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Long-Term Outcome of Thermal Anterior Capsulotomy for Chronic, Treatment-Refractory Depression

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Background: There is very limited evidence for the efficacy of any specific therapeutic intervention in chronic, treatment-refractory, Major Depression. Thermal Anterior Capsulotomy (ACAPS) is a rarely-performed but established therapeutic procedure for this patient group. Whilst benefit has been claimed, previous ACAPS reports have provided limited information. Detailed prospective reporting of therapeutic effects and side-effects is required.

Objective: To report a prospective study of therapeutic effect, mental status, quality of life, social functioning, and neurocognitive functioning in individuals with chronic treatment-refractory Major Depression, treated with ACAPS.

Method: A prospective case series of 20 patients treated by ACAPS between 1992 and 1999 were reassessed at a mean follow-up of 7.0 ± 3.4 years. Data were collected preoperatively and at long-term follow-up. Structural magnetic resonance imaging was performed in 14 participants.

Results: According to *a priori* criteria, at long-term follow-up, 50% were classified as 'responders', 40% as 'remitters'. Fifty-five percent were classified as 'improved'; 35% were 'unchanged'; and 10% had 'deteriorated'. Neurocognitive and personality testing were not significantly different at follow up. A trend towards improvement in some aspects of executive neuropsychological functioning was observed. Significant adverse effects were infrequent and there were no deaths.

Conclusions: ACAPS may represent an effective intervention for some patients with chronic, disabling, treatment-refractory Major Depression that has failed to respond to other therapeutic approaches. The adverse effect burden within this population was modest, with no evidence of generalised impairment of neurocognitive functioning.

INTRODUCTION

Chronic depression, defined by DSM-IV as an episode persisting for over two years in duration, occurs in approximately 20% of patients with major depression.[1, 2] Remission rates decline substantially with increasing numbers of failed antidepressant trials, with one-third of individuals not remitting after four antidepressant trials.[3] There is limited evidence to support specific interventions for chronic treatment-refractory depression.[4] In recent years, Vagus Nerve Stimulation (VNS), Deep Brain Stimulation (DBS) and the Cognitive Behavioural Analysis System of Psychotherapy (CBASP)[5, 6] have been reported to confer benefit. However, numbers of patients treated by DBS remain low with limited long term data. Also, efficacy for VNS and CBASP appears modest compared with treatment-as-usual[7] and there is no evidence for either of these treatments being effective in chronic, highly treatment-refractory populations such as reported here.

First described by Talairach in 1949, Anterior Capsulotomy (ACAPS) places lesions in the anterior one-third of the anterior limb of the internal capsule, a large white-matter bundle connecting prefrontal and anterior cingulate cortices with the thalamus, hippocampus, and amygdala. ACAPS lesions are generated by the thermal effects of radiofrequency current or focal irradiation. Whilst several published studies report the clinical outcomes of ACAPS for Obsessive-Compulsive Disorder[8] and anxiety disorders,[9] there is only one report on the outcome of ACAPS as a treatment for depression. Herner (1961) described outcomes for 19 patients with a diagnosis of “*a depressive state*” (not otherwise defined clinically), treated by thermal ACAPS with a maximum follow-up of two years.[10] Fourteen (74%) were rated as showing

“*permanent improvement*”; three (16%) showed “*temporary improvement*”; one (5%) was “*unchanged*”; and one (5%) was “*worse*”. Fifteen (75%) experienced permanent side effects which were mild in 47%. Additionally, Simpson and colleagues reported “*marked*” improvements in almost 60% of 24 patients undergoing ACAPS for depression.[11] However, details of these outcomes have not been published.

Although ACAPS has now been superseded in our unit (Dundee) by Anterior Cingulotomy, ACAPS remains the only neurosurgical procedure performed in England and Wales for intractable psychiatric illness. Between 2005 and 2009, the Mental Health Commission approved seven procedures which were performed at the University Hospital of Wales in Cardiff.[12, 13] ACAPS is also offered as a treatment for refractory OCD and Major Depression in several other European countries. The anterior limb of the internal capsule is one of the preferred targets for studies of Deep Brain Stimulation (DBS) for OCD[14] and remains a target for ablative neurosurgery for OCD. It is also emerging as a DBS target for major depression.[15] This anatomical region, therefore, remains very important for neurosurgical interventions for psychiatric illness.

In Dundee, Anterior Cingulotomy became the procedure of choice due to early reports of adverse effects from ACAPS for OCD and anxiety disorders, many of which came from Sweden. We have previously highlighted the possibility of differences in adverse effects depending on the indication,[16] but given the similar clinical outcomes reported for Anterior Cingulotomy,[17] a decision was made to change procedures.

METHODS

Subjects

All patients who underwent ACAPS in Dundee from 1992 were considered. The only *a priori* exclusion criteria were inability to trace a participant, or inability of the participant to provide written informed consent for the study. Ethical approval for this study was provided by the Tayside Medical Research Ethics Committee. Written informed consent was obtained from all patients, and as a requirement of the relevant Scottish Mental Health Acts (1984 and 2003), all patients undergoing neurosurgery were independently assessed pre-operatively by three panel members from the Mental Welfare Commission for Scotland with regard to the suitability of the proposed intervention and capacity to provide sustained informed consent. Diagnosis before surgery was determined according to ICD-10 by the lead psychiatrist for the neurosurgical programme. This diagnosis was subsequently corroborated retrospectively by the current study authors using OPCRIT.^[18] Information regarding the number of previous illness episodes and the duration of inter-illness episode recovery was extracted from detailed case note review, to identify the course of individual episodes according to the ACNP Task Force definitions.^[19]

Clinical assessments

The following rating scales were completed at pre-operative baseline, 12-month follow-up, and long term follow-up: Hamilton Rating Scale for Depression, 17-item version (HRSD₁₇);^[20] Montgomery-Åsberg Depression Rating Scale (MADRS);^[21] Clinical Global Impression (CGI);^[22] Pippard Postoperative Scale;^[23] Lancashire Quality of Life Profile (LQoLP);^[24] and the Personality Assessment Schedule (PAS).^[25] In addition, a semi-structured interview for adverse effects was conducted at long-term

follow-up. Case notes were reviewed for the occurrence of adverse effects occurring in the first post-operative year that were not recalled at later interview.

Assessment of Treatment Resistance

Ratings of the adequacy of previous antidepressant trials were made according to the Antidepressant Treatment History Form (ATHF).[26] Each treatment had to score ≥ 3 on the Antidepressant Resistance Rating (ARR) to be defined as '*adequate*'. Treatment resistance was also rated according to the Massachusetts' General Hospital Scoring Method (MGH-S),[27] and classified using the Thase & Rush Treatment-Resistant Depression Staging (TR-S) method.[28]

Definitions of response

'*Response*' and '*remission*' were defined *a priori*. Using the HRSD-17, '*response*' was $\geq 50\%$ reduction in baseline score, with '*remission*' being a score of ≤ 7 . For the MADRS, '*response*' was $\geq 50\%$ reduction in baseline score and '*remission*' was a score of ≤ 10 . On the clinician-rated CGI-I, '*response*' was a score of 1 or 2. Participants were deemed to meet criteria for clinical response if they met '*response*' criteria on the HRSD-17, MADRS, or the CGI ratings. Similarly, '*remission*' was deemed present if criteria were met on either the HRSD-17 or MADRS scales. Categorical outcomes were also defined by CGI-I and the Pippard Postoperative Scale. '*Improved*' was defined as a score of 1 or 2 on the CGI-I *or* I or II on the Pippard Scale. '*Unchanged*' was defined as a score of 3 or 4 on the CGI-I *or* III or IV on the Pippard Scale. '*Worse*' was a score of 5, 6, or 7 on the CGI-I *or* V on the Pippard Scale. Since statistically significant changes may not necessarily reflect meaningful benefit to a particular individual, '*clinically significant*

change' (CSC) was calculated for each participant. These methods are described in detail by Jacobson & Truax.[29]

Clinical Neuropsychological Assessment

The following tests were performed at baseline and long-term follow-up: National Adult Reading Test (NART);[30] Information/Orientation, Word Lists, Paired Associates Learning, Logical Memory, Visual Reproduction and Digit Span tasks taken from the Wechsler Memory Scale – Revised (WMS-R)[31] and subsequently the WMS-III;[32] Arithmetic, Comprehension, Block Design, Digit Symbol and Similarities tasks from the Wechsler Adult Intelligence Scale – Revised (WAIS-R)[33] and more latterly the WAIS-III ;[34] '6 elements' test from the Behavioral Assessment of the Dysexecutive Syndrome (BADs);[35] the Verbal Fluency Test/ Controlled Oral Word Association Test (COWAT);[36] Stroop Neuropsychological Screening Test;[37] and Trail-Making Test (TMT).[38] Individuals who had been tested on a version of the WMS or WAIS prior to revision were tested again on the same version, with each new patient being tested on the most current version. Data at 12 months post-op were available for some patients.

Cambridge Neuropsychological Test Automated Battery (CANTAB)

CANTAB was used to assess a variety of cognitive domains (attention; memory; non-strategic learning; and '*executive*' functions). These tests are sensitive to the effects of a range of neuropsychiatric disorders including major depression.[39-41]

Surgical procedure

Surgical procedures were conducted under general anaesthesia. Volumetric CT and MRI images were obtained parallel to the intercommisural plane for each patient and merged using the FrameLink Stereotactic Linking System (Medtronic Inc., Minneapolis, MN,

USA). The bilateral target volume was 19-21mm anterior to the Anterior Commissure. Two small scalp incisions and two burr holes were made at the entry points. A 3 mm wide, 6 mm long radiofrequency probe was sited within the target such that its tip was at the inferior aspect of the target volume. Single lesions were made in each hemisphere by heating the probe to 70° Celsius for 90 seconds using a Radionics radiofrequency lesion generator. Additional bilateral lesions were similarly made such that the initial lesion was extended caudally to produce a total lesion within each capsule of approximately 18-20mm height and 8mm width. Individual lesion volumes were therefore predicted to range from 670mm³ (ellipsoid) to 1000mm³ (cylinder) depending on shape.

Statistical Methods

Where data were normally distributed, summary data were reported using the mean \pm standard deviation (SD). Where data were not normally-distributed, the median and range were chosen as measures of central tendency. Differences between two normally-distributed variables were assessed using t-tests. Comparison between groups was performed with independent samples t-tests and comparison between two time points was performed with paired samples t-tests. Corresponding non-parametric tests were the Mann-Whitney U-test.

Incomplete HRSD-17 scores

Pre-operative HRSD-17 scores were unavailable for 30% of participants but pre-operative MADRS scores were available. To test the validity of inferring HRSD-17 scores from MADRS scores, MADRS-imputed HRSD-17 scores for all participants at long-term follow-up were compared to actual clinician-rated scores (completed for all participants) completed at the same time. The correlation between the two scores was

highly significant (Pearson Correlation Coefficient, $r = 0.963$, $p < 0.001$). Consequently, pre-operative MADRS scores were used to infer pre-operative HRSD-17 scores.

Incomplete MADRS scores

Baseline MADRS scores were not available for one participant, and missing at 12-months for eight (40%). To determine if there were differences between those with complete data and those with missing data at 12-months, groups were compared on a number of demographic variables (gender, age at surgery) and indices of severity (duration of presenting episode, number of previous episodes, number of adequate treatment trials, and baseline MADRS scores). The only significant difference was a greater number of pre-operative hospital admissions in those with missing data.

Neuroimaging assessment

Magnetic Resonance (MR) imaging was obtained for 14 patients 6.5 ± 3.6 years after ACAPS using a Siemens 1.5T scanner (Magnetom Avanto and Symphony models). T2-weighted images were obtained with a matrix of 512x512 and a slice thickness of 4.5-5mm. Using SPM2 (<http://www.fil.ion.ucl.ac.uk/spm>), images were spatially normalised to the SPM2 template, which conforms to Montreal Neurological Institute (MNI) anatomical space, then resliced to form 1mm^3 isotropic voxels. Each spatially normalised image was then segmented to form separate grey matter, white matter, and cerebrospinal fluid (CSF) images. ACAPS lesions appear as CSF density structures. For each scan, the outline of each lesion was highlighted as a 'region of interest' (ROI) on each slice using MRIcro (<http://www.sph.sc.edu/comd/rorden/>) independently by two raters (DC and JDS). The former based the estimation on the spatially normalised T2 image; the latter used the CSF images. The ratings made by both assessors were averaged. The centres of

mass of the lesions were calculated by averaging the voxel coordinates in the ROIs in each dimension, and the volumes were calculated from the sum of all voxels within the ROIs (each being 1 mm³).

At long-term follow-up, seven participants had undergone subsequent procedures: Since data were available to determine ‘*response*’ at 12-months, lesion coordinates for ACAPS were compared between responders ($n=4$) and non-responders ($n=6$) at 12-months post-op. Differences between groups were examined using Mann-Whitney U -tests (recognising the low power of this comparison to reject the null hypothesis of no difference). In order to visualise possible differences in lesions between responders and non-responders, the ROI for each participant was plotted on the same spatially normalised MRI.

RESULTS

Participant sample

Twenty-three patients were identified as suitable for inclusion. Three subjects were excluded (one had died; one was untraceable; and one had a previous subcaudate tractotomy), leaving a study sample of 20 patients. Long-term follow-up assessments were completed 7.0 ± 3.4 years (range, 47.4 – 662.2 weeks) after ACAPS. These data represent outcomes from the initial ACAPS only. Seven participants went on to have a second procedure (ACAPS=1; Anterior Cingulotomy=6) due to inadequate clinical response. One individual subsequently had a Vagus Nerve Stimulator implanted (outwith the Dundee service). The second procedure was performed after a mean interval of 154.5 ± 55.2 weeks. For two participants, this interval was less than 120 weeks and the longest follow-up reported below represents the assessment prior to the second procedure. Long-term outcome data, therefore, represent outcomes from the first ACAPS only. Demographic details for participants (n=20) are shown in Table 1, diagnoses are given in Table 2. All were Caucasian and six (30%) were subject to compulsory detention at the time of neurosurgery.

INSERT Table 1

INSERT Table 2

Treatment resistance

Indices of treatment resistance are shown in Table 3. All participants had at least two lifetime courses of ECT. Fifty-percent of participants had four or more courses of ECT during the presenting Major Depressive Episode (MDE) and only one participant (5%) had not had ECT in the presenting MDE due to previous non-response.

INSERT Table 3**Clinical outcomes**

At 12-months, five (25%) participants met criteria for ‘*Response*’ and two (10%) also met criteria for ‘*Remission*’. At long-term follow-up, 10 (50%) met criteria for ‘*Response*’ with eight (40%) also meeting criteria for ‘*Remission*’. These categories are not mutually exclusive and remitters also met criteria for response. According to categorical rating scales, at long-term follow-up, 11 (55%) were ‘*Improved*’, seven (35%) were ‘*Unchanged*’, and two (10%) were ‘*Worse*’. Categorical scores were also obtained from participants and next-of-kin. Correlations between raters were highly significant and ranged from $p=0.025$ to $p<0.001$. Changes in scores are shown in Table 4. At 12-months, 4/20 (20%) participants had achieved CSC, and at long-term follow-up, nine (45%) met criteria for CSC. Correlations between rates of CSC and clinical definitions of ‘*response*’ at 12-months were highly significant using Spearman’s rank correlation [$r=0.909$, $p<0.001$], and remained significant for ‘*remission*’ at 12-months [$r=0.592$, $p=0.002$], and for both ‘*response*’ [$r=0.761$, $p<0.001$] and ‘*remission*’ [$r=0.757$, $p<0.001$] at long-term follow-up.

INSERT Table 4**Neuropsychological outcomes**

A summary of changes in score on a variety of neuropsychological measures is presented in Table 5. The median duration of follow-up for clinical neuropsychological assessment was 396.0 (range 117.8 – 625.8) weeks, and for CANTAB testing the median was 401.1

(48.4 – 662.2) weeks. There were non-significant improvements in the majority of tests of general intelligence, memory, and executive function.

INSERT Table 5

Personality Assessments

Scores on the PAS were available at baseline for 11 (55%) participants, long-term follow-up for 11 (55%), and at both time points for six (30%) participants. At baseline, 2/11 had either personality difficulties or disorder, and at long-term follow-up, 1/6 of those with scores at both time points had moved from the ‘personality difficulties’ to ‘no personality disorder’ category. Clinical interview at long-term follow-up did not identify features that were suggestive of significant personality dysfunction. The IIP-PD, a self-report scale reflecting “*personality dysfunction*”[42] was completed by 14 participants at long-term follow-up, seven (50%) of whom had scores suggestive of personality disorder (Cluster C = 6, Cluster B = 1). Four of the seven had undergone a subsequent anterior cingulotomy (ACING) and only one had a score suggestive of personality disorder (Cluster C) at long-term follow-up.

The study team did consider that some subtle deficits in reciprocal social communication may have been evident for a small number of participants ($n=4$) during informal interactions, but it is not known if these were present prior to surgery. Despite these subjective perceptions, it is worth noting these patients seemed to function with considerable social competence and did not show significant deteriorations in neurocognitive functioning on the clinical or computerised batteries. Gross frontal-lobe symptoms or signs were not detected in any of the participants at clinical interview.

Adverse effects

There were no deaths by suicide. One patient died prior to study completion at the age of 70 years. This occurred 12 years after ACAPS and was considered attributable to causes unrelated to neurosurgery. One individual developed a left-sided temporal haematoma approximately 6 years after ACAPS. Smoking and hypertension were considered key aetiological factors. The most common adverse effects reported are shown in Table 6.

Adverse effects were typically transient and there were no adverse effects present at long-term follow-up that could be reliably attributed to ACAPS, with the exception of disturbance of bladder control ($n=2$) which was mild in both cases. All but one participant were taking prophylactic antidepressant medication at long-term follow-up. Vulnerability to addiction was difficult to assess. One participant had given up smoking four years after ACAPS, whilst another participant developed alcohol dependence following a period of psychosocial stress. A possible relationship with surgery was unclear in both cases. There were self-reported weight gains made by many of the study participants over the follow-up period. Although this could not be attributed definitively to the procedure, such findings are consistent with other reports of ACAPS in the literature. Similarly, reduced motivation was reported by a number of participants and it was not possible to fully distinguish between amotivation consistent with frontal lobe impairment and lack of motivation caused by depression and/ or medication. A classic frontal lobe syndrome was not observed in any participants.

INSERT Table 6

Neuroimaging Results

Lesion coordinates and volumes are shown in Table 7. The measured lesion volumes for both hemispheres lay within the surgically expected range. The results are depicted in Figure 1. Although the differences are not statistically significant, which is unsurprising given the small numbers in each group, there is a suggestion of a trend for ‘responder’ lesions to be placed more inferiorly within the internal capsule. There were no significant differences between groups in *x*, *y*, or *z* planes.

INSERT Table 7

INSERT Figure 1: Comparison of lesions (overlaid as Regions of Interest) for responders (n=4) and non-responders (n=6). Lighter shades represent greater frequency of overlap in responders. Darker shades represent regions more commonly lesioned in non-responders. The regions of interest in the coronal section are enlarged to show a trend towards more inferior lesions in responders.

A colour version of the figure is included as a supplemental file (description under ‘Figure Legends’ below).

DISCUSSION

This is the largest follow-up study of ACAPS for chronic, refractory Major Depression and the first since 1961. These data represent the most complete and the most detailed assessment of the clinical outcomes of ACAPS for treatment-refractory Major Depression. In our study, we found that 10/20 (50%) patients met criteria to be described as responders approximately 7 years after surgery, with 8/20 (40%) meeting criteria for clinical remission (categories not mutually exclusive). The population described in our study is drawn from the extreme end of the treatment-refractory depressive spectrum. Recent reports of the outcomes for Vagus Nerve Stimulation and electrical Deep Brain Stimulation for chronic, refractory depression describe populations that are less chronic and refractory than our cohort.[7, 43, 44]

Detailed, prospective testing of neuropsychological function failed to demonstrate consistent deteriorations over time in any cognitive domain. Indeed, there was a general trend towards improvement on many measures of executive function. We believe this may be mediated indirectly by reduced global symptom burden. However, it could be argued that the neuropsychological battery used in this study was insufficient to detect all potential sequelae of ACAPS. Previously, we have reported that patients treated with Anterior Cingulotomy and ACAPS exhibited a general impairment of accuracy of recognition of dynamic emotional displays compared to healthy controls.[45]

This study differs from recent reports from ACAPS for OCD and anxiety disorders[9, 46] in a number of important respects: data on both clinical and neuropsychological measures for our cohort was collected prospectively and we used modern quantitative voxel-based methods (VBM) to examine lesion characteristics.

Importantly, VBM overcomes the problems inherent with traditional radiological subjective descriptive methods which do not correct for individual differences in brain size and differences in brain orientation at the time of scanning. Whilst attempts have been made to describe the optimal target for OCD or anxiety disorders,[47, 48] almost nothing is known about optimal ACAPS lesion characteristics for treating depressive illness. Based on our current work,[49] we suggest that the reporting of lesion coordinates in MNI space and the use of VBM should be generally adopted.

There are several limitations to our study. First, the dataset is incomplete. However, full data on symptom severity were available for 95% of participants at long-term follow-up. Second, the timing of the assessments (12-months and long-term follow-up) can provide only a snapshot of an individual's level of functioning over time and the results should be viewed within the context of a chronic and relapsing-remitting illness. Third, this study, like many others, suffers from a lack of validated psychometric tools for assessing personality before and after intervention. There are, to our knowledge, no validated scales that are designed for repeated testing, that are insensitive to changes in depressive symptoms, and which have sufficient sensitivity to detect potentially subtle alterations in personality characteristics. We currently use the Iowa Scales of Personality Change,[50] an informant-rated tool, in addition to other assessments to rate personality post-operatively. Finally, the absence of a control group is common to all reports of interventions of this type. Available data would suggest that response rates to 'treatment-as-usual' in much less refractory populations are low,[7] and in a more refractory cohort 'spontaneous' remission is unlikely to account for the improvements seen.

The target of ACAPS is the horizontally-oriented fibres in the inferior part of the capsule which connect the frontal lobes with the thalamus.[51] The orbitofrontal cortex (OFC) has rich connections with limbic structures including the subgenual cingulate cortex, the insular cortex, and the hippocampus.[52] Fibres within the anterior limb of the internal capsule constitute three distinct fibre tracts [53]: 1) Fibres originating in the anterior thalamic peduncle, which connects to the cingulum bundle,[54] the target of Anterior Cingulotomy; 2) A deeper system of fibres made up of frontopontine fibres; 3) A third set which does not run in bundles and connects the caudate nucleus and the lentiform nucleus. A recent neuroimaging study demonstrated neuronal degeneration within these three pathways in five patients after ACAPS.[55] A mechanism of action for ACAPS is, as yet, unknown. Dalglish *et al* suggested that the therapeutic effects of a different ablative neurosurgical procedure, subcaudate tractotomy, might be effected by a relative insensitivity to negative feedback information.[56] However, prospective data were not available to confirm whether such changes were, indeed, acquired.

One persisting criticism of psychiatric neurosurgery is that the benefits occur in a minority and that the risk of neuropsychological and/ or personality dysfunction is high. This ignores varying surgical techniques and patient selection criteria at different centres. We have not been able to find empirical support for either of these statements, for the technique and criteria used in Dundee. More broadly, ACAPS remains a treatment option for patients with chronic, treatment-refractory Major Depression and is offered by a number of centres performing psychiatric neurosurgery. The ACAPS lesion target is of active interest in trials of DBS for OCD and depression, and patients are often offered ablative ACAPS should their trial of DBS prove unsuccessful. Therefore, the clinical

outcomes of ACAPS remain of importance for contemporary clinical practice. In our series, the ACAPS procedure was associated with significant long-term clinical improvements for almost half of all patients. In addition, the adverse effect burden does not appear to be as great as described in the literature, at least with our selection criteria and neurosurgical procedure. ACAPS, as defined here, remains a viable treatment option for highly selected patients with chronic, refractory depression.

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Declaration(s) of Interest

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FIGURE LEGENDS

Figure 1: Comparison of lesions (overlaid as Regions of Interest) for responders ($n=4$) and non-responders ($n=6$). Lighter shades represent greater frequency of overlap in responders. Darker shades represent regions more commonly lesioned in non-responders. The regions of interest in the coronal section are enlarged to show a trend towards more inferior lesions in responders.

A colour version of the figure is included as a supplemental file, and the description of this file is:

Figure 1 (Supplemental): Comparison of lesions (overlaid as Regions of Interest) for responders ($n=4$) and non-responders ($n=6$). Each colour bar represents a frequency of 16.7%; more extreme colours represent greater frequency. Responders are represented by dark red to yellow and non-responders are blue to cyan. The regions of interest in the coronal section are enlarged to show a trend towards more inferior lesions in responders.

TABLES**Table 1. Participant characteristics (n=20)**

<i>Values are mean ± SD or median (range)</i>	
Gender (M:F)	5:15
Median age at time of ACAPS	40.4 (30.2 – 64.2)
Mean age of first episode of major depression	30.1 ± 11.0
Mean age of onset of current MDE	37.8 ± 11.6
Median number of previous episodes †	1.5 (1 – 6)
Median duration of all lifetime episodes (months)	89.0 (35.5 – 289.1)
Median duration of current MDE at time of surgery (months)	78.0 (31.3 – 238.2)
Mean number of previous admissions to hospital (lifetime)	7.0 ± 4.5
Median duration (months) of hospital admissions (lifetime)	26.4 (1.3 – 108.2)
Mean number of suicide attempts (lifetime) ‡	4.6 ± 2.6

† Recovery from episode defined as ≥ 6 months of remission [57]

‡ This information was reliable in only 10 (50%) cases

Table 2. Participant Diagnoses

<i>Diagnosis</i>	<i>N (%)</i>
ICD-10	
F31.4 Bipolar Affective Disorder, current episode severe depression	3 (15%)
F32.x Depressive Episode	8 (40%); Severe in 7 (35%)
F33.x Recurrent Depressive Disorder	9 (45%); Severe in 8 (40%)
DSM-III-R	
Major Depressive Disorder, Moderate	1 (5%)
Major Depressive Disorder, Severe	14 (70%)
Major Depressive Disorder, with psychosis	4 (20%)
Bipolar Disorder (Most Recent Episode Depressed, Severe)	1 (5%)

Table 3. Indices of treatment resistance (n=20)

<i>Values are mean ± SD or median (range).</i>	
Mean number of failed antidepressant treatments in presenting MDE †	8.1 ± 2.8
Median number of failed antidepressant treatments from different classes †	4.0 (3 – 6)
Median number of courses of ECT (presenting MDE)	3.5 (0 – 10)
Median number of courses of ECT (lifetime)	4.0 (2 – 10)
Median Thase and Rush staging score (TR-S)	5.0 (3 – 5)
Mean MGH Staging Score (MGH-S)	13.1 ± 2.2

† Includes ECT; measured using the Antidepressant Treatment History Form [26]

Table 4. Changes in Rating Scales following ACAPS (n=20)

<i>Rating Scale</i>	<i>Baseline</i>	<i>Post-Op</i>	<i>12- months</i>	<i>Long- term follow-up</i>	<i>Percentage change at long-term</i>	<i>P (baseline to long- term)</i>
HRSD-17 (actual scores)	26.8 ± 3.9 (n=6)	20.8 ± 10.6 (n=4)	15.3 ± 10.7 (n=6)	13.3 ± 12.0 (n=18)	-50.7%	0.101 (n=6)
HRSD-17 (imputed scores)	23.3 ± 4.6 (n=18)	15.8 ± 7.0 (n=16)	16.2 ± 7.0 (n=12)	13.8 ± 11.6 (n=20) [†]	-44.2%	0.004 (n=18)
MADRS (not imputed)	39.6 ± 6.5 (n=18)	24.2 ± 11.6 (n=16)	24.1 ± 12.2 (n=12)	22.6 ± 16.4 (n=20)	-42.9%	0.001 (n=18)
LqoLP (mean satisfaction scores)	3.9 ± 1.1 (n=12)	N/A	4.5 ± 0.92 (n=7)	4.9 ± 0.9 (n=17)	+25.6%	0.049 (n=11)
HADS (anxiety subscale)	14.7 ± 5.0 (n=10)	8.5 ± 6.9 (n=6)	8.4 ± 8.0 (n=5)	10.4 ± 4.9 (n=17)	-29.3%	0.132 (n=9)

HRSD-17 Hamilton Rating Scale for Depression; **MADRS** Montgomery Asperg Depression Rating Scale; **LQoLP** Lancashire Quality of Life Profile; **HADS** Hospital Anxiety and Depression Scale.

Paired samples t-test used to calculate P values.

[†] Data not imputed at long-term follow-up.

Table 5: Neuropsychological test scores at baseline and long-term follow-up. Positive scores indicate improvement. CANTAB tests are italicised.

	N	Change in Performance	P
<i>General Intelligence</i>			
NART – Verbal IQ	12	1.0%	NS
NART – Performance IQ	12	1.2%	NS
NART – Full Scale IQ	12	1.2%	NS
WAIS – Arithmetic (Scaled Score)	8	-7.3%	NS
WAIS – Comprehension (Scaled Score)	9	-11.4%	NS
WAIS – Digit Symbol (Scaled Score)	9	0.0%	NS
<i>MTS (Percent Correct)</i>	11	-2.1%	NS
<i>Memory</i>			
<i>DMS (Percent correct – all delays)</i>	14	-9.6%	NS
<i>SRM (Percent correct)</i>	14	28.5%	0.04
<i>PRM (Percent Correct)</i>	14	8.1%	NS
<i>SSP</i>	14	13.8%	NS [†]
Digit Span (Forwards)	16	1.1%	NS
Digit Span (Backwards)	15	27.4%	0.03
Verbal Paired Associates (Immediate)	8	18.8%	NS
Verbal Paired Associates (Delayed)	8	14.7%	NS
Logical Memory (Immediate Recall)	14	18.0%	NS
Logical Memory (Delayed Recall)	14	25.8%	NS
Visual Reproduction (Immediate)	15	27.8%	NS
Visual Reproduction (Delayed)	14	15.2%	NS
<i>Executive Function</i>			
Verbal Fluency (Animals)	15	27.4%	NS
Verbal Fluency ('S')	12	16.3%	NS
Block Design	9	-7.9%	NS
Trail Making Test (A)	11	-7.3%	NS
Trail Making Test (B)	9	-0.2%	NS
<i>SWM (Total Errors)</i>	13	23.6%	0.04
<i>ID/ED Shift (Stages completed)</i>	13	24.9%	0.034 [†]
<i>ID/ED Shift (Total Errors, Adjusted)</i>	13	67.6%	0.009 [†]
<i>SOC (Problems Solved in Minimum Moves)</i>	12	12.0%	NS

MTS = Matching to Sample; **DMS** = Delayed Matching to Sample; **SRM** = Spatial Recognition Memory; **PRM** = Pattern Recognition Memory; **PAL** = Paired Associate Learning; **SSP** = Spatial Span; **SWM** = Spatial Working Memory; **ID/ED** = Intradimensional/ Extradimensional Shift; **SOC** = Stockings of Cambridge.

All tests paired-samples *t*-test, unless specified ([†]=Mann-Whitney *U*-test)

Table 6. Adverse effects reported following ACAPS (n=20)

<i>Adverse Effect</i>	<i>Immediate post-op</i>	<i>12-months</i>	<i>Long-term follow-up</i>
Urinary incontinence	3 (15%)	1 (5%)	2 (10%)
Nausea	0 (0%)	0 (0%)	0 (0%)
Dizziness	1 (5%)	0 (0%)	2 (10%)
Headache	8 (40%)	0 (0%)	3 (15%)
Confusion	5 (25%)	0 (0%)	0 (0%)
Ataxia	1 (5%)	0 (0%)	0 (0%)
Concentration problems	0 (0%)	1 (5%)	2 (10%)
Memory problems	0 (0%)	1 (5%)	2 (10%)
Amotivation	1 (5%)	0 (0%)	4 (20%)
Tiredness	3 (15%)	0 (0%)	0 (0%)
Somnolence	1 (5%)	0 (0%)	0 (0%)
Seizures/ Epilepsy	0 (0%)	0 (0%)	1 (5%)
Weight gain	0 (0%)	0 (0%)	3 (15%) ^a
Subjective personality change	0 (0%)	0 (0%)	2 (10%)
Lack of emotional response	0 (0%)	0 (0%)	1 (5%)
Addiction	0 (0%)	0 (0%)	1 (5%)

^a Range = 10-13kg.. Unfortunately, pre-operative weight was not available for all participants.

Table 7: Summary of lesion characteristics (n=14)

	<i>MNI Coordinate</i> (<i>mean ± SD</i>)	<i>Volume</i> (<i>mm³</i>)
<i>Left</i>		709.86 ± 313.66
<i>x</i>	20.44 ± 2.94	
<i>y</i>	16.09 ± 3.25	
<i>z</i>	7.08 ± 6.11	
<i>Right</i>		851.07 ± 526.24
<i>x</i>	-21.36 ± 2.16	
<i>y</i>	17.76 ± 2.53	
<i>z</i>	7.29 ± 5.24	
<i>Total Volume</i>		1560.93 ± 789.10

