hartung H, Sharp T *et al.* Electrical stimulation alleviates depressive-like behaviors of rats: investigation of brain targets and potential mechanisms. *Transl Psychiatry* 2015b; **5**: e535.
88 Jimenez-Sanchez L, Castane A, Perez-Caballero L, Grifoll-Escoda M, Lopez-Gil X, Campa L *et al.* Activation of AMPA receptors mediates the antidepressant action of deep brain stimulation of the infralimbic prefrontal cortex. *Cereb cortex* 2016a; **26**: 2778–2789.
89 Jimenez-Sanchez L, Linge R, Campa L, Valdizan EM, Pazos A, Diaz A *et al.* Behavioral, neurochemical and molecular changes after acute deep brain stimulation of the infralimbic prefrontal cortex. *Neuropharmacology* 2016b; **108**: 91–102.
90 Rea E, Rummel J, Schmidt TT, Hadar R, Heinz A, Mathe AA *et al.* Anti-anhedonic effect of deep brain stimulation of the prefrontal cortex and the dopaminergic reward system in a genetic rat model of depression: an intracranial self-stimulation paradigm study. *Brain Stimul* 2014; **7**: 21–28.
91 Schmuckermair C, Gaburro S, Sah A, Landgraf R, Sartori SB, Singewald N. Behavioral and neurobiological effects of deep brain stimulation in a mouse model of high anxiety- and depression-like behavior. *Neuropsychopharmacology* 2013; **38**: 1234–1244.
92 Edemann-Callesen H, Voget M, Empl L, Vogel M, Wieske F, Rummel J *et al.* Medial forebrain bundle deep brain stimulation has symptom-specific anti-depressant effects in rats and as opposed to ventromedial prefrontal cortex stimulation interacts with the reward system. *Brain Stimul* 2015; **8**: 714–723.
93 Gersner R, Toth E, Isserles M, Zangen A. Site-specific antidepressant effects of repeated subconvulsive electrical stimulation: potential role of brain-derived neurotrophic factor. *Biol Psychiatry* 2010; **67**: 125–132.
94 Veerakumar A, Challis C, Gupta P, Da J, Upadhyay A, Beck SG *et al.* Antidepressant-like effects of cortical deep brain stimulation coincide with pro-neuroplastic adaptations of serotonin systems. *Biol Psychiatry* 2014; **76**: 203–212.
95 Moshe H, Gal R, Barnea-Ygael N, Gulevsky T, Alyagon U, Zangen A. Prelimbic stimulation ameliorates depressive-like behaviors and increases regional bdnf expression in a novel drug-resistant animal model of depression. *Brain Stimul* 2016; **9**: 243–250.
96 Etievant A, Oosterhof C, Betry C, Abrial E, Novo-Perez M, Rovera R *et al.* Astroglial control of the antidepressant-like effects of prefrontal cortex deep brain stimulation. *EBioMedicine* 2015a; **2**: 898–908.
97 Insel N, Pilkiw M, Nobrega JN, Hutchison WD, Takehara-Nishiuchi K, Hamani C. Chronic deep brain stimulation of the rat ventral medial prefrontal cortex disrupts hippocampal-prefrontal coherence. *Exp Neurol* 2015; **269**: 1–7.
98 Bezchlibnyk YB, Stone SS, Hamani C, Lozano AM. High frequency stimulation of the infralimbic cortex induces morphological changes in rat hippocampal neurons. *Brain Stimul* 2017; **10**: 315–323.
99 Parthoens J, Verhaeghe J, Stroobants S, Staelens S. Deep brain stimulation of the prelimbic medial prefrontal cortex: quantification of the effect on glucose metabolism in the rat brain using [(18) F]FDG microPET. *Mol Imaging Biol* 2014; **16**: 838–845.
100 Dournes C, Beeske S, Belzung C, Griebel G. Deep brain stimulation in treatment-resistant depression in mice: comparison with the CRF1 antagonist, SSR125543. *Progr Neuropsychopharmacol Biol Psychiatry* 2013; **40**: 213–220.
101 Bambico FR, Bregman T, Diwan M, Li J, Darvish-Ghane S, Li Z *et al.* Neuroplasticity-dependent and -independent mechanisms of chronic deep brain stimulation in stressed rats. *Transl Psychiatry* 2015; **5**: e674.
102 Chakravarty MM, Hamani C, Martinez-Canabal A, Ellegood J, Laliberte C, Nobrega JN *et al.* Deep brain stimulation of the ventromedial prefrontal cortex causes reorganization of neuronal processes and vasculature. *NeuroImage* 2016; **125**: 422–427.
103 Bregman T, Nona C, Volle J, Diwan M, Raymond R, Fletcher PJ *et al.* Deep brain stimulation induces antidepressant-like effects in serotonin transporter knockout mice. *Brain Stimul* 2018; **11**: 423–425.
104 Srejic LR, Hamani C, Hutchison WD. High-frequency stimulation of the medial prefrontal cortex decreases cellular firing in the dorsal raphe. *Eur J Neurosci* 2015; **41**: 1219–1226.
105 Laver B, Diwan M, Nobrega JN, Hamani C. Augmentative therapies do not potentiate the antidepressant-like effects of deep brain stimulation in rats. *J Affect Disord* 2014; **161**: 87–90.
106 Bruchim-Samuel M, Lax E, Gazit T, Friedman A, Ahdoot H, Bairachnaya M *et al.* Electrical stimulation of the vmPFC serves as a remote control to affect VTA activity and improve depressive-like behavior. *Exp Neurol* 2016; **283**(Pt A): 255–263.
107 Torres-Sanchez S, Perez-Caballero L, Mico JA, Celada P, Berrocoso E. Effect of Deep Brain Stimulation of the ventromedial prefrontal cortex on the noradrenergic system in rats. *Brain Stimul* 2017; **11**: 222–230.
108 Mayberg HS. Limbic-cortical dysregulation: a proposed model of depression. *J Neuropsychiatr Clin Neurosci* 1997; **9**: 471–481.
109 Hamani C, Mayberg H, Stone S, Laxton A, Haber S, Lozano AM. The subcallosal cingulate gyrus in the context of major depression. *Biol Psychiatry* 2011; **69**: 301–308.
110 Etievant A, Lucas G, Dkhissi-Benyahya O, Haddjeri N. The role of astroglia in the antidepressant action of deep brain stimulation. *Front Cell Neurosci* 2015b; **9**: 509.
111 Hamani C, Nobrega JN. Reply to: deep brain stimulation for depression: is it a gray or white "matter"? *Biol Psychiatry* 2016; **80**: e45.
112 Laxton AW, Lipsman N, Lozano AM. Deep brain stimulation for cognitive disorders. *Handb Clin Neurol* 2013; **116**: 307–311.
113 Eggers AE. Treatment of depression with deep brain stimulation works by altering in specific ways the conscious perception of the core symptoms of sadness or anhedonia, not by modulating network circuitry. *Med Hypotheses* 2014; **83**: 62–64.
114 Broadway JM, Holtzheimer PE, Hilimire MR, Parks NA, Devylder JE, Mayberg HS *et al.* Frontal theta cordance predicts 6-month antidepressant response to subcallosal cingulate deep brain stimulation for treatment-resistant depression: a pilot study. *Neuropsychopharmacology* 2012; **37**: 1764–1772.
115 Neumann WJ, Huebl J, Brucke C, Gabriels L, Bajbouj M, Merkl A *et al.* Different patterns of local field potentials from limbic DBS targets in patients with major depressive and obsessive compulsive disorder. *Mol Psychiatry* 2014; **19**: 1186–1192.

116 Quraan MA, Protzner AB, Daskalakis ZJ, Giacobbe P, Tang CW, Kennedy SH *et al.* EEG power asymmetry and functional connectivity as a marker of treatment effectiveness in DBS surgery for depression. *Neuropsychopharmacology* 2014; **39**: 1270–1281.
117 Sun Y, Giacobbe P, Tang CW, Barr MS, Rajji T, Kennedy SH *et al.* Deep brain stimulation modulates gamma oscillations and theta-gamma coupling in treatment resistant depression. *Brain Stimul* 2015; **8**: 1033–1042.
118 Bewernick BH, Hurlemann R, Matusch A, Kayser S, Grubert C, Hadrysiewicz B *et al.* Nucleus accumbens deep brain stimulation decreases ratings of depression and anxiety in treatment-resistant depression. *Biol Psychiatry* 2010; **67**: 110–116.
119 Grubert C, Hurlemann R, Bewernick BH, Kayser S, Hadrysiewicz B, Axmacher N *et al.* Neuropsychological safety of nucleus accumbens deep brain stimulation for major depression: effects of 12-month stimulation. *World J Biol Psychiatry* 2011; **12**: 516–527.
120 Millet B, Jaafari N, Polosan M, Baup N, Giordana B, Haegelen C *et al.* Limbic versus cognitive target for deep brain stimulation in treatment-resistant depression: accumbens more promising than caudate. *Eur Neuropsychopharmacol* 2014; **24**: 1229–1239.
121 Sesia T, Bulthuis V, Tan S, Lim LW, Vlamings R, Blokland A *et al.* Deep brain stimulation of the nucleus accumbens shell increases impulsive behavior and tissue levels of dopamine and serotonin. *Exp Neurol* 2010; **225**: 302–309.
122 van Dijk A, Mason O, Klompmakers AA, Feenstra MG, Denys D. Unilateral deep brain stimulation in the nucleus accumbens core does not affect local monoamine release. *J Neurosci Methods* 2011; **202**: 113–118.
123 van Dijk A, Klompmakers AA, Feenstra MG, Denys D. Deep brain stimulation of the accumbens increases dopamine, serotonin, and noradrenaline in the prefrontal cortex. *J Neurochem* 2012; **123**: 897–903.
124 McCracken CB, Grace AA. Nucleus accumbens deep brain stimulation produces region-specific alterations in local field potential oscillations and evoked responses in vivo. *J Neurosci* 2009; **29**: 5354–5363.
125 van der Plasse G, Schrama R, van Seters SP, Vanderschuren LJ, Westenberg HG. Deep brain stimulation reveals a dissociation of consummatory and motivated behaviour in the medial and lateral nucleus accumbens shell of the rat. *PLoS ONE* 2012; **7**: e33455.
126 Hamani C, Amorim BO, Wheeler AL, Diwan M, Driesslein K, Covolan L *et al.* Deep brain stimulation in rats: different targets induce similar antidepressant-like effects but influence different circuits. *Neurobiol Dis* 2014; **71**: 205–214.
127 Rummel J, Voget M, Hadar R, Ewing S, Sohr R, Klein J *et al.* Testing different paradigms to optimize antidepressant deep brain stimulation in different rat models of depression. *J Psychiatr Res* 2016; **81**: 36–45.
128 Kim Y, McGee S, Czeczor JK, Walker AJ, Kale RP, Kouzani AZ *et al.* Nucleus accumbens deep brain stimulation efficacy in ACTH-pretreated rats: alterations in mitochondrial function relate to antidepressant-like effects. *Transl Psychiatry* 2016a; **6**: e842.
129 Falowski SM, Sharan A, Reyes BA, Sikkema C, Szot P, Van Bockstaele EJ. An evaluation of neuroplasticity and behavior after deep brain stimulation of the nucleus accumbens in an animal model of depression. *Neurosurgery* 2011; **69**: 1281–1290.
130 Winter C, Bregman T, Voget M, Raymond R, Hadar R, Nobrega JN *et al.* Acute high frequency stimulation of the prefrontal cortex or nucleus accumbens does not increase hippocampal neurogenesis in rats. *J Psychiatr Res* 2015; **68**: 27–29.
131 Huguet G, Kadar E, Temel Y, Lim LW. Electrical stimulation normalizes c-Fos expression in the deep cerebellar nuclei of depressive-like rats: implication of antidepressant activity. *Cerebellum* 2017; **16**: 398–410.
132 Knight EJ, Min HK, Hwang SC, Marsh MP, Paek S, Kim I *et al.* Nucleus accumbens deep brain stimulation results in insula and prefrontal activation: a large animal FMRI study. *PLoS ONE* 2013; **8**: e56640.
133 Aouizerate B, Cuny E, Martin-Guehl C, Guehl D, Amieva H, Benazzouz A *et al.* Deep brain stimulation of the ventral caudate nucleus in the treatment of obsessive-compulsive disorder and major depression. Case report. *J Neurosurg* 2004; **101**: 682–686.
134 van den Munckhof P, Bosch DA, Mantione MH, Figee M, Denys DA, Schuurman PR. Active stimulation site of nucleus accumbens deep brain stimulation in obsessive-compulsive disorder is localized in the ventral internal capsule. *Acta Neurochir Suppl* 2013; **117**: 53–59.
135 Malone DA Jr.. Use of deep brain stimulation in treatment-resistant depression. *Cleveland Clin J Med* 2010; **77**(Suppl 3): S77–S80.
136 Strong DR, Haber SN, Tyrka AR, Bernier JA, Rassmussen SA, Greenberg BD. Reversible increase in smoking after withdrawal of ventral capsule/ventral striatum deep brain stimulation in a depressed smoker. *J Addict Med* 2012; **6**: 94–95.
137 Dougherty DD, Rezai AR, Carpenter LL, Howland RH, Bhati MT, O'Reardon JP *et al.* A randomized sham-controlled trial of deep brain stimulation of the ventral capsule/ventral striatum for chronic treatment-resistant depression. *Biol Psychiatry* 2015; **78**: 240–248.
138 Richardson RM, Ghuman AS, Karp JF. Results of the first randomized controlled trial of deep brain stimulation in treatment-resistant depression. *Neurosurgery* 2015; **77**: N23–N24.
139 Kubu CS, Brelje T, Butters MA, Deckersbach T, Malloy P, Moberg P *et al.* Cognitive outcome after ventral capsule/ventral striatum stimulation for treatment-resistant major depression. *J Neurol Neurosurg Psychiatry* 2017; **88**: 262–265.
140 Bergfeld IO, Mantione M, Hoogendoorn ML, Ruhe HG, Notten P, van Laarhoven J *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; **73**: 456–464.
141 Bergfeld IO, Mantione M, Hoogendoorn MLC, Ruhe HG, Horst F, Notten P *et al.* Impact of deep brain stimulation of the ventral anterior limb of the internal capsule on cognition in depression. *Psychol Med* 2017; **47**: 1647–1658.
142 Rauch SL, Dougherty DD, Malone D, Rezai A, Friehs G, Fischman AJ *et al.* A functional neuroimaging investigation of deep brain stimulation in patients with obsessive-compulsive disorder. *J Neurosurg* 2006; **104**: 558–565.
143 Van Laere K, Nuttin B, Gabriels L, Dupont P, Rasmussen S, Greenberg BD *et al.* Metabolic imaging of anterior capsular stimulation in refractory obsessive-compulsive disorder: a key role for the subgenual anterior cingulate and ventral striatum. *J Nucl Med* 2006; **47**: 740–747.
144 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.
145 Epstein J, Pan H, Kocsis JH, Yang Y, Butler T, Chusid J *et al.* Lack of ventral striatal response to positive stimuli in depressed versus normal subjects. *Am J Psychiatry* 2006; **163**: 1784–1790.
146 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. *Clin Case Rep* 2017; **5**: 679–684.
147 Mavridis IN. Deep brain stimulation for psychiatric disorders: Are nucleus accumbens and medial forebrain bundle two branches of the same tree? *Neurosci Biobehav Rev* 2015; **56**: 345–346.
148 Furlanetti LL, Coenen VA, Aranda IA, Dobrossy MD. Chronic deep brain stimulation of the medial forebrain bundle reverses depressive-like behavior in a hemiparkinsonian rodent model. *Exp Brain Res* 2015a; **233**: 3073–3085.
149 Furlanetti LL, Dobrossy MD, Aranda IA, Coenen VA. Feasibility and safety of continuous and chronic bilateral deep brain stimulation of the medial forebrain bundle in the naive Sprague-Dawley rat. *Behav Neurol* 2015b; **2015**: 256196.
150 Bregman T, Reznikov R, Diwan M, Raymond R, Butson CR, Nobrega JN *et al.* Antidepressant-like effects of medial forebrain bundle deep brain stimulation in rats are not associated with accumbens dopamine release. *Brain Stimul* 2015; **8**: 708–713.
151 Furlanetti LL, Coenen VA, Dobrossy MD. Ventral tegmental area dopaminergic lesion-induced depressive phenotype in the rat is reversed by deep brain stimulation of the medial forebrain bundle. *Behav Brain Res* 2016; **299**: 132–140.
152 Dandekar MP, Luse D, Hoffmann C, Cotton P, Peery T, Ruiz C *et al.* Increased dopamine receptor expression and anti-depressant response following deep brain stimulation of the medial forebrain bundle. *J Affect Disord* 2017; **217**: 80–88.
153 Coenen VA, Honey CR, Hurwitz T, Rahman AA, McMaster J, Burgel U *et al.* Medial forebrain bundle stimulation as a pathophysiological mechanism for hypomania in subthalamic nucleus deep brain stimulation for Parkinson's disease. *Neurosurgery* 2009; **64**: 1106–1114, discussion 1114-1105.
154 Cho YT, Fromm S, Guyer AE, Detloff A, Pine DS, Fudge JL *et al.* Nucleus accumbens, thalamus and insula connectivity during incentive anticipation in typical adults and adolescents. *NeuroImage* 2013; **66**: 508–521.
155 Galvez JF, Keser Z, Mwangi B, Ghouse AA, Fenoy AJ, Schulz PE *et al.* The medial forebrain bundle as a deep brain stimulation target for treatment resistant depression: a review of published data. *Progr Neuropsychopharmacol Biol Psychiatry* 2015; **58**: 59–70.
156 Coenen VA, Panksepp J, Hurwitz TA, Urbach H, Madler B. 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 Neuropsychiatr Clin Neurosci* 2012a; **24**: 223–236.
157 Coenen VA, Schlaepfer TE, Maedler B, Panksepp J. Cross-species affective functions of the medial forebrain bundle-implications for the treatment of affective pain and depression in humans. *Neurosci Biobehav Rev* 2011; **35**: 1971–1981.
158 Sesack SR, Pickel VM. Prefrontal cortical efferents in the rat synapse on unlabeled neuronal targets of catecholamine terminals in the nucleus accumbens septi and on dopamine neurons in the ventral tegmental area. *J Comp Neurol* 1992; **320**: 145–160.
159 You ZB, Chen YQ, Wise RA. Dopamine and glutamate release in the nucleus accumbens and ventral tegmental area of rat following lateral hypothalamic self-stimulation. *Neuroscience* 2001; **107**: 629–639.

160 Ferenczi EA, Zalocusky KA, Liston C, Grosenick L, Warden MR, Amatya D *et al.* Prefrontal cortical regulation of brainwide circuit dynamics and reward-related behavior. *Science* 2016; **351**: aac9698.
161 Taber MT, Das S, Fibiger HC. Cortical regulation of subcortical dopamine release: mediation via the ventral tegmental area. *J Neurochem* 1995; **65**: 1407–1410.
162 Sartorius A, Henn FA. Deep brain stimulation of the lateral habenula in treatment resistant major depression. *Med Hypotheses* 2007; **69**: 1305–1308.
163 Sartorius A, Kiening KL, Kirsch P, von Gall CC, Haberkorn U, Unterberg AW *et al.* Remission of major depression under deep brain stimulation of the lateral habenula in a therapy-refractory patient. *Biol Psychiatry* 2010; **67**: e9–e11.
164 Friedman A, Lax E, Dikshtein Y, Abraham L, Flaumenhaft Y, Sudai E *et al.* Electrical stimulation of the lateral habenula produces an inhibitory effect on sucrose self-administration. *Neuropharmacology* 2011; **60**: 381–387.
165 Kim Y, Morath B, Hu C, Byrne LK, Sutor SL, Frye MA *et al.* Antidepressant actions of lateral habenula deep brain stimulation differentially correlate with CaMKII/GSK3/AMPK signaling locally and in the infralimbic cortex. *Behav Brain Res* 2016b; **306**: 170–177.
166 Christoph GR, Leonzio RJ, Wilcox KS. Stimulation of the lateral habenula inhibits dopamine-containing neurons in the substantia nigra and ventral tegmental area of the rat. *J Neurosci* 1986; **6**: 613–619.
167 Ji H, Shepard PD. Lateral habenula stimulation inhibits rat midbrain dopamine neurons through a GABA(A) receptor-mediated mechanism. *J Neurosci* 2007; **27**: 6923–6930.
168 Kiening K, Sartorius A. A new translational target for deep brain stimulation to treat depression. *EMBO Mol Med* 2013; **5**: 1151–1153.
169 Geisler S, Trimble M. The lateral habenula: no longer neglected. *CNS Spectr* 2008; **13**: 484–489.
170 Kopell BH, Greenberg BD. Anatomy and physiology of the basal ganglia: implications for DBS in psychiatry. *Neurosci Biobehav Rev* 2008; **32**: 408–422.
171 Drevets WC. Functional anatomical abnormalities in limbic and prefrontal cortical structures in major depression. *Progr Brain Res* 2000; **126**: 413–431.
172 Velasco M, Velasco F, Jimenez F, Carrillo-Ruiz JD, Velasco AL, Salin-Pascual R. Electrocortical and behavioral responses elicited by acute electrical stimulation of inferior thalamic peduncle and nucleus reticularis thalami in a patient with major depression disorder. *Clin Neurophysiol* 2006; **117**: 320–327.
173 Jimenez F, Velasco F, Salin-Pascual R, Hernandez JA, Velasco M, Criales JL *et al.* A patient with a resistant major depression disorder treated with deep brain stimulation in the inferior thalamic peduncle. *Neurosurgery* 2005; **57**: 585–593, discussion 585-593.
174 Jimenez F, Velasco F, Salin-Pascual R, Velasco M, Nicolini H, Velasco AL *et al.* Neuromodulation of the inferior thalamic peduncle for major depression and obsessive compulsive disorder. *Acta Neurochir Suppl* 2007; **97**(Pt 2): 393–398.
175 Jimenez F, Nicolini H, Lozano AM, Piedimonte F, Salin R, Velasco F. Electrical stimulation of the inferior thalamic peduncle in the treatment of major depression and obsessive compulsive disorders. *World Neurosurg* 2013; **80**: S30 e17–25.
176 Raymaekers S, Luyten L, Bervoets C, Gabriels L, Nuttin B. Deep brain stimulation for treatment-resistant major depressive disorder: a comparison of two targets and long-term follow-up. *Transl Psychiatry* 2017; **7**: e1251.
177 Faggiani E, Delaville C, Benazzouz A. The combined depletion of monoamines alters the effectiveness of subthalamic deep brain stimulation. *Neurobiol Dis* 2015; **82**: 342–348.
178 Creed MC, Hamani C, Nobrega JN. Effects of repeated deep brain stimulation on depressive- and anxiety-like behavior in rats: comparing entopeduncular and subthalamic nuclei. *Brain Stimul* 2013; **6**: 506–514.
179 Schneider F, Habel U, Volkmann J, Regel S, Kornischka J, Sturm V *et al.* Deep brain stimulation of the subthalamic nucleus enhances emotional processing in Parkinson disease. *Arch Gen Psychiatry* 2003; **60**: 296–302.
180 Funkiewiez A, Ardouin C, Caputo E, Krack P, Fraix V, Klinger H *et al.* Long term effects of bilateral subthalamic nucleus stimulation on cognitive function, mood, and behaviour in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2004; **75**: 834–839.
181 Czernecki V, Pillon B, Houeto JL, Welter ML, Mesnage V, Agid Y *et al.* Does bilateral stimulation of the subthalamic nucleus aggravate apathy in Parkinson's disease? *J Neurol Neurosurg Psychiatry* 2005; **76**: 775–779.
182 Campbell MC, Black KJ, Weaver PM, Lugar HM, Videen TO, Tabbal SD *et al.* Mood response to deep brain stimulation of the subthalamic nucleus in Parkinson's disease. *J Neuropsychiatr Clin Neurosci* 2012; **24**: 28–36.
183 Eisenstein SA, Dewispelaere WB, Campbell MC, Lugar HM, Perlmutter JS, Black KJ *et al.* Acute changes in mood induced by subthalamic deep brain stimulation in Parkinson disease are modulated by psychiatric diagnosis. *Brain Stimul* 2014; **7**: 701–708.
184 Temel Y, Wilbrink P, Duits A, Boon P, Tromp S, Ackermans L *et al.* Single electrode and multiple electrode guided electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. *Neurosurgery* 2007; **61**(5 Suppl 2): 346–355, discussion 355-347.
185 Aono M, Iga J, Ueno S, Agawa M, Tsuda T, Ohmori T. Neuropsychological and psychiatric assessments following bilateral deep brain stimulation of the subthalamic nucleus in Japanese patients with Parkinson's disease. *J Clin Neurosci* 2014; **21**: 1595–1598.
186 Bejjani BP, Houeto JL, Hariz M, Yelnik J, Mesnage V, Bonnet AM *et al.* Aggressive behavior induced by intraoperative stimulation in the triangle of Sano. *Neurology* 2002; **59**: 1425–1427.
187 Sako W, Miyazaki Y, Izumi Y, Kaji R. Which target is best for patients with Parkinson's disease? A meta-analysis of pallidal and subthalamic stimulation. *J Neurol Neurosurg Psychiatry* 2014; **85**: 982–986.
188 Mahgoub NA, Kotbi N. Acute depression and suicidal attempt following lowering the frequency of deep brain stimulation. *J Neuropsychiatr Clin Neurosci* 2009; **21**: 468.
189 Appleby BS, Duggan PS, Regenberg A, Rabins PV. Psychiatric and neuropsychiatric adverse events associated with deep brain stimulation: A meta-analysis of ten years' experience. *Mov Disord* 2007; **22**: 1722–1728.
190 Narang P, Retzlaff A, Brar K, Lippmann S. Deep brain stimulation for treatment-refractory depression. *Southern Med J* 2016; **109**: 700–703.
191 Zhou C, Zhang H, Qin Y, Tian T, Xu B, Chen J *et al.* A systematic review and meta-analysis of deep brain stimulation in treatment-resistant depression. *Progr Neuropsychopharmacol Biol Psychiatry* 2018; **82**: 224–232.
192 Hamani C, Mayberg H, Snyder B, Giacobbe P, Kennedy S, Lozano AM. Deep brain stimulation of the subcallosal cingulate gyrus for depression: anatomical location of active contacts in clinical responders and a suggested guideline for targeting. *J Neurosurg* 2009; **111**: 1209–1215.
193 Schlaepfer TE. Deep brain stimulation for major depression-steps on a long and winding road. *Biol Psychiatry* 2015; **78**: 218–219.
194 Schlaepfer TE, Bewernick BH, Kayser S, Hurlemann R, Coenen VA. Deep brain stimulation of the human reward system for major depression--rationale, outcomes and outlook. *Neuropsychopharmacology* 2014; **39**: 1303–1314.
195 Nestler EJ, Carlezon WA Jr.. The mesolimbic dopamine reward circuit in depression. *Biol Psychiatry* 2006; **59**: 1151–1159.
196 Krishnan V, Nestler EJ. Linking molecules to mood: new insight into the biology of depression. *Am J Psychiatry* 2010; **167**: 1305–1320.
197 Coenen VA, Schlaepfer TE, Allert N, Madler B. Diffusion tensor imaging and neuromodulation: DTI as key technology for deep brain stimulation. *Int Rev Neurobiol* 2012b; **107**: 207–234.
198 Hoyer C, Sartorius A, Lecourtier L, Kiening KL, Meyer-Lindenberg A, Gass P. One ring to rule them all?--Temporospatial specificity of deep brain stimulation for treatment-resistant depression. *Med Hypotheses* 2013; **81**: 611–618.
199 Fernandes BS, Williams LM, Steiner J, Leboyer M, Carvalho AF, Berk M. The new field of 'precision psychiatry'. *BMC Med* 2017; **15**: 80.
200 Guinjoan SM, Mayberg HS, Costanzo EY, Fahrer RD, Tenca E, Antico J *et al.* Asymmetrical contribution of brain structures to treatment-resistant depression as illustrated by effects of right subgenual cingulum stimulation. *J Neuropsychiatr Clin Neurosci* 2010; **22**: 265–277.