Clinical improvements following bilateral anterior capsulotomy in treatment-resistant depression

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Abstract:

Background: The purpose of the present study was to evaluate a programme of lesion surgery carried out on patients with treatment-resistant depression (TRD).

Methods: This was a retrospective study looking at clinical and psychometric data from 45 patients with TRD who had undergone bilateral stereotactic anterior capsulotomy surgery over a period of 15 years, with the approval of the Mental Health Act Commission (MHAC), (37 with unipolar depression and eight with bipolar disorder). The Beck Depression Inventory (BDI) before and after surgery was used as the primary outcome measure. The Montgomery Asberg Depression Rating Scale (MADRS) was administered and cognitive aspects of executive and memory functions were also examined. We carried out a paired samples t-test on the outcome measures to determine any statistically significant change in the group as a consequence of surgery.

Results: Patients improved on clinical measure of depression after surgery by -21.20 points on the BDI with a 52% change. There were no significant cognitive changes post-surgery. Six patients were followed up in 2013 by phone interview and reported a generally positive experience. No major surgical complications occurred.

Conclusions: With the limitations of an uncontrolled, observational study, our data suggest that capsulotomy can be an effective treatment for otherwise TRD. Performance on neuropsychological tests did not deteriorate.

Keywords: (1) Anterior capsulotomy, (2) Depression, (3) Mood disorder, (4) Stereotactic neurosurgery, (5) Treatment resistance

INTRODUCTION:

Current first line treatments for depression are antidepressant medication and psychotherapy, but 70% of patients do not respond to the first choice of treatment (Carvalho *et al.* 2014). Non-response to two or more antidepressant regimes of adequate duration and dosage is considered to denote a “treatment-refractory” depression (El-Hage *et al.* 2013). Several lines of pharmacological augmentation are available, but even with optimal drug regime and augmentation 10-30% of patients remain refractory (Rakofsky *et al.* 2009). Many of these patients will still get – at least temporary – relief from electroconvulsive therapy (ECT) (UK ECT Review Group, 2003). However, some patients will not respond to any of these interventions even after years of treatment (Schlaepfer *et al.* 2013). For such completely treatment-refractory patients, neurosurgical approaches can be considered. With such invasive approaches, which entail a lesion or implantation of a device without previous demonstration of underlying brain pathology, careful evaluation of risk/benefit ratios, patients’ consenting capacity, ethical aspects and national legal regulation are paramount (Nuttin *et al.* 2014).

Over the last decade deep brain stimulation (DBS), first developed for pain, later mainly for movement disorders and then for OCD, has emerged as a possible invasive treatment for depression

(Mayberg *et al.* 2005). The main DBS target sites for treating psychiatric disorders have been in the anterior limb of the internal capsule, nucleus accumbens, subgenual cingulate gyrus and the medial forebrain bundle (MFB) (Schlaepfer *et al.* 2013). Most studies of DBS for depression have reported responder rates between 50-60% and remission rates around 35%. However, lack of control conditions in the studies published so far, limited follow-up and a number of surgical and psychiatric side effects need to be taken into consideration when evaluating the clinical scope of this method (Schlaepfer *et al.* 2014; Kocabicak *et al.* 2015).

The other surgical approach is based on stereotactic lesions to key components of the cortical-subcortical networks. Stereotactic lesions of the cingulum bundle (cingulotomy) and anterior limb of the internal capsule (capsulotomy) have been performed on many hundreds of patients, mainly for the indication of OCD (Greenberg *et al.* 2010). The main stereotactic procedure for depression has been subcaudate tractotomy (Schoene-Bake *et al.* 2010). All these stereotactic procedures disrupt connections between frontal and subcortical/limbic areas of the brain (Greenberg et al. 2010; Rauch, 1995). One common feature of all these approaches may be that they disrupt the MFB, which carries the dopaminergic projections from the midbrain to the frontal lobe (Schoene-Bake et al. 2010; Coenen *et al.* 2011).

The success rates (significant improvement) for inferior frontal (subcaudate and orbitomedial) tractotomy in depression in older studies have varied between 34% and 72·7% (Göktepe *et al.* 1975; Hodgkiss *et al.* 1995; Sachdev & Sachdev, 2005). A more recent study included 33 patients with depression who had all undergone bilateral cingulotomy. About 75% of patients were classified as partial or full responders. In addition, this study included formal clinical rating scales and found a significant improvement on the BDI (Shields *et al.* 2008). In a cingulotomy case series of eight depressed patients from Dundee, Scotland, two patients had responded and three remitted after one year (Steele *et al.* 2008).

Capsulotomy for depression has been studied in fewer and smaller studies. After an initial positive report from Sweden (Herner, 1961), there was a publication gap of half a century until a group in Scotland (Christmas *et al.* 2011) published their series of 20 cases from 1992-1999. Their generally positive clinical impression was supported by significant and long-term improvements on clinical ratings of depression severity. However, not all measures were available for the same patients pre- and post-operatively and thus had to be imputed. Another smaller study of 8 patients was published by the Vancouver Limbic Surgery Group (Hurwitz *et al.* 2012) and their main finding was the reduction or abolition of suicidal ideation experienced by all the patients. In the present study we report on the other British case series of capsulotomy, covering 45 operations conducted in Cardiff, Wales, between 1993 and 2008.

METHODS:

Design and Patients: We carried out a retrospective study on 45 patients who underwent bilateral stereotactic anterior capsulotomy at the University Hospital of Wales (UHW), Cardiff from 1993-2008 for TRD. This surgery is regulated under the Mental Health Act, 1983, which ensures that all other appropriate treatment has been exhausted. All patients had received adequate periods of treatment with a tricyclic antidepressant, an SSRI, a monoamine oxidase inhibitor, augmentation strategies and ECT (except for 2 patients) with no or insufficient benefit. Patients were referred by psychiatrists across the UK and assessed by the psychiatrist and neurosurgeon on the team and if suitable referred to the Mental Health Act Commission (MHAC), as required by UK law (Mental Health Act 1983, Section 57). Once assessed and approved by the MHAC panel (comprising a psychiatrist and two non-medical members who reviewed all the case notes and conferred with the referring consultant and with two other professionals involved with the case, and interviewed the patient, before confirming that the surgery was appropriate, and consent was freely given and fully informed) patients gave their written consent for the surgery.

Patients were discharged back to the care of the referring psychiatrist 1-2 weeks after surgery and followed up clinically at one, three, six months and one year where possible and some (9 patients) up to 6 years for clinical assessment. Psychometric assessment was carried out in most cases between 6 and 12 months after surgery.

Here we report on the audit and clinical follow-up of this capsulotomy programme. Because of the nature of the evaluation, the local Research and Development Office confirmed that this study was exempt from ethical approval.

Staging of treatment resistant depression:

All patients who underwent surgery were diagnosed as treatment-resistant by the clinical team. For this study we applied the Maudsley staging method which was used to determine the level of treatment resistance. This method takes into consideration the duration of the presenting depressive episode, symptom severity and treatment failures (Table 1).

Surgical procedure:

All patients were operated at the UHW by neurosurgeon BAS. Under general anaesthesia and with a Leksell stereotactic frame applied, computerised tomographic (CT) guidance located the targets in the anterior limbs of the internal capsules. Anatomical variation/asymmetry required bespoke coordinates. These were based on the foramen of Monro – posterior commissure (FMPC) plane. Via twist-drill holes, a stack of three (two in the first four cases) radiofrequency-generated thermocoagulative lesions was made bilaterally at a single operation. Electrode tip 4mm x 1·6mm; each lesion 75 degrees C (first 12 cases) or 80 degrees C (later cases) for 60 seconds (40 seconds in the first seven cases). The 12mm column of targets was centred on the middle third (in the axial plane) of the anterior limb of the internal capsule. The depth was increased during the series: in the later cases the deepest target was 12mm below FMPC, 5mm deeper than in the early cases. This would have been approximately 4 to 7mm below the anterior commissure (AC) level (the relation to AC was not specifically recorded).

Second Operations:

Eleven of the 45 patients (of whom six are included in the psychometric analysis group; see Statistical Analysis) had a second operation. All of them had initially experienced post-operative improvement in their depression but this was lost, typically after approximately six to eight weeks. This may reflect the effects of perilesional oedema and neuropraxia and their subsequent resolution. In these 11 cases magnetic resonance (MR) scanning at six months post-operatively indicated one or more lesions, on one or both sides, to be significantly smaller than the others or even not visible, emphasised by any left-right asymmetry. These lesions were then enlarged at a second operation after obtaining MHAC approval.

Clinical imaging:

All patients underwent CT scanning approximately one week post-operatively for an initial assessment of lesion position, reactive oedema and any haemorrhage. Clinical MRI (T1 and T2 sequences) was performed at six months follow-up (Fig. 1).

Clinical and Cognitive Measures:

Pre- and post-surgical data were available on the BDI, Montgomery Asberg Depression Rating Scale (MADRS) and Beck Anxiety Inventory (BAI) for subgroups of patients (see Table 2). A neuropsychological battery of tests was also administered before and after surgery for some patients. Measures used were the Wechsler Abbreviated Scale of Intelligence (WASI), Adult Memory and Information Processing Battery, test of verbal fluency and tests of attention and concentration. With a sample size of N=17 (which is our largest sample for complete cognitive data: verbal fluency category) we had 80% power to detect medium effects on cognitive functioning (estimated required effect size for one-tailed t-test: 0.53). (See Supplementary material Table 1S for all available data on the clinical and cognitive measures).

Statistical Analysis:

Of the 45 operated patients demographic details, basic clinical information (Table 1) and adverse outcomes are reported for all while psychometric measures are reported for 30 patients, as no psychometric files were available for the remaining (early) cases.

The time of post-surgery psychometric follow-up varied for the measures. Follow-up MADRS evaluations were performed between from one year and 4 years after surgery (except for 3 patients who had follow-up of 3-6 months). Post-surgery BDI scores were from 3-6 months for half of the patients and > 6 months follow-up for the other half of the patients. Follow-up of the other cognitive measures varied from 3 months to >1 year.

For patients who had undergone a second operation where BDI pre and post-surgery scores were available (four patients) the later scores were used in the analysis.

The outcome measures were analysed using the SPSS statistical package (IBM SPSS Statistics Version 20). For all measures we computed % change from pre to post surgery and confidence intervals (Table 2). We also carried out a paired samples t-test on the outcome measures to determine any statistically significant change in the group as a consequence of surgery.

RESULTS:

The Maudsley treatment resistant staging shows that all patients were categorised as having moderately to severely treatment-resistant depression (Table 1). It is likely that our retrospective staging process underestimated the severity of treatment resistance because information on duration of current episode and medication treatment was incomplete for the patients classified as moderately treatment resistant.

We compared the duration of illness and age at time of surgery between the patients with and without psychometric measures using an independent samples t test. There was no difference in the duration of illness (t (43) = -.94; p = .35) although those without psychometric measures were older at the time of surgery (t (43) = -2.03; p = .05). As shown in Table 1, the groups with and without psychometric data did not differ on any relevant parameter. For example, a Chi-Square test for severity of treatment refractoriness yields $x^2(1) = .207$, p = .65 and thus no significant group difference.

Even for the thirty patients for whom we had the psychometric files, data are in some cases incomplete. This was due to difficulties in motivating them to attend to the full battery of tests. Patients often requested testing to be terminated resulting in incomplete acquisition of data. Table 2 gives a summary of the psychometric analysis.

Clinical outcomes:

Pre and post-operative BDI scores were available for 24 patients. These showed an improvement by -21.20 points (95% confidence interval -28.37 to -14.03) which represents a -52% change. A paired samples t-test (2 tailed) showed a statistically significant difference between pre and post-surgery BDI scores (t (23) = -6.12, p = .00).

Based on the BDI scores, 10 improved over 75%, 3 improved between 51 and 75%, 5 improved between 26 and 50%, 3 improved by 25% or less. Three patients were worse than before surgery, by 3%, 14% and 38%.

This subgroup of 24 patients incorporated a stepwise increase in lesion depth. Initially, one lesion was placed 5mm above the FM-PC plane and two deep to it. However, over time the lesions were placed more deeply; in the later cases the highest was on the FM-PC plane, one 6mm below and one 12mm below. Of the last 10 patients (those with the deepest lesion sites), improvement by more than 75% was seen after one operation in six; in the first 10 (those with the highest lesion sites) this occurred in one after one operation, and subsequently in two more following a second operation. We regard this as anecdotal evidence for an effect of lesion depth although our data do not allow for a more formal investigation of a relationship between lesion depth and clinical improvement.

The BAI, available pre- and post-surgery for 13 patients, showed an improvement of 49% which was significant ($t(12) = -3.27$, $p = .007$) (Table 2).

Neuropsychological outcomes:

Measures of executive functions, memory, concentration and attention showed no significant change after surgery except for a small decline of digit span but very few patients (N= 5) were included in the digit span analysis (Table 2).

Adverse events (Table 3):

One, chronically anorectic, patient died from pneumonia within a month of surgery. No motor or sensory deficits occurred. One patient had transient focal seizures but one with medically-controlled epilepsy had no seizures after either of his two operations. Another exhibited mildly increased muscle tone and “cogwheeling” in both upper limbs for several months, which did not recur after a second operation 16 months later and was not related to antipsychotic medication. Some patients showed transient and mild confusion, transient incontinence of urine, fatigue and weight gain (similar to the Dundee series (Christmas *et al.* 2011)). Data beyond 12 months are incomplete.

Phone interviews:

Psychiatrist DL conducted phone interviews with six patients who responded to letters from the neurosurgeon inviting them for follow-up interviews in 2013. All had surgery for unipolar depression except one (unipolar + comorbidity). These covered patients' experience between 5 and 15 years post-surgery. This group reported a generally positive experience. Their mood symptoms had improved considerably, and they had required many fewer hospital admissions than before the operation, if any. Most of them did not need further ECT, although all of them continued to take antidepressant medication. Memory problems and fatigue were reported as important side effects (Table 4).

DISCUSSION:

The clinical outcome data from the capsulotomy series show considerable improvement of depression and anxiety symptoms in this group of patients with otherwise treatment-refractory depression. We found an improvement of 20 points on the BDI, which is similar to, or even larger than, the effects commonly observed for ECT (Feliu *et al.* 2008) which is regarded to be the most effective antidepressant treatment. It is thus remarkable that we found these antidepressant benefits from capsulotomy in the present sample of patients who had been refractory to ECT. Importantly, anxiety symptoms improved to a similar extent. Anecdotally, increasing lesion depth improved the outcomes.

The profile of intra- and post-operative side effects was relatively favourable. There were no surgical deaths and no motor or sensory deficits. One patient had focal seizures transiently, controlled with medication. This incidence of seizures was similar to that reported after implantation of DBS electrodes (Pouratian *et al.* 2011). One patient experienced transient extrapyramidal features. The only infection, in a patient with diabetes, was superficial. Transient post-operative confusion and urinary incontinence were relatively common. We did not detect deterioration in executive functions, attention and concentration or memory functions on formal psychometric testing, but cannot rule out changes in other cognitive domains (Dalgleish *et al.* 2004). Some patients reported fatigue, memory problems and lack of motivation, which had also been commonly reported problems in previous studies of psychiatric surgery. Although we did not have formal long-term follow-up data, the relatively high rate of memory complaints at the follow-up phone interviews suggests that cognitive deficits may develop late.

Anhedonia, the core symptom of inability to experience pleasure, may be linked to a dysregulation of networks of the reward system including the MFB and the anterior thalamic radiation (ATR). Both these pathways are likely to be affected by anterior capsulotomy (Coenen *et al.* 2011; Bracht *et al.* 2014). The MFB is traditionally considered as the major “reward pathway” and the adjacent ATR may mediate the experience of “grief” (Coenen *et al.* 2011). There is also some evidence for altered structural connectivity of the MFB (Bracht et al. 2014) and ATR (Henderson *et al.* 2013) in depression. DBS targeting the MFB led to remarkable clinical improvements in treatment-refractory patients with major depressive disorder (Schlaepfer *et al.* 2013). Clinical improvement of patients with depression following surgical interventions affecting these pathways may therefore be an effect of rebalancing activation between the reward and grief system (Schlaepfer *et al.* 2013).

Diffusion Tensor Imaging (DTI)-based fibre-tracking enables the *in vivo* reconstruction of connection pathways of the human brain (Catani *et al.* 2002) and may therefore be used for preoperative planning and postoperative evaluation of putatively dissected pathways (Schlaepfer *et al.* 2013). In three patients of our data set pre- and postoperative DTI data were available. We demonstrate and discuss the potential use of DTI-data for future operations in a separate supplementary material (see supplementary material).

Although patients with depression who do not respond to any non-invasive treatment continue to pose a considerable clinical challenge, the number of patients undergoing surgery for depression worldwide is at present very low. Cost and local availability of the procedures, evaluation of risk/benefit ratios, lack of knowledge about this treatment modality for severely refractory patients and fear of a potentially irreversible intervention are likely to contribute to this relatively low uptake. However, the recent development of several DBS procedures for depression and other mental disorders is likely to boost the interest in psychiatric surgery amongst patients and clinicians. The published evidence base for DBS (Delaloye *et al.* 2014) and stereotactic lesion surgery for depression is broadly similar –clinical improvements in uncontrolled studies with an acceptable side effect profile, but with little supporting evidence from randomized controlled studies. The failure of a recent DBS trial (Dougherty *et al.* 2015) to demonstrate superiority over sham stimulation in depression may further rekindle interest in the results of ablative surgery.

The present study contributes a well-documented patient sample for the evaluation of adverse events of psychiatric surgery and suggests that capsulotomy can be effective in the long term for patients with otherwise refractory depression.

Supplementary material:

The supplementary material for this article can be found at https://doi.org/10.1017/S0033291716003159.

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Declaration of interest:

None.

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Tables:

Table 1: Demographics and Treatment resistance according to the Maudsley staging method: N=45

Demographics	**Patients with Psychometric data**				**Patients without Psychometric data**		
	Unipolar	**Unipolar + Comorbidity**	**Bipolar**	**Bipolar + Comorbidity**	**Unipolar**	**Unipolar + Comorbidity**	**Bipolar**
Number of Patients	16	11	2	1	6	4	5
Male	1	5	1	1	3	1	3
Female	15	6	1	0	3	3	2
Age at time of surgery in years							
Median	45.50	41	46.50	34	55.50	35.50	69
Interquartile Range	13.50	14	18.50	0	13.25	9.75	20.50
Last follow-up after surgery in months							
Median	30	24	36	72	66	45	39
Interquartile Range	57	52	24	0	73.25	160.50	46
Total duration of illness in years							
Median	20	20	16.75	10	16.50	17.50	35
Interquartile Range	15.50	11	10.25	0	26	17	31
History regarding Suicide							
Attempts	13	5	1	1	3	2	2
Ideation	3	2	0	0	0	1	2
None	0	0	0	0	0	0	0
Not known	0	3	1	0	3	1	1
Treatment resistance: Maudsley staging							
Symptom severity:							
Severe without psychosis	13	10	2	1	6	4	4
Severe with psychosis	3	1	0	0	0	0	1
Duration of current episode:							
Acute	1	0	1	0	0	0	0
Sub-acute	5	3	0	0	2	2	2

Chronic	10	5	0	1	4	2	2
Not known	0	3	1	0	0	0	1
Treatment failures:							
Antidepressants (No. of medications):							
3-4	10	8	2	0	4	2	3
5-6	6	2	0	1	2	0	1
7-10	0	0	0	0	0	1	0
>10	0	1	0	0	0	1	1
Augmentation: Used	16	11	2	1	6	4	5
Electroconvulsive therapy (ECT): Used	16	9	2	1	6	4	5
Known Psychological therapies	14	7	1	1	1	1	0
Severity category::							
Moderate	4	4	2	0	1	1	2
Severe	12	7	0	1	5	3	3

Footnote: All patients had had psychiatric hospital admissions but details were not available in all cases.

Table 2: Pre and Post-surgery clinical and cognitive measures:

Measures	**N[a]**	**Pre-surgery Mean**	**± SE**	**Treatment change (Post - Pre surgery Mean**	**± SE**	**95% CI**	**% change[h]**	**t**	**P (2-tailed)**
Clinical Rating Scales:									
BDI[b]	24	41.17	2.0	-21.20	3.46	-28.37 to -14.03	-52	-6.12	.000
BAI[d]	13	27.38	3.04	-13.61	4.15	-22.66 to -4.56	-49	-3.27	.007
Cognitive Measures:									
General intelligence (WASI)[e]:									
Verbal IQ	11	100.36	5.88						
Performance IQ	11	96.82	5.59						
Full Scale IQ	9	96.11	6.50						
Executive functions:									
Verbal fluency	17	33.76	3.64	-3.35	2.53	-8.73 to 2.02	-10	-1.32	.20
Similarities	5	8.40	1.74	1.40	2.58	-5.76 to 8.56	17	.54	.61
Attention and concentration:									
Speed processing	9	36.67	2.42	6.11	4.64	-4.59 to 16.81	17	1.31	.22
Information processing	12	45.83	4.98	2.58	3.21	-4.49 to 9.66	6	.80	.43
Digit span (scaled scores)	5	8	1.81	1.20	.37	.16 to 2.23	15	3.20	.03
Digit symbol (scaled scores)	6	5.83	.40	.50	.50	-.78 to 1.78	9	1.0	.36
Memory: Immediate and delayed:									
List learning	12	41.83	3.34	-3.50	2.48	-8.96 to 1.96	-8	-1.40	.18
Story IR[f]	19	27.47	2.14	1.10	3.04	-5.28 to 7.49	4	.36	.72

Story DR[g]	19	21.53	2.32	2.0	3.06	-4.44 to 8.44	9	.65	.52
Figure IR	18	58.61	6.33	4.72	4.68	-5.16 to 14.60	8	1.00	.32
Figure DR	18	54.39	6.34	.50	6.33	-12.86 to 13.86	1	.07	.93

Footnote: a) N = number of patients; b) BDI = Beck Depression Inventory; d) BAI = Beck Anxiety Inventory; e) WASI = Wechsler Abbreviated Scale of Intelligence; f) IR= Immediate Recall; g) DR = Delayed Recall.

h) A negative score on the clinical scales indicates an improvement and for the cognitive measures a positive score indicates an improvement.

Table 3: Frequency and duration of adverse effects: N = 45

Adverse Events	**Patients with Psychometric data**				**Patients without Psychometric data**		**Total**
	Unipolar	**Unipolar + Comorbidity**	**Bipolar**	**Bipolar + Comorbidity**	**Unipolar**	**Unipolar + Comorbidity**	
Seizures:							1
Up to 1 week	0						
Up to 1 year	1						
>1 year	0						
Extrapyramidal S/E:							1
Up to 1 week	0						
Up to 1 year	1						
>1 year	0						
Infection[a]:							1
Up to 1 week					1		
Up to 1 year					0		
>1 year					0		
Urinary incontinence:							24
Up to 1 week	9	5	1	1	5	2	
Up to 1 year	1	0	0	0	0	0	
>1 year	0	0	0	0	0	0	
Confusion/disorientation:							24
Up to 1 week	7	8	2	1	5	1	
Up to 1 year	0	0	0	0	0	0	
>1 year	0	0	0	0	0	0	
Tiredness/Fatigue:							14
Up to 1 week	1	0	0		2	1	
Up to 1 year	4	2	2		0	1	
>1 year	0	1	0		0	0	
Short term memory problems:							10
Up to 1 week	1	0		0	0	0	

Up to 1 year	3	1		1	0	0	
>1 year	2	0		0	1	1	
Weight gain:							3
Up to 1 week	0	0			1		
Up to 1 year	1	0			0		
>1 year	0	1			0		
Personality change:							2
Up to 1 week	0						
Up to 1 year	0						
>1 year	2						
Lack of motivation:							6
Up to 1 week	0					1	
Up to 1 year	1					0	
>1 year	4					0	
Impaired attention & concentration:							4
Up to 1 week	0	0					
Up to 1 year	0	1					
>1 year	3	0					

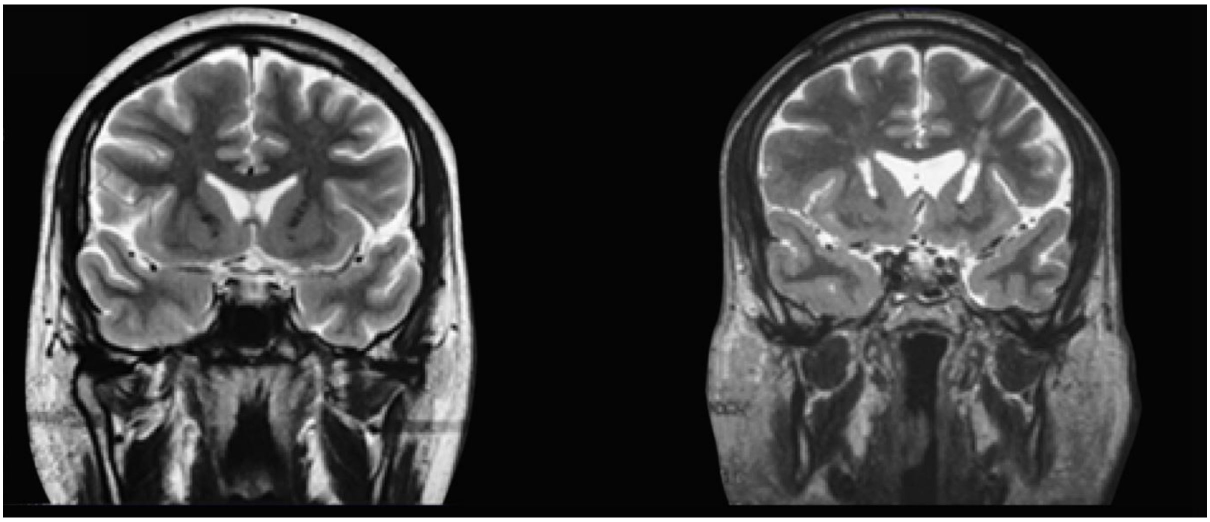
Footnote: a) A superficial pin-site infection occurred in a type-1 diabetic.

Data beyond 1 year are incomplete

Table 4: Interviewed patients:

Age at interview/ year of surgery	Pre-OP history	Outcome	Antidepressant Medication	Side effects
63/ 2004	10 years	"I think it was wonderful" – whole life has improved – she became a "different person" as if waking from "deep sleep"	Yes	Memory problems
63/ 2003	35 years	"Transformed my life" – does not feel depressed any longer – but "would not recommend it" because of side effects	Yes	Weight gain, fatigue, lost ability to visualise places
53/ 2001	12 years	"Quite pleased" but has not stopped depression	Yes	Memory problems
62/ 2000	3 years	Depressive episodes have become much less frequent, "highs" more frequent	Mood stabilisers	Memory problems
67/ 2008	23 years	Depression and nihilistic thoughts went immediately	Yes	Memory problems, lack of motivation
59/ 1998	5·5 years	Has made a difference, although benefits becoming smaller as time moves on – would have the procedure again	Yes	None

Figure 1: T2 weighted MRI coronal scans: left: unoperated; right: 6 months post-surgery.



Supplementary Material:

Table 1S: The pre- and post-surgical clinical and cognitive psychometric scores which were available for 30 patients. Subjects not in surgical date order.

Measures	Subjects														
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
BDI-Pre	40	15 (HADS)	17 (HADS)	49	42	59	23	32	38	42	49		51	43	56
BDI-Post	24	13 (HADS)	4 (HADS)	14	18	9	3	6	39	29	9	39	5	1	53
MADRS-Pre									22						
MADRS-Post		24			14	12	5	9	4					18	40
BAI-Pre		15 (HADS)	13 (HADS)	30	26	14	25	35	25	17	28				
BAI-Post		16 (HADS)	15 (HADS)	29	17	1	2	4	26	27	15				23
V-IQ	118		97				126	91		95			129	76	
P-IQ	89		91				133	108		108			84	63	
FS-IQ			94				133	90		102				69	
VF-Pre		37	58	21	23	13	57	41	36	24	34				
VF-Post		24	42	12	28	23	56	35	34	29	15	28	42		21
S-Pre	13	7		10		6	15	11		9			15	5	
S-Post	9	6				17						11			8
SP-Pre				48	5	30	42		33	41	31				
SP-Post				43		60	58	50	28	29	30	36	47	35	41
IP-Pre				50	29	35	79	44	28	38	23				
IP-Post				60	30	54	101	46	30	40	10	65	60	33	34
DS-Pre	12	5	7	6		10							6	6	
DS-Post		5	9			11						13			8
DSy-Pre	6	6	7						5					2	
DSy-Post	5	6	9												
LL-Pre				39		29	56	49	36	38				20	
LL-Post				30	43	35	40	35	34	40			40	30	37
S_IR-Pre	36	29	28	32	5	10	35	24	18	24	26		30	34	
S_IR-Post	39	19	32	14	38	30	22	44	26	25	10	39	23	29	35
S_DR-Pre	31	21	24	22	3	3	35	16	16	16	15		21	23	
S_DR-Post	36	6	30	0	37	20	25	38	24	21	2	36	25	21	26
F_IR-Pre	49	75	38	67	3	55	90	75	41	96	26		51	56	
F_IR-Post	33	90	53	63	70	65	97	84	34	92	21	61	80	38	48
F_DR-Pre	59	43	38	63	0	60	90	59	42	93	25		36	38	
F_DR_Post	33	38	44	0	70	61	97	68	34	95	18	50	81	33	56
Measures	**Subjects**														
	16	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**
BDI-Pre	42		26	32	56	37	37	25	47	29	52	34	30		42
BDI-Post	23	40	36	24	54	42	25		5	5	25	25	1		4
MADRS-Pre		40										25			23
MADRS-Post	11	21	21	11					13		22			12	6
BAI-Pre	50		35			41		0	40	12					18
BAI-Post	2		23	36	17	18	25			4					11
V-IQ	82					107				111			72		
P-IQ	102					97				110			80		
FS-IQ	88					102				113			74		
VF-Pre	19		11	39		45		17		51			18		47
VF-Post	22		12	36	24	21	38			44		23	33		51
S-Pre	9		4			12		6	12	38			4		
S-Post		11				11							6		
SP-Pre							40	54		25					40
SP-Post							44			47					46
IP-Pre	61						65	44		38					60
IP-Post	50						53			45					62
DS-Pre	8		6			14		8					4		
DS-Post		13				15	6						6		
DSy-Pre	10		4			6		2					6		
DSy-Post			4			6	6						8		
LL-Pre	43		33					39		50	49				60
LL-Post	32		24							55	42				63

S_IR-Pre	20		25	44		36		17		36			32		42
S_IR-Post	21	39	18		10	25	24			41			40		47
S_DR-Pre	14		18			28		16		37			25		41
S_DR-Post	6	36	15	44	7	23	26			38			35		45
F_IR-Pre	95		18			53		97					84		83
F_IR-Post	94		27	75	30	46	59						67		85
F_DR-Pre	95		18			58		89					78		84
F_DR_Post	95		28	83	26	46	59						67		80

Footnote: Footnote: BDI = Beck Depression Inventory; HADS = Hospital anxiety and depression scale (these scores were available for 2 patients and replace the BDI (HADS depression scale) and BAI (HADS anxiety scale) where indicated); MADRS = Montgomery Asberg Depression Rating Scale; BAI = Beck Anxiety Inventory; I = Imputed; V = Verbal; P = Performance; FS = Full Scale; VF = Verbal Fluency; S = Similarities; SP = Speed Processing; IP = Information Processing; DS = Digit Span; DSy = Digit Symbol; LL = List Learning; S = Story; F = Figure; IR= Immediate Recall; DR = Delayed Recall.

Diffusion Tensor Imaging:

The potential use of DTI-based fibre tracking

Diffusion Tensor Imaging (DTI)-based fibre-tracking enables the *in vivo* reconstruction of connection pathways of the human brain (Catani *et al.* 2002). Previous research suggests that white matter microstructure of the medial forebrain bundle (MFB) and the anterior thalamic radiation (ATR), pathways that are likely to be interrupted during anterior capsulotomy, are altered in depression (Jia et al. 2014; Bracht et al. 2014). Based on a recent review these changes are most pronounced in MDD patients with severe/ treatment-resistant depression (Bracht et al. 2015). Thus the MFB and ATR may be of particular relevance regarding the clinical effects of anterior capsulotomy. Pre-operative DTI-based identification of target fibre tracts that may underlie depression symptomatology may therefore potentially represent an important step forward in psychiatric surgery. Furthermore, DTI fibre tracking may be used for evaluation of surgical outcome, and to link side effects to the lesioning of specific pathways. In three patients pre- and postoperative DTI data were available and analyzed.

Methods:

Diffusion Tensor Imaging (DTI):

Data were acquired on a clinical GE Medical System 1·5 Tesla scanner with the following parameters: 24 diffusion encoding directions with a b-value of 1000 s/mm2, 1B0 image without diffusion weighting, 30 slices, voxel size 2x2x5 mm. Pre and post diffusion-MRI data were available for three patients.

Imaging Analysis:

Data were pre-processed and analysed using the software package *ExploreDTI (*Leemans *et al.* 2009). Regions of interest of connection pathways were chosen from the automated anatomical labelling (AAL) atlas (Tzourio-Mazoyer *et al.* 2002), implemented in *ExploreDTI (*Leemans *et al.* 2009). We hypothesized the thalamo-orbitofrontal cortex (OFC) connection pathway to be interrupted by the operation. For reconstruction of this pathway the thalamus and Brodmann areas 10 and 11 were chosen as seed regions. The thalamo-primary motor cortex (PMC) connection was reconstructed as a comparison tract which we did not expect to be affected by the operation. These two connection pathways were separately reconstructed for individual pre-surgical and post-surgical datasets.

Results:

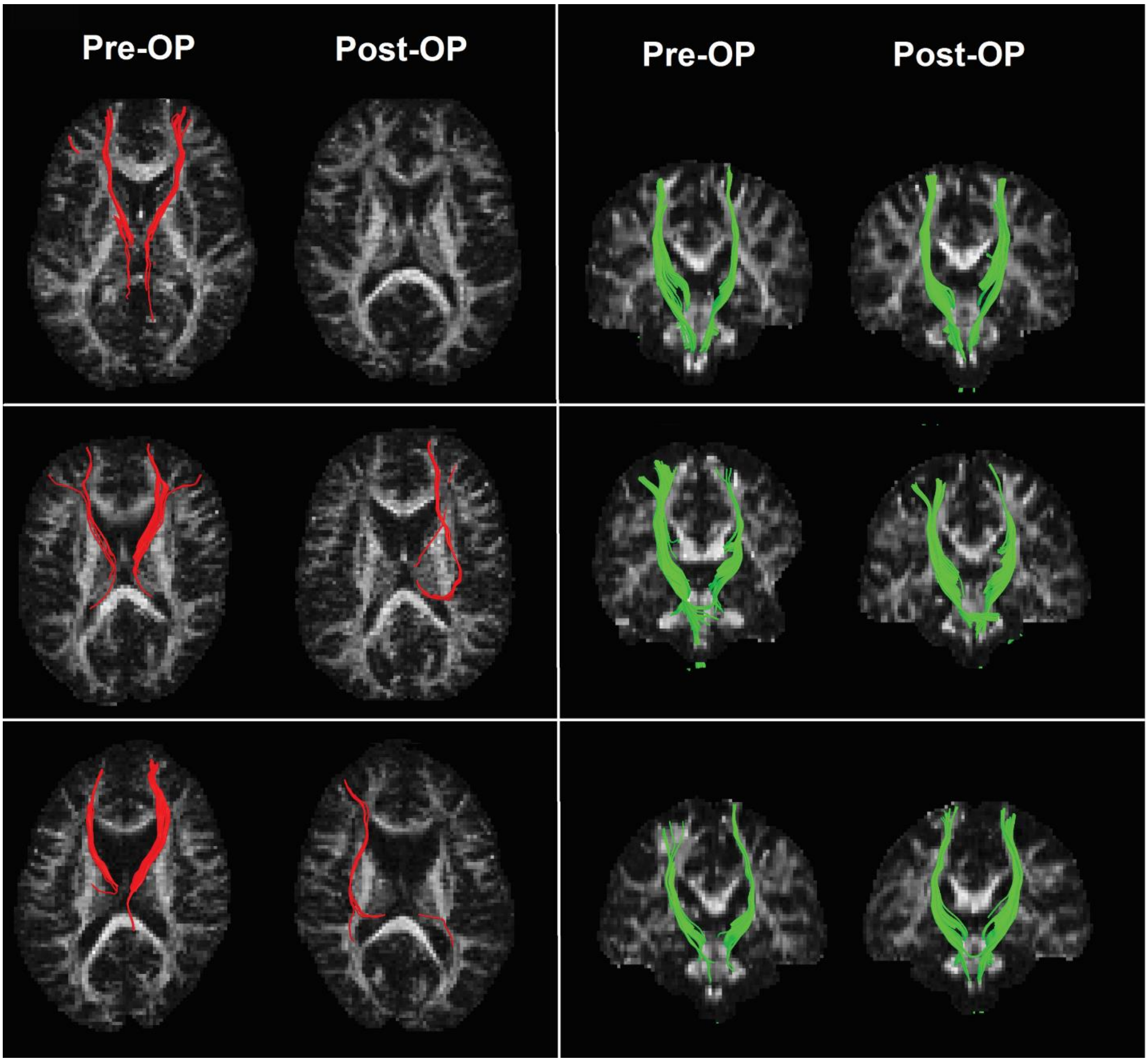


Figure 1S: **Fibre connections between the thalamus and orbitofrontal cortex pre and post-surgery (left panel) and fibre connections between the thalamus and primary motor cortex pre and post-surgery (right panel). BDI clinical scores for the 3 patients: Row 1: Pre-42, Post-4, 90% change; Row 2: Pre-42, Post-29, 31% change; Row 3: Pre-49, Post-9, 82% change.**

In all pre-surgery DTI scans both bilateral thalamo-OFC connection pathways travelling through the anterior limb in the internal capsule and bilateral thalamo-PMC pathways running through the cortico-spinal tract could be identified reliably.

In the post-operative DTI scans in one participant no fibres connecting thalamus and OFC could be identified (row 1, Figure 1B). In two participants DTI-fibre-tracking revealed sparse unilateral connection pathways between the OFC and the thalamus running through the external capsule (row 2 and row 3, Figure 1B). These fibres had not been reconstructed before the operation. Bilateral thalamo-PMC connections remained unchanged in comparison to the pre-operative DTI scan.

Discussion

At present diffusion MRI is the only available method for in vivo reconstruction of fibre pathways and thus offers unique opportunities in psychiatric surgery and stimulation studies. Our DTI-fibre tracking results support the assumption that pathways connecting the thalamus and OFC have been successfully interrupted. DTI fibre tracking results of the thalamo-PMC comparison pathway remained unchanged after the operation, indicating that the surgical intervention had no effect on more posterior thalamo-cortical connections.

We suggest that DTI-fibre tracking will find more widespread use in future applications of psychiatric surgery. It may be used to reconstruct pathways before the operation and serve as guidance to specifically modulate pathways of interest; postoperative DTI-fibre tracking may validate surgery outcome; follow-up studies could link the lesioning of specific pathways to treatment outcome and side effects. This may contribute to the development of more specific and less invasive surgery, potentially being associated with fewer side effects. DTI-based tractography has already informed new protocols for DBS (Coenen *et al.* 2011) and is being used to localize stimulation targets (Schlaepfer *et al.* 2013).

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