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Efficacy and quality of life after 6–9 years of deep brain stimulation for depression

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ABSTRACT

Background: Given the invasiveness of deep brain stimulation (DBS), the effect should prove to be stable over the long-term and translate into an improvement of quality of life (QOL).
Objective: To study the effectiveness and QOL up to nine years after the DBS surgery.
Methods: We treated 25 adult patients with major depression with DBS of the ventral anterior limb of the internal capsule (vALIC). We followed them up naturalistically for 6–9 years after surgery (mean: 7.7 [SD:1.5] years), including a randomized crossover phase after the first year comparing sham with active DBS. Symptom severity was quantified using the Hamilton Depression Scale with response defined as a ≥50% decrease of the score compared to baseline. Quality of life was measured using the WHOQOL-BREF, assessing 5 domains (general, physical, psychological, social, environmental).
Results: Intention-to-treat response rates remained mostly stable from Year 3 to last follow-up (Year 3, 5 and 6: 40%; Year 4: 36%; Last observation: 44%). General, physical, psychological (all $P < 0.001$) and the environmental ($P = 0.02$) domain scores increased during DBS optimization and remained stable over the long term. No statistically significant changes were detected on the social domain. Patients scored significantly higher during active than sham DBS on the psychological, social and environmental domains, and trended towards a higher score on the general and physical domains.
Conclusion: This study shows continued efficacy of vALIC DBS in depression, which translates into an improvement of QOL providing further support for DBS as a durable treatment for TRD.

1. Introduction

Treatment-resistant depression (TRD) is one of the most challenging problems in psychiatry. Not only does major depression affect 5% of the population every year [1], but also one third of patients do not respond to four different antidepressant strategies [2]. TRD has a devastating impact on personal as well as societal levels, given the high suicide risk [3], decreased levels of daily functioning [4], higher health care utilization and decreased productivity [5]. Finding new treatment strategies for TRD is thus of utmost importance.

One such strategy is deep brain stimulation (DBS). DBS works by modulating brain circuitry through electrical current given off by electrodes implanted in specific brain areas. Electrical parameters (e.g. amplitude) can be adapted to optimize effectiveness and minimize adverse events. Open-label trials have shown response rates of 40–60% following DBS targeted at the subcallosal cingulate gyrus (SCG) [6–10], the bed nucleus of the stria terminalis (BST) [11] or ventral capsular and ventral striatal (VC/VS) areas [12,13], and up to 80% after medial forebrain bundle (MFB) DBS [14,15].

Abbreviations: BST, bed nucleus of the stria terminalis; DBS, deep brain stimulation; HAM-D, Hamilton Depression Rating Scale; MFB, medial forebrain bundle; SCG, subcallosal gyrus; TRD, treatment-resistant depression; QOL, quality of life; vALIC, ventral anterior limb of the internal capsule; VC/VS, ventral capsule / ventral striatum.

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However, a randomized controlled trial (RCT) of SCG as well as VC/VS DBS failed to find a difference between sham and active DBS [16,17]. Other RCTs, however, have shown superiority of active DBS targeted to the ventral anterior limb of the internal capsule (vALIC), BST or MFB compared to sham DBS [11,18,19].

Given the cost and its invasiveness, the effectiveness of DBS should also be established in the long-term. So far, only five studies have focused on outcomes of different DBS targets after 3 years or later [11,14,20–22], which mostly find continued efficacy in those who respond to DBS. Optimally, symptomatic improvement should also translate into an increased quality of life (QOL), which quantify the patient's own views on social relationships, work, health and (dis)ability [23]. Patients with TRD score in severely disabled ranges and these scores correlate only modestly with clinician or patient rated symptom severity [24]. The impact of DBS on QOL, however, has only been scarcely reported in mostly small, open-label studies. These show that QOL scores increase in concordance with symptomatic improvement in the first year [11,25–27], and increase further in the years thereafter, despite a stabilization of symptom improvement [13,21].

Here we aim to quantify effectiveness and QOL over the course of six to nine years following vALIC DBS in patients with TRD. In addition, we examine the acute effects on QOL of turning DBS off in a randomized, controlled crossover phase.

2. Methods

Between March 2010 and May 2014, we included 25 patients with TRD in one academic and one general hospital in The Netherlands (Amsterdam UMC, location AMC, Amsterdam, and ETZ, location Elisabeth, Tilburg) in a clinical trial with last follow-up completed in August 2016. The study was approved by the Medical Ethical Boards of both hospitals and was registered in the Dutch Trial Register (http://www.trialregister.nl/trial/2001). All patients gave their written informed consent for inclusion in the clinical trial. The clinical results of the first two years have been detailed earlier [18,28]. In September 2019, we asked consent from all participants to re-evaluate symptom severity and a quality of life questionnaire as well as to analyze the data collected in clinical practice after the trial, which was given by all but 3 patients. The medical ethical board of the AMC ruled that no formal medical-ethical approval was needed for this analysis.

Patients had to meet the following inclusion criteria for the original trial: aged between 18 and 65; a primary diagnosis of MDD which was treatment resistant, defined as: a failure of at least two distinctly different classes of second-generation antidepressants (e.g. Selective Serotonin Reuptake Inhibitor, Selective Norepinephrine Reuptake Inhibitor) *and* one trial of a tricylic antidepressant (TCA) *and* one trial of TCA with lithium addition *and* one trial of a Monoamine Oxidase Inhibitor *and* ≥6 sessions of bilateral ECT. Patients who fulfilled the above criteria and were kept stable with maintenance ECT, but relapsed after discontinuation hereof were also eligible; had a Hamilton Depression Rating Scale – 17 items (HAM-D-17) score of at least 18; a Global Assessment of Function (GAF) score of a maximum of 45, which was persistent for at least 2 years. Exclusion criteria were: bipolar disorder or a (history of) psychosis; substance abuse in the past 6 months; comorbid neurologic disorders; an unstable physical condition; and pregnancy or general contra-indications for DBS surgery.

2.1. DBS surgery and optimization

DBS surgery and optimization were described in detail earlier [18]. In summary, two four-contact electrodes (model 3389, Medtronic) were implanted bilaterally and connected to a neurostimulator (Activa PC) at initial implant, which was replaced with a rechargeable Activa RC after depletion. The most ventral contact point was positioned in the nucleus accumbens and the three upper contact points in the vALIC. Following a three-week recovery period after surgery, a standardized, open-label DBS parameter optimization period of maximally 52 weeks started. A psychologist or psychiatrist tested combinations of active contacts, voltage, pulse width and frequency for optimal efficacy.

2.2. Study design

The study consisted of several phases: baseline (1–3 weeks before surgery); the surgery and subsequent 3-week recovery phase with DBS still off; an open-label optimization of DBS parameters of maximally 12 months; a randomized, double-blind crossover phase (see below for a detailed description); a maintenance phase of 12 months; and lastly, a naturalistic follow-up phase until September 2019 (5–9 years after surgery). In the maintenance phase patients were seen at least once every 6 months and in the naturalistic follow-up phase on clinical indication only. Consequently, responders to DBS were seen less often than those who did not or only partially responded. Clinicians strived to keep medication stable during the open label phase, but were allowed to change medication on clinical indication. From the maintenance phase onwards, clinicians were free to change DBS parameters and medication on indication (see Supplementary Tables 1 and 2 for medication use and DBS settings at different sessions).

The randomized, crossover phase consisted of two blocks of six weeks during which the DBS stimulator was on (active stimulation) or off (sham stimulation). The settings were blinded for patients, raters and clinicians. The phases were terminated if the treating psychiatrist or research team deemed it clinically indicated and the HAM-D-17 ≥ 15, or if the patient requested discontinuation. In these cases, patients crossed over to the next phase while blinding was maintained. Medication and DBS settings (except for stimulation 'on' or 'off') were kept stable during the crossover phase.

Clinicians assessed symptom severity and in addition, patients rated their quality of life at 7 time points (see Fig. 1): three weeks before DBS surgery (Baseline), three weeks after the surgery with stimulation still off (T1), after the optimization of DBS settings (T2), after the first (T3) and second crossover block (T4), after the maintenance phase (T5) and after the naturalistic follow-up phase (T6, between 5 and 9 years after surgery). Between T5 and T6, HAM-D was also repeatedly administered in patients during the naturalistic outpatient visits, but quality of life was only assessed at the aforementioned end points.

2.3. Outcome measures

Clinicians rated symptom severity with the Hamilton Depression Rating Scale, 17 items (HAM-D, range 0–52), with higher scores representing more severe symptoms [29]. Response was defined as ≥50% reduction of HAM-D score compared to baseline. Response status was further subdivided into four categories, as done before [28]: strong improver (≥75% reduction), clear improver (≥50%, less than 75%), partial improver (≥25%, less than 50%) and no/minimal improver (<25% reduction).

To quantify quality of life, patients filled in the World Health Organization Quality of Life scale, brief version (WHOQOL-BREF) [30,31]. The WHOQOL-BREF consists of 26 Likert items (range 1–5) falling on 5 domains: physical (7 items), psychological (6 items), social (3 items), environmental (8 items) and general (2 items). Domain scores are calculated as the mean score of the items multiplied by four (range 4–20), except for the general domain,

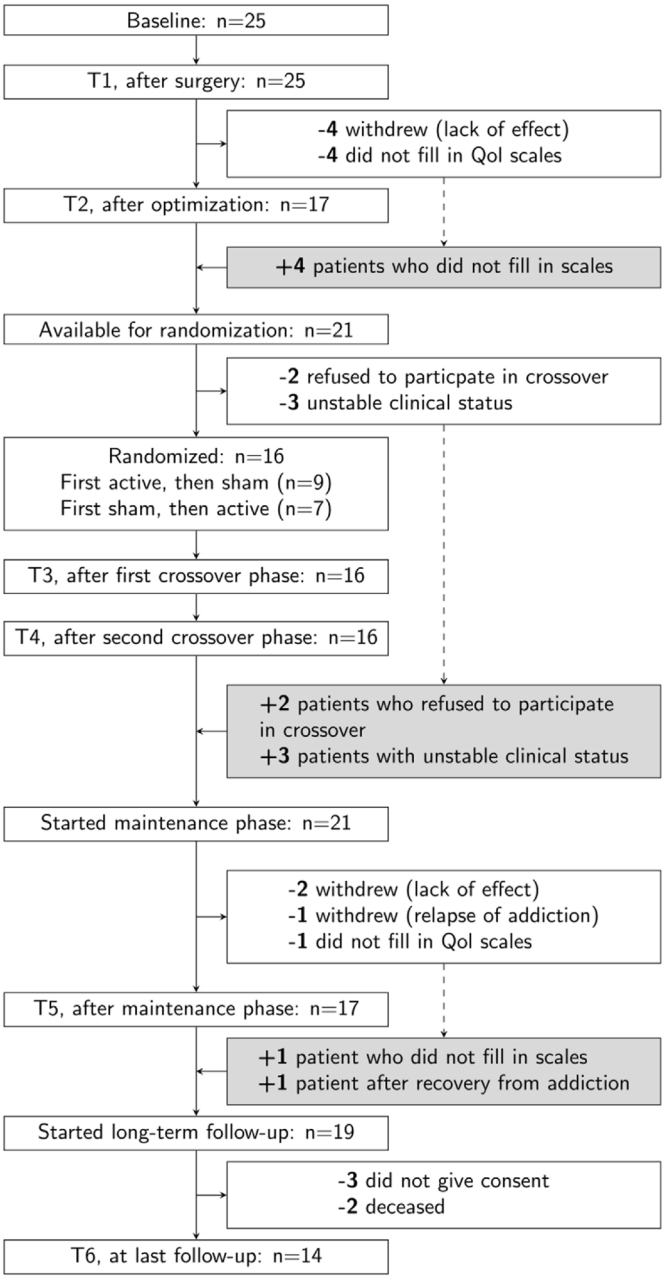

Fig. 1. Flowchart of the study and drop-outs Abbreviation: QoL = Quality of Life.

which is the sum score of the 2 items (range 2–10). Higher scores represent better QOL.

In addition, we recorded serious adverse events (SAEs) in clinical practice during the naturalistic follow-up phase (between T5 and T6). An SAE is defined as any untoward medical occurrence - not necessarily causally related to DBS - which leads to death, a life threatening situation, (prolongation of) hospitalization, persistent disability, or a congenital birth defect [32].

2.4. Statistical analysis

The effectiveness over the long term is analyzed descriptively as response rates and mean and standard deviation per year from 3 years after surgery onwards. To select the most representative HAM-D score for every subject in every year, we entered all recorded HAM-D scores and their recording dates into a database. Then we selected the recorded HAM-D, which was closest to every full year since the surgery±the half year before and after. For example, the HAM-D for year 3 was identified as the HAM-D score closest to 1095 days since the surgery from the pool of scores between 912 and 1277 days. If in the interval of any given year no HAM-D score was recorded, we carried the observation of the previous year forward. A last observation carried forward (LOCF) method is needed, since the data wat naturalistically collected in clinical practice. Consequently, there is variability between subjects in the number and the time interval of recorded HAM-D scores, which can introduce bias in both directions. On the one hand, non-responders tend to visit the hospital more often than responders, introducing a bias towards higher HAM-D scores and lower response rates in some years. On the other, non-responders might withdraw from the treatment, because of a lack of effect, resulting in lower average HAM-D scores in later years. To get a reliable estimate of the number of responders, we have assumed that the HAM-D and responder status remain stable until a new measurement. We deem the LOCF method justifiable, since it is standard practice to record a new HAM-D in case of a relapse or a major symptom improvement. Of the patients who refused consent for the retrospective analysis in the naturalistic follow-up phase, we used the HAM-D score and associated response status of T5. For the clinical results and HAM-D scores from up to T5 (on average 2 years after surgery) we refer to previous publications [18,28].

The change over time of the WHOQOL subdomains (general, physical, psychological, social and environmental) are analyzed separately with 5 linear, mixed models, which adjust for missing data using maximum likelihood estimation. The domain score is entered as the dependent variable, session as independent factor (levels: Baseline, T1, T2, T5, T6) with a random intercept with subject as grouping variable. Post-hoc, we added HAM-D score as an independent covariate to the models of the domains that increased over time, to explore whether quality of life was independent from symptom severity. As a second check, we performed a post-hoc model with response status (response/non-response) at every session added as a covariate, to explore whether quality of life was independent of response status.

The WHOQOL domain scores in the crossover active/sham phase are also analyzed using linear mixed models. The dependent variable is the domain score, and independent factors are session (levels: T3, T4) and stimulation setting (levels: On, Off). The intercept is made random based on subject as grouping variable. We tested for carry-over effects using the interaction effect between session and stimulation setting, but this turned out to be non-significant in all models. Therefore, the interaction term was removed from all models to get a more accurate estimation of the main effects.

The sample size was based on the original clinical trial described by Bergfeld et al. [18]. All analyses were done with R, version 3.6.1 [33]. The packages 'lme4' and 'lmerTest' were used to estimate the mixed models and derivate the p-values [34,35]. A P-value of <0.05 was considered statistically significant.

3. Results

Between March 2010 and May 2014, 25 patients were included in the trial, of which 17 provided QOL data at T2 (after the DBS parameter optimization), 17 at T5 (one year after optimization), and 14 at T6 (September 2019, on average 7.7 years after surgery, SD 1.5 years). In the crossover phase, 16 patients provided QOL data after both phases. Fig. 1 shows a flowchart of the study with a description of the reasons for drop-out. In Table 1 descriptive variables (as they were at inclusion) of the sample at baseline and T6 are given.

Table 1
Descriptive variables before surgery (at baseline and T6).

		Baseline (n = 25)			T6 (n = 14)		
		N	*Mean*	*SD*	*N*	*Mean*	*SD*
Sex	*Female*	17			11		
	Male	8			3		
Age		25	53,2	8,4	14	52,1	7,2
Education (ISCED 2011)		25	4,0	1,9	14	3,6	1,8
Estimated IQ		25	95,3	15,0	14	96,5	15,2
Age of onset (diagnosis)		25	37,8	9,8	14	37,3	8,9
Nr episodes	*1 episode*	11			6		
	2 episodes	3			3		
	>2 episodes	11			5		
Duration episode (months)		25	83,8	76,2	14	91,0	75,9
Nr past medications		25	10,8	3,3	14	10,1	2,9
Nr past ECT series		25	2,3	1,7	14	2,0	1,0
Nr past ECT sessions		25	68,9	103,6	14	52,5	48,3
Suicide attempt, life	*No*	18			10		
	Yes	7			4		

Note: the table displays the descriptive variables before surgery of both the entire sample (n = 25) and the subsample who filled in the WHOQOL at T6 (n = 14). Abbreviations: ECT = Electroconvulsive therapy; Nr = Number; IQ=Intelligence Quotient; ISCED=International Standardized Classification of Education.

Intention-to-treat response rates remained mostly stable from Year 3 to last follow-up (Year 3, 5 and 6: 40%; Year 4: 36%; Last observation: 44%, see Table 2 and Supplementary Fig. 1). The number of strong improvers (>75% HAMD-D decrease) relative to clear improvers (>50% HAMD-D decrease) increases over time: from 6:4 in Year 3, 5 and 6 and 6:3 in Year 4, to 9:2 at the last observation. The mean intention-to-treat HAM-D score decreased slightly from Year 3 (15.2, SD: 9.9) to Year 6 (14.1, SD: 9.6) and further to 12.0 (SD: 9.2) at the last observation (see Table 2).

A statistically significant increase over time was found on the General ($F(4,73.5) = 12.5$, $P < 0.001$), Physical ($F(4,72.2) = 12.4$, $P < 0.001$), Psychological ($F(4,71.9) = 14.8$, $P < 0.001$) and Environmental ($F(4,69.5) = 3.1$, $P = 0.02$) domains (see Table 3 and Fig. 2). Post-hoc exploration of the coefficients shows an increase from Baseline to T2 (after optimization), which remains stable until T6. No statistically significant differences over time were found on the social domain ($F(4,71.2) = 0.9$, $P = 0.49$).

Post-hoc, we added HAM-D score as an independent covariate to the models of the domains that increased over time, to explore whether quality of life was independent from symptom severity. The HAM-D was a significant predictor for the domain scores in all 4 models, but the effect for time remained significant for the physical ($F(4,72.8) = 2.7$, $P = 0.04$) and psychological domains ($F(4,71.2) = 4.4$, $P = 0.003$). In addition, the effect of time trended towards statistical significance for the general domain ($F(4,73.8) = 2.4$, $P = 0.06$). However, the effect of time turned out to be non-significant for the environmental domain after correcting for HAM-D score ($F(4,68.2) = 0.9$, $P = 0.45$). Similarly, the quality of life increased significantly more in responders than non-responders in all four models. In these models, the effect of time remained significant for the physical (F(4,71.3)-3.3, P = 0.02), psychological ($F(4,70.5) = 5.3$, $P < 0.001$) and general ($F(4,73.0) = 2.6$, $P = 0.04$) domains, but not for the environmental domain (F4,68.0) = 0.5, P = 0.72).

Table 2
HAM-D scores and response rates over time.

N = 25	HAM-D		Improvement, n			
	Mean	SD	No/Minimal	Partial	Clear	Strong
Baseline	22,2	4,9	25	0	0	0
Year 3	15,2	9,9	11	4	4	6
Year 4	15,0	9,8	11	5	3	6
Year 5	14,2	9,4	10	5	4	6
Year 6	14,1	9,6	9	6	4	6
Last observation	12,0	9,2	7	7	2	9

Note: the table displays the mean and SD of the HAM-D and the improvement status on an intention-to-treat basis. All rows, therefore, are based on n = 25. In case of missing values, we carried the last observation forward, until a new observation was done. Improvement status was defined as: strong as ≥75%, clear as ≥50% and <75%, partial as ≥25% and <50%, and no/minimal as <25% reduction of HAM-D score compared to baseline. Abbreviations: HAM-D = Hamilton Depression Rating Scale; SD=Standard deviation.

In the crossover phase we included 16 patients, of which 9 were randomized to active DBS first and 7 to sham DBS first. After correcting for order effects, patients scored statistically significant higher in the active versus sham phase on the WOQOL Psychological ($F(1,13.7) = 8.8$, $P = 0.01$), Social ($F(1,12.9) = 11.1$, $P = 0.005$) and Environmental ($F(1,13.0) = 7.4$, $P = 0.02$) domains. A trend towards statistically significant higher score was found on the General ($F(1,13.7) = 4.1$, $P = 0.06$) and Physical ($F(1,12.2) = 4.3$, $P = 0.06$) domains.

In the naturalistic follow-up phase (2–9 years after surgery), we recorded 12 SAEs in 10 patients (see Table 4). Two patients died of somatic reasons (liver failure and cancer). In addition, one non-responder attempted suicide in this period, which was not related in time to DBS parameter changes or malfunctioning of the DBS system. Furthermore, one responder had to be admitted for one month due to suicidal ideation after a temporary relapse, which also was not related to parameter change or system malfunctioning. The patient recovered completely during the admittance after increasing the amplitude. Lastly, the extension cable of a responder broke, leading to unilateral malfunctioning of an electrode and a subsequent increase in depressive symptoms. The patient recovered completely after replacing the extension cable.

4. Discussion

This study shows that the symptomatic improvement of patients with treatment-resistant depression after vALIC DBS in the first two years is maintained up to 7.5 years after surgery. This is accompanied by higher ratings of quality of life, which are partly independent of symptomatic changes.

The maintained improvement over several years is in line with other studies that have reported on DBS after 3 years or more. Continued efficacy has been shown after DBS targeted at the SCG (up to 8 years after surgery) [20,21], BST (up to 7 years) [11] and MFB (up to 5 years) [14,22]. Importantly, the symptom improvement translates into an increased satisfaction with everyday functioning. This is in concordance with findings of Kennedy et al. (2011) and Raymaekers et al. (2017), who also showed sustained increases in quality of life in patients with depression.

These combined results show that DBS induces a long-lasting and durable effect in patients with highly resistant depression, irrespective of targeting. This is a promising outcome, certainly in light of the high relapse rates seen after other treatments for TRD such as electroconvulsive therapy [36]. It also justifies the invasiveness and high frequency of visits optimizing parameters. The durable improvement also most likely would result in cost-effectiveness of DBS in the long term. In patients with obsessive-compulsive disorder (OCD), the initial costs of surgery and optimization were estimated to be cost-effective over the run of four years [37] – a time frame which is easily met by this and aforementioned studies. However, a formal estimation of cost-effectiveness is yet to be performed.

Interestingly, the physical and psychological quality of life improve more than can be explained by symptom improvement alone. In a previous study on vALIC DBS in patients with OCD, we

Table 3
WHOQOL scores over time and in the crossover phase.

				WHOQOL domains				
		HAM-D	R/NR	General	Physical	Psychological	Social	Environmental
Baseline	*N*	25	0/25	25	25	25	25	24
	Mean	22,2		2,9	9,7	7,4	11,6	13,4
	SD	4,9		1,0	1,6	2,0	3,2	2,2
T1	*N*	25	1/24	25	25	25	25	25
	Mean	21,9		3,3	9,6	7,4	11,1	13,3
	SD	6,2		1,2	1,6	1,8	2,6	1,8
T2	*N*	17	8/9	17	17	17	17	17
	Mean	14,5		4,8	12,0	9,7	11,7	14,7
	SD	9,1		2,4	3,0	3,4	3,4	2,2
T5	*N*	17	7/10	17	17	17	17	17
	Mean	14,1		5,3	12,7	10,9	12,5	14,4
	SD	9,3		2,3	3,5	4,1	3,6	2,9
T6	*N*	14	9/5	14	14	14	14	14
	Mean	8,9		5,5	12,8	10,8	11,8	14,6
	SD	7,9		2,0	3,4	2,9	3,8	2,1
Crossover phase								
T3	*N*	16	5/11	16	15	15	15	15
	Mean	16,0		4,6	12,3	10,3	13,2	14,7
	SD	7,8		2,5	3,6	4,1	3,7	2,8
T4	*N*	16	2/14	16	16	16	16	16
	Mean	20,7		4,0	10,7	8,5	11,2	13,4
	SD	7,8		1,8	2,5	2,7	3,0	2,1
Sham	*N*	16	0/16	16	15	15	15	15
	Mean	23,1		3,6	10,5	8,0	11,3	13,4
	SD	5,1		1,4	2,0	2,1	3,2	2,1
Active	*N*	16	7/9	16	16	16	16	16
	Mean	13,6		5,0	12,4	10,6	12,9	14,6
	SD	7,8		2,6	3,7	4,1	3,7	2,8

Note: Baseline: before DBS surgery; T1: 3 weeks after surgery with stimulation still off; T2; after DBS parameter optimization (on average one year after surgery); T3: after the first crossover phase (n = 9 active DBS, n = 7 sham DBS); T4: after the second crossover phase (n = 7 active DBS, n = 9 sham DBS); T5: after the maintenance phase (1 year after T2); T6: after the long-term follow-up (on average 7.7 years after surgery). Mean and SD of HAM-D and IDS-SR scores at T2 and T5 are calculated for the subjects who also filled in the WHOQOL. Therefore, these numbers slightly differ from those presented in Bergfeld et al. (2016) and Van der Wal et al. (2020). At T3, on several domains one patient did not fill in sufficient items to calculate the domain score. Abbreviations: HAM-D = Hamilton Depression Rating Scale; IDS-SR=Inventory of Depressive Symptamotology-Self Report; R/NR=Responders/Non-responders (response defined as ≥50% reduction of HAM-D score relative to baseline); SD=Standard deviation; WHOQOL=World Health Organization - Quality of Life.

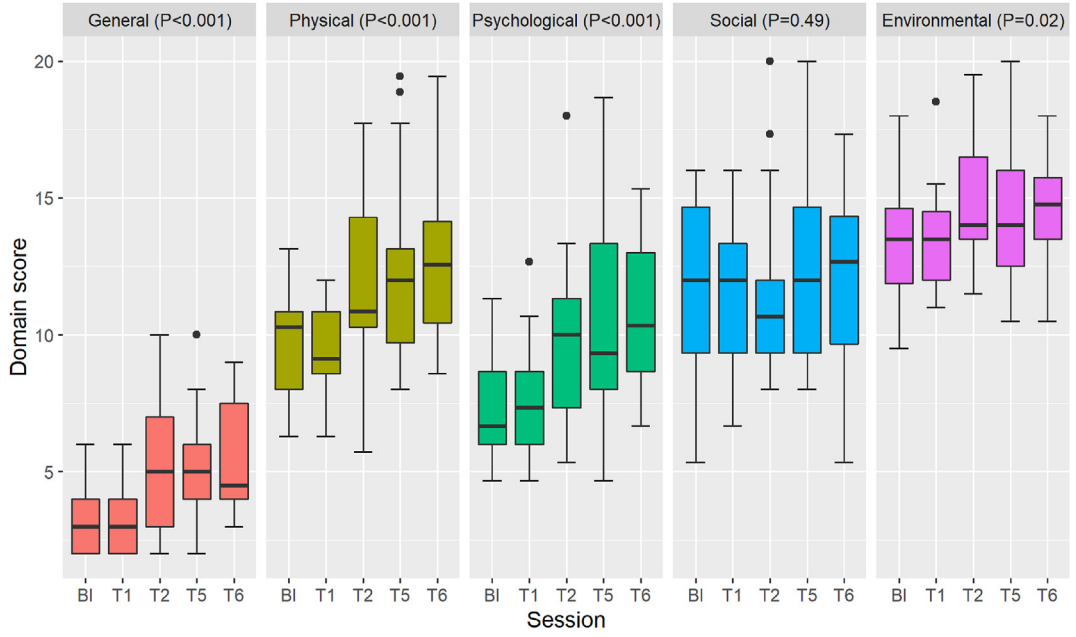

Fig. 2. Boxplot of WHOQOL domain scores over time *Note:* The figure shows the WHOQOL scores over time, excluding the scores from the crossover phase (T3 and T4). The P-values in the headings represent the effect of time from the mixed models. The boxes represent the interquartile range (IQR, i.e. between quartiles 1 and 3), with the line representing the median. The bars represent the range, with the dots being identified as outliers (i.e. more than 1.5*IQR above or under the IQR). Baseline: before DBS surgery; T1: 3 weeks after surgery with stimulation still off; T2; after DBS parameter optimization (on average one year after surgery); T5: after the maintenance phase (1 year after T2); T6: after the long-term follow-up (on average 7.7 years after surgery). Note that the General domain score ranges from 2 to 10, all other domain scores range from 4 to 20. Abbreviation: Bl = Baseline; WHOQOL: World Health Organization – Quality of Life.

Table 4
Serious adverse events since T5.

Phase	Relation to DBS	Serious adverse event	Nr Patients	Nr Events
Stimulation	Unrelated	Deceased (somatic cause)	2	2
Stimulation	Unrelated	Transient ischemic attack	1	2
Stimulation	Unrelated	Myocardial infarction	1	1
Stimulation	Unrelated	Pneumonia with lung embolisms	1	1
Stimulation	Unclear	Suicidal ideation	1	1
Stimulation	Unclear	Suicide attempt	1	1
Stimulation	Unclear	Syncope, possible seizure	1	1
Surgery	Probably	Dyspnea after IPG replacement	1	1
Surgery	Probably	Relapse in depression after IPG replacement	1	1
DBS system	Certainly	Break in extension cable	1	1

Note: Phase describes with which phase the adverse event was temporally related; Relation to DBS describes an evaluation of whether the AE was causally related to DBS. Abbreviations: DBS = deep brain stimulation; Nr = number.

did not find correlations between symptom and QOL improvement. Possibly, the modulation of the reward network by vALIC DBS may impact QOL directly by increasing motivation, vitality or drive [38]. This might also explain the acute decrease of QOL during sham DBS off in the crossover phase.

Most quality of life domains improve over time, except for the social domain. This is in line with QOL ratings in patients with OCD after vALIC DBS [39]. Treatment with CBT or SSRI, on the other hand, often results in an increase of social quality of life in patients with depression [40,41]. This could be due to lower levels of treatment-resistance in these trials. The more chronic disease course could have led to a neglect of personal relationships or even divorce, making it more difficult to re-establish social relationships than after a less chronic course. Alternatively, increased assertiveness or a change from a patient to a healthy role as a result of DBS sometimes results in conflicts with spouses or friends [42].

In terms of safety, we recorded a total of 12 serious AEs in the 2–9 years after surgery. Two patients died in this period, both as a result of somatic conditions and neither as a result of depression nor DBS. Importantly, only one suicide attempt was recorded, which is far less than the number recorded in the first two years after DBS (5 suicide attempts), indicating a stabilization of suicide risk on the long term [18,28]. This could be due to non-responding patients stopping the treatment after several years, but also to the gradual increase in quality of life over the years.

This study has obvious limitations given the naturalistic, open-label design of the long-term follow-up phase. This means we cannot causally attribute the continued efficacy and the possible slow further improvement to DBS. Changes in medication, DBS settings or the addition of psychotherapy might have contributed to the effect, amongst other things such as the psychosocial situation of the patient. However, it is very unlikely this improvement would have arisen without DBS in this severely affected group. In addition, QOL scales quantify a person's views on several domains, but does not quantify an actual functional change. For instance, someone can experience the same amount of physical complaints over time, but suffer less from them (e.g. because the patients has learned to focus on other things than the physical complaints). Future work should explore whether there QOL improvement is caused by functional change or other mechanisms. Moreover, we only followed 25 patients, of which 14 filled in QOL scales at the last follow-up point. This drop-out rate is similar to other studies with long-term follow-up [11,20,21], but nonetheless, we lack the power to detect subtle changes over time. Furthermore, it might have led to an overestimation of QOL scores at T6, since non-responders are more likely to discontinue DBS. We have attempted to reduce this bias by running multilevel models, which correct for missing values with maximum likelihood estimation.

5. Conclusions

In conclusion, DBS in the vALIC induces a long-lasting improvement in a group of patients with severe TRD, and the improvement in symptoms is translated into an increased satisfaction with everyday life. In addition, the treatment also seems to be safe, given the minimal number of SAEs. This shows DBS could be a suitable and durable treatment option for TRD. Future studies should focus on improving social quality of life and attempt to formally quantify the cost-effectiveness of DBS.

CRediT authorship contribution statement

Isidoor O. Bergfeld: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Visualization, Project administration, Funding acquisition. **Pieter Ooms:** Conceptualization, Validation, Investigation, Writing – original draft, Writing – review & editing, Funding acquisition. **Anja Lok:** Investigation, Writing – original draft, Writing – review & editing. **Lara de Rue:** Validation, Investigation, Writing – original draft, Writing – review & editing. **Pieter Vissers:** Investigation, Writing – review & editing. **Dirk de Knijff:** Investigation, Writing – review & editing. **Ferdinand Horst:** Investigation, Writing – review & editing. **Guus Beute:** Investigation, Writing – review & editing. **Pepijn van den Munckhof:** Investigation, Writing – review & editing. **P. Richard Schuurman:** Conceptualization, Investigation, Writing – review & editing, Supervision, Funding acquisition. **Damiaan Denys:** Conceptualization, Investigation, Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2022.06.010.

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