Psychological Medicine (2014), **44**, 3533–3542. © Cambridge University Press 2014
doi:10.1017/S0033291714000981

ORIGINAL ARTICLE

Deep brain stimulation for obsessive–compulsive disorder: a systematic review and meta-analysis

S. Kisely[1,2,3,4]*, K. Hall[1], D. Siskind[2,4], J. Frater[2], S. Olson[2] and D. Crompton[2,4]

[1] *The University of Queensland Rural Clinical School, QLD, Australia*
[2] *Metro South Health Service, Woolloongabba, QLD, Australia*
[3] *Griffith Institute of Health, Griffith University, QLD, Australia*
[4] *Diamantina Health Partners, QLD, Australia*

Background. Deep brain stimulation (DBS) is increasingly being applied to psychiatric conditions such as obsessive–compulsive disorder (OCD), major depression and anorexia nervosa. Double-blind, randomized controlled trials (RCTs) of active *versus* sham treatment have been limited to small numbers. We therefore undertook a systematic review and meta-analysis of the effectiveness of DBS in psychiatric conditions to maximize study power.

Method. We conducted a systematic literature search for double-blind, RCTs of active *versus* sham treatment using Pubmed/Medline and EMBASE up to April 2013. Where possible, we combined results from studies in a meta-analysis. We assessed differences in final values between the active and sham treatments for parallel-group studies and compared changes from baseline score for cross-over designs.

Results. Inclusion criteria were met by five studies, all of which were of OCD. Forty-four subjects provided data for the meta-analysis. The main outcome was a reduction in obsessive symptoms as measured by the Yale–Brown Obsessive Compulsive Scale (YBOCS). Patients on active, as opposed to sham, treatment had a significantly lower mean score [mean difference (MD) −8.93, 95% confidence interval (CI) −13.35 to −5.76, $p<0.001$], representing partial remission. However, one-third of patients experienced significant adverse effects ($n=16$). There were no differences between the two groups in terms of other outcomes.

Conclusions. DBS may show promise for treatment-resistant OCD but there are insufficient randomized controlled data for other psychiatric conditions. DBS remains an experimental treatment in adults for severe, medically refractory conditions until further data are available.

Received 5 December 2013; Revised 25 March 2014; Accepted 28 March 2014; First published online 25 April 2014

Key words: Deep brain stimulation, meta-analysis, neurosurgery, obsessive-compulsive disorder, YBOCS.

Introduction

Deep brain stimulation (DBS) has been shown to be effective in the treatment of movement disorders, such as Parkinson's disease and tremor (Kleiner-Fisman *et al.* 2006; Perlmutter & Mink, 2006). It has also been used in conditions as diverse as chronic pain and Tourette's syndrome (Bittar *et al.* 2005; Steeves *et al.* 2012). High-frequency stimulating electrodes are placed in one of several target areas, including the ventrolateral thalamus, subthalamic nucleus, internal segment of the globus pallidus and periaqueductal grey matter.

The original idea behind DBS as an alternative for ablative neurosurgery was that high-frequency DBS served as a 'reversible lesion' by inhibiting activity in the targeted grey matter (Benabid *et al.* 1991; Benazzouz *et al.* 1995). However, further research suggests that the mechanism of action is more complicated and includes elements of both excitation and inhibition (McIntyre *et al.* 2004; Iremonger *et al.* 2006).

An emerging field is the use of DBS for psychiatric disorders, including obsessive–compulsive disorder (OCD) (Greenberg *et al.* 2010), depression (Schlaepfer & Lieb, 2005; Lozano *et al.* 2008) and anorexia nervosa (Wu *et al.* 2013). Central to this approach is the notion that psychiatric disorders result from deregulation of limbic-cortical connections (Schlaepfer & Bewernick, 2013). DBS is thought to inhibit or functionally override hyperactivity in, for example, the subgenual cingulate cortex (Cg25) in the case of depression, or the cortical-striatal-pallidal-thalamic-cortical network in OCD. The nucleus accumbens (NAcc) also plays a role, possibly as the motivation gateway between limbic systems involved in emotion and motor control.

* Address for correspondence: Dr S. Kisely, School of Medicine, The University of Queensland, Level 4, Building 1, Princess Alexandra Hospital, Ipswich Road, Woolloongabba, QLD 4102, Australia.
(Email: s.kisely@uq.edu.au)

Targets for DBS have therefore included the Cg25, ventral capsule/ventral striatum (VC/VS) and median forebrain bundle for major depression (Kubu *et al.* 2013; Schlaepfer & Bewernick, 2013), and the VC/VS, NAcc and anterior limb of the capsula interna for OCD (Greenberg *et al.* 2010; D'Astous *et al.* 2013; Kubu *et al.* 2013; Schlaepfer & Bewernick, 2013).

Most of the literature on effectiveness of DBS consists of uncontrolled case reports, series or trials, but in the case of OCD, there have been several double-blind, randomized controlled evaluations (Nuttin *et al.* 2003; Abelson *et al.* 2005; Mallet *et al.* 2008; Denys *et al.* 2010; Goodman *et al.* 2010). These studies randomly assigned patients to real or sham stimulation for several weeks on the basis that, as with motor disorders, DBS only works with concurrent stimulation. Importantly, they are double blinded to control for the information bias, and consequent placebo effect, for both the patient and rater of knowing who has had surgery. This approach also addresses ethical objections to randomizing patients to insertion or non-insertion of the device itself.

OCD has a lifetime prevalence of 2–3% of the general population (Kessler *et al.* 2005). It is characterized by intrusive and persistent thoughts, impulses or images, and the resulting excessive repetitive behaviours or mental acts, according to rigid rules or unrealistically aimed at reducing distress (APA, 2000). At least 50% of people with OCD have co-morbid anxiety or depression (Torres *et al.* 2006). OCD has been linked to disturbances in the brain's serotonin and glutamate systems, with disruption of pathways in the frontal orbitostriatal area and dorsolateral prefrontal cortex, although these models do not fully account for symptom heterogeneity (Abramowitz *et al.* 2009).

The mainstays of treatment are cognitive behavioural therapy (CBT) and pharmacotherapy with serotonin selective reuptake inhibitors (SSRIs) or clomipramine (Abramowitz *et al.* 2009). Unfortunately, approximately 25% of patients drop out of CBT and 40–60% do not respond adequately to SSRIs or clomipramine (Bloch *et al.* 2006). Although one-third of these may improve with antipsychotic augmentation, this leaves up to 30% who fail to respond adequately to any first- and second-line pharmacological or psychological treatments (Aouizerate *et al.* 2006). In the past, surgical techniques have been used in such treatment-refractory cases, including anterior capsulotomy, anterior cingulotomy, subcaudate tractotomy and limbic leucotomy. Outcomes for these procedures have improved with better patient selection and refinement of techniques including stereotaxis (Shah *et al.* 2008). For instance, a 7-year follow-up of 16 patients with intractable major affective disorders who underwent a limbic leucotomy reported significant halving in mean scores on the Hamilton Depression Rating Scale (HAMD; Cho *et al.* 2008). There was no surgical mortality, and only three patients experienced temporary minor complications. In the case of treatment-refractory OCD, a study of 17 patients following bilateral stereotactic cingulotomy reported a mean reduction of 48% in their baseline Yale–Brown Obsessive Compulsive Scale (YBOCS) scores over a period of 24 months (Jung *et al.* 2006). However, the nature of these procedures means that data are restricted to uncontrolled open-label studies (Hariz & Hariz, 2013). As a result, the safety and efficacy of irreversible surgical interventions remain controversial (Abramowitz *et al.* 2009), with consequent increasing interest in DBS as an alternative (Aouizerate *et al.* 2006). Availability of this intervention varies by jurisdiction. For example, in the USA, DBS is approved by the Federal Drugs Administration under a Humanitarian Device Exemption (HDE) for the treatment of chronic, severe, treatment-resistant OCD as an alternative to anterior capsulotomy (Medtronic, 2014). Surgery can only be performed in a medical centre following Institutional Review Board (IRB) approval. In most Australian states, surgery has generally to be approved by the Mental Health or Psychosurgery Review Board (Loo *et al.* 2010). However, DBS is not permitted at all in New South Wales (Loo *et al.* 2010).

To date, there has been one narrative review of OCD but it did not include any meta-analyses (de Koning *et al.* 2011). There have been no reviews of other psychiatric disorders. We therefore undertook a systematic review of the effectiveness of DBS in psychiatric conditions. We focused on OCD but also included all double-blind sham-controlled studies of both depression and anorexia nervosa.

Method

Search strategy

We conducted a comprehensive search using PubMed/Medline and EMBASE in April 2013 for all studies up to that date, using various combinations of the following free text and MeSH terms: deep brain stimulation; DBS; obsessive compulsive disorder; OCD; depression; anorexia. We inspected titles and abstracts of all papers identified in the electronic searches. The full text of all randomized controlled trials (RCTs) was obtained for examination for relevance and for snowball searches of reference lists. We selected only double-blind, placebo-controlled, cross-over and parallel-group RCTs for the purpose of this review. Narrative and systematic reviews, posters, conference abstracts, case reports, letters to editors and other articles that did

https://doi.org/10.1017/S0033291714000981 Published online by Cambridge University Press

not meet the inclusion criteria were cross-referenced for additional potential sources of RCTs.

Inclusion and exclusion criteria

We included all relevant double-blind RCTs in which DBS was compared with sham treatment for at least 2 weeks. The primary outcome was the effect of DBS on the psychiatric diagnosis that was the main focus of the study as assessed by validated scales. Secondary outcomes included co-morbid psychiatric symptoms, global functioning, cognition and adverse effects.

Both cross-over and parallel-group RCTs trials with contemporary cases and controls were eligible for inclusion. Cross-over trials were included on the basis that there were unlikely to be long-term carry-over effects of turning stimulation on or off. To further minimize this possibility, we used results of the first phase of treatment where possible. This was to minimize the bias of study designs where participants experience both active and sham treatment and, in the context of informed consent, know that what they are allocated to in the second phase of a study will be the opposite of what they have already experienced in the first (Elbourne *et al.* 2002; Higgins & Green, 2011). This can potentially introduce complex problems of either positive or negative placebo effects. In addition, we undertook sensitivity analyses of the effect of excluding cross-over trials to further minimize any carry-over effects on the primary outcome variable (Grimley Evans *et al.* 2006).

Studies of transcranial magnetic stimulation, transcranial direct current stimulation and magnetic seizure therapy were excluded, as were articles addressing only physical measurements such as cerebral blood flow.

We assessed the quality of included studies using the following four criteria of the risk of bias assessment tool, developed by the Cochrane Collaboration to assess possible sources of bias in RCTs (Higgins & Green, 2011): (1) adequate generation of allocation sequence; (2) concealment of allocation to conditions; (3) prevention of knowledge of the allocated intervention to assessors of outcome; and (4) dealing with incomplete outcome data.

Data extraction was conducted by two independent researchers (J.H. and J.F.). All discrepancies during all stages of study selection, data extraction and quality assessment were resolved by re-checking source papers and further discussion among two other authors (S.K. and D.S.) to reach consensus.

Statistical analysis

We used Review Manager version 5.2 for Windows, a statistical software package for analysing Cochrane Collaboration systematic reviews. We calculated the mean differences (MDs) for continuous data where studies used the same scale for each outcome, and the standardized mean differences (SMDs) for data that used different scales. For studies using a parallel-groups design, we assessed differences in final values between the active and sham treatments. In studies using a cross-over design, we compared the results of paired analyses in changes from baseline score (Elbourne *et al.* 2002; Grimley Evans *et al.* 2006; Higgins & Green, 2011). We gave preference to data from the first treatment period only where such data were available, but undertook sensitivity analyses of the effect of using the second treatment period instead. Even though the two types of outcome can be legitimately pooled using the (unstandardized) MD, we placed them in separate subgroups to avoid confusion (Higgins & Green, 2011). We did not combine final value and change scores in any analysis of SMDs. We also undertook subgroup analyses by site of electrode insertion. We reported the relative risk (RR) for any dichotomous outcome. Intention-to-treat (ITT) analyses were used in all cases.

We assessed heterogeneity using the I^2 statistic, a measure that does not depend on the number of studies in the meta-analysis and hence has greater power to detect heterogeneity when the number of studies is small. I^2 provides an estimate of the percentage of variability due to heterogeneity rather than chance alone. An estimate of 50% or greater indicates possible heterogeneity, and scores of 75–100% indicate considerable heterogeneity. The I^2 estimate is calculated using the χ^2 statistic (Q) and its degrees of freedom.

We used the random effects model for all the analyses as we could not definitely exclude between-study variation even in the absence of statistical heterogeneity, given the range of DBS interventions.

For any outcomes where there were at least 10 studies, we tested for publication bias using funnel plot asymmetry, where low p values suggest publication bias (Higgins & Green, 2011).

Results

We found 139 studies of interest in the initial electronic searches, of which 45 abstracts were screened (Fig. 1). Of these, 17 full-text papers were potentially relevant and assessed for eligibility. In 10 of these, there were no controls, and in another two, data were not presented in a way that could be incorporated into a meta-analysis. One of the excluded studies (of major depression) reported the results of single-blind sham stimulation prior to, and following, active stimulation for 24 weeks (Holtzheimer

https://doi.org/10.1017/S0033291714000981 Published online by Cambridge University Press

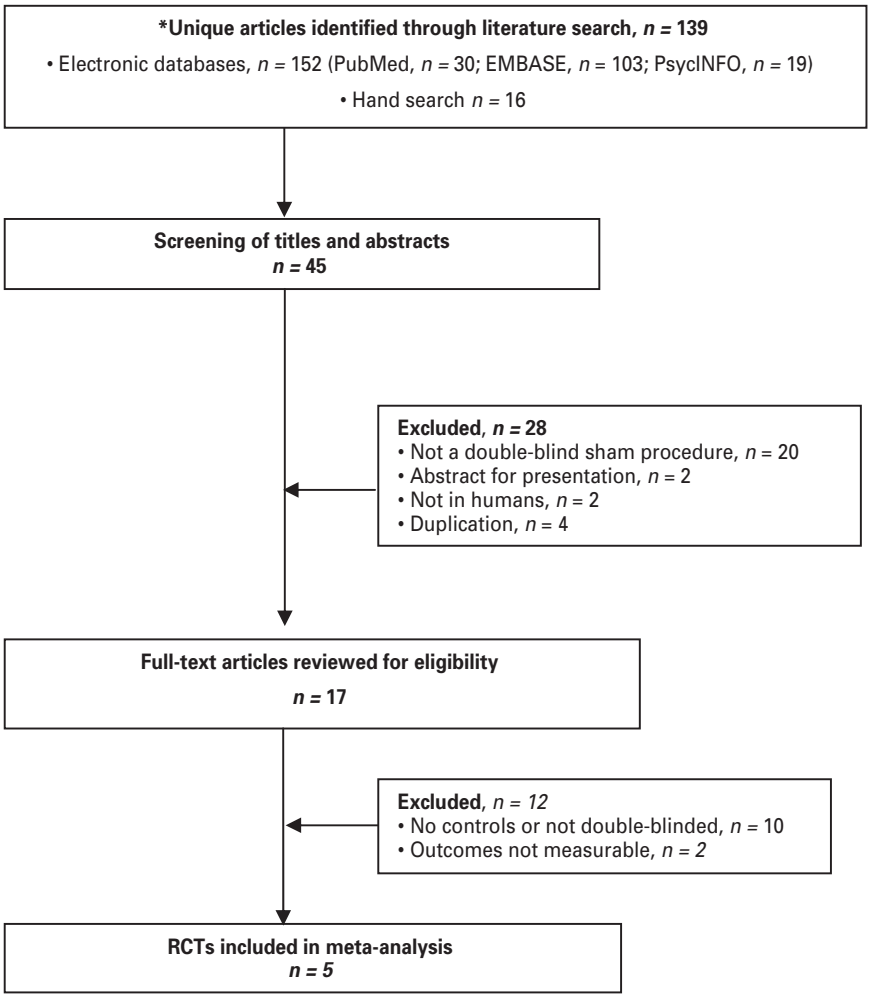

Fig. 1. Selection of double-blind, parallel and cross-over group, placebo-controlled randomized controlled trials (RCTs) for inclusion in the systematic review and meta-analysis.

et al. 2012). Patients in the study were told that they were being randomized to receive either active stimulation or sham stimulation, but in fact all patients received sham stimulation. The five included studies were all of OCD (Nuttin *et al.* 2003; Abelson *et al.* 2005; Mallet *et al.* 2008; Denys *et al.* 2010; Goodman *et al.* 2010). In three of these studies the most common intervention site was the anterior limb of the internal capsule (Table 1) (Nuttin *et al.* 2003; Abelson *et al.* 2005; Goodman *et al.* 2010). In the other two, it was the nucleus accumbens (Denys *et al.* 2010) or the subthalamic nucleus (Mallet *et al.* 2008). Three were parallel trials (Mallet *et al.* 2008; Denys *et al.* 2010; Goodman *et al.* 2010), with or without cross-over phases, and the remainder were solely cross-over trials (Nuttin *et al.* 2003; Abelson *et al.* 2005). Four had a period of open treatment (Nuttin *et al.* 2003; Abelson *et al.* 2005; Mallet *et al.* 2008; Denys *et al.* 2010) where all subjects had active treatment followed by entry into the randomized sham-controlled phase. The duration of open treatment to randomization ranged from 3 days (Abelson *et al.* 2005) to 8 months (Denys *et al.* 2010). The allocation and staging or timing of active and sham treatment were determined by randomization in all the studies.

Two studies used an adequate method to generate the random allocation sequence, including allocation concealment (Mallet *et al.* 2008; Denys *et al.* 2010); in all studies assessors were blind to the treatment condition; there was no loss to follow-up after randomization and ITT analyses were reported for at least some of the outcomes in all of the studies. However, only one study reported all outcomes following randomization (Mallet *et al.* 2008). Accordingly, this was the only study to meet all four of the quality criteria.

Table 1 summarizes the characteristics of the five included studies that provided data for a total of 50 patients with OCD. Of these, 44 subjects provided data for the meta-analysis. The remainder dropped out for a variety of reasons. The duration of treatment

https://doi.org/10.1017/S0033291714000981 Published online by Cambridge University Press

from initial randomization ranged from 2 to 12 weeks. All of the included studies used the YBOCS score as the primary outcome measure. The scale is a clinician-rated, 10-item scale, in which each item is rated from 0 (no symptoms) to 4 (extreme symptoms), yielding a total possible score range from 0 to 40. Full treatment response is generally considered to be a reduction of at least 35% of the YBOCS score whereas partial response is defined as a 25–35% reduction in score. One study also compared the proportion of patients following active and sham treatment as a dichotomous variable (Mallet *et al.* 2008).

With regard to other outcomes, two studies also reported scores from the HAMD that we were able to incorporate into a meta-analysis (Abelson *et al.* 2005; Denys *et al.* 2010). As all the studies used the same outcome measure for either OCD or depressive symptoms, we calculated (unstandardized) MDs for each outcome. Lastly, two studies reported the results of anxiety scales, the Hamilton Rating Scale for Anxiety (HAMA; Denys *et al.* 2010) and the Brief Anxiety Scale (BAS; Mallet *et al.* 2008). We combined these results using SMDs.

Obsessive–compulsive symptoms (YBOCS scores)

The average YBOCS score at baseline across the five studies was 31.98 (S.D. = 4.47). Two studies presented separate data for the first and second study periods (Mallet *et al.* 2008; Denys *et al.* 2010) and we used the data from the first study period for our primary analysis (Fig. 2). This showed a statistically significant mean reduction in score of 8.49. We also found similar results when we used data from the second phase of the same trials instead (Mallet *et al.* 2008; Denys *et al.* 2010) [MD −9.05, 95% confidence interval (CI) −12.65 to −5.45, $p<0.001$]. Restricting the analyses to the three parallel-group RCTs with end-point data gave similar results (Fig. 2).

Because of the small number of studies, we were only able to undertake subgroup analyses of the effect of the operation site for one procedure: the anterior limb of the internal capsule. This showed similar results to the overall meta-analyses (MD −8.13, 95% CI −14.24 to −2.02, $p=0.009$). No other sensitivity analyses were possible because of the small number of studies.

Only one study reported the randomized results of clinically significant improvement on the YBOCS as a clinically significant dichotomous variable. At the end of the first phase, six out of eight patients (75%) had at least a partial response as shown by a 25% reduction in the YBOCS score, compared with only three of eight (38%) after sham stimulation. However, this did not reach statistical significance (RR 2.0, 95% CI 0.75–5.33).

Depression and anxiety in patients with OCD

Two studies reported outcomes using the HAMD (Abelson *et al.* 2005; Denys *et al.* 2010). There was no statistically significant difference between active and sham treatments (MD −7.69, 95% CI −16.29 to 0.90, $p=0.08$). Another two studies reported symptoms of anxiety using the HAMA and BAS (Mallet *et al.* 2008; Denys *et al.* 2010). As both were parallel-group trials, it was appropriate to calculate the SMD, which, as for depression, was not significant (SMD −0.67, 95% CI −1.43 to 0.10, $p=0.09$).

Other therapeutic effects

Two studies reported global measures of outcome such as the Global Assessment of Functioning (GAF) and Clinical Global Impression (CGI) (Nuttin *et al.* 2003; Mallet *et al.* 2008). Although we could not combine the data, patients on active treatment showed significantly greater improvement than those on sham treatment. Mallet *et al.* (2008) also compared active and sham treatment groups using the Montgomery–Åsberg Depression Rating Scale (MADRS) and the Social Disability Schedule (SDS), but found no difference in outcome.

Adverse events

Table 2 illustrates the main adverse events, defined as any adverse effect that was reported more than once. Of these, 16 were classed by study authors as serious. The most serious of these were one intracerebral haemorrhage and two infections requiring removal of the electrode (Mallet *et al.* 2008). A further patient required a capsulotomy because the electrical stimulation consumed so much energy (Nuttin *et al.* 2003). Other adverse events were divided into those related to the surgical procedure and those secondary to stimulation, and in a third group it was difficult to assign the exact cause (Table 2). These in turn were divided into permanent and transient. Most side-effects were transient and related to the stimulation. These included hypomania, anxiety, paraesthesias, dyskinesias, impulsivity, facial asymmetry, dysarthria, dysphagia and walking difficulties.

In terms of cognition, some patients reported mild forgetfulness and word-finding problems but formal neuropsychological tests showed no consistent patterns of change in performance scores with stimulation across subjects (Mallet *et al.* 2008; Denys *et al.* 2010).

https://doi.org/10.1017/S0033291714000981 Published online by Cambridge University Press

Table 1. *Characteristics of randomized controlled trials (RCTs) included in the meta-analysis*

Authors	Year	No. of subjects (baseline)	No. in RCT	Study design	Patient sample group	Intervention	Outcome	Duration of treatment from randomization to assessment	Statistics
Abelson *et al.*	2005	4	4	Short-term, blinded, on–off design up to 8 days post-operatively with long-term, open follow-up subsequently All patients completed the randomized phase	OCD	Anterior limb of the internal capsule	One of four subjects met criterion for a positive response; a second subject showed a more moderate decline in YBOCS score. There was little impact on OCD symptoms in two other subjects	12 weeks	Percentage change from baseline YBOCS score declined more with stimulators on (19.8%, S.D. = 29.8) than off (10.5%, S.D. = 17.8)
Denys *et al.*	2010	16	14	Open 8-month treatment phase, followed by a double-blind parallel trial with cross-over. Patients were randomly assigned to 2-week periods of active or sham stimulation in two blocks: one group had active followed by sham, the other sham followed by active. Both ended with an open 12-month maintenance phase One patient refused to participate in the RCT because of the risk of losing the improvements during the open phase, the other because of lack of efficacy over the same time All patients completed the randomized phase	OCD (YBOCS >28; 5-year OCD history, treatment-refractory OCD)	Nucleus accumbens	Nine out of 16 were responders	2 weeks	Open phase: YBOCS score decrease by 46% ($p<0.001$) lDouble-blind, sham-controlled phase: the mean (S.D.) YBOCS score was 25% ($p=0.004$).
Goodman *et al.*	2010	6	6	Randomized active *versus* sham, parallel staggered-onset design 1 month post-op All patients completed the randomized phase	OCD (YBOCS >28 and treatment-refractory OCD)	Anterior limb of the internal capsule	Four met criterion for responders. Depressive symptoms improved significantly in the group as a whole; global functioning improved in the four responders	4 weeks	>35% improvement in YBOCS and end-point YBOCS severity <16
Mallet *et al.*	2008	18	16	Double-blind parallel-group design with two 3-month cross-over phases separated by a 1-month wash-out period. Patients randomized 3 months post-operatively to allow determination of stimulation settings One patient refused randomization and the other was excluded because of post-operative infection. All patients completed the randomized phase	OCD (YBOCS >25, GAF score <40	Subthalamic nucleus	YBOCS scores were significantly lower than the score after sham stimulation; GAF score was significantly higher	12 weeks	YBOCS ($p=001$) GAF ($p=0.005$) CGI ($p=0.008$)

Nuttin *et al.*	2003	6	4	A blinded random cross-over design after 6 months of continuous stimulation	OCD (YBOCS >30 and treatment-refractory OCD)	Anterior limbs of the internal capsule	DBS reduced core symptoms 21 months after surgery	5 weeks to 3 months depending on patient	In patients 2, 3 and 4, all post-operative YBOCS scores were at least 35% lower than the preoperative scores. Patient 1 was a non-responder CGS scores decreased by 54% in all four patients
				One patient was not included in the cross-over design phase because a capsulotomy was performed early after the implantation of the electrodes, the other because the patient was still in the post-operative screening phase. All patients completed the randomized phase					

OCD, Obsessive–compulsive disorder; YBOCS, Yale–Brown Obsessive Compulsive Scale; GAF, Global Assessment of Functioning; CGI, Clinical Global Impression; CGS, Clinical Global Severity; DBS, deep brain stimulation; S.D., standard deviation.

Publication bias

We were unable to test for publication bias as there were insufficient studies for any of the outcomes.

Discussion

There have been previous meta-analyses of the effect of DBS on disorders such as Parkinson's disease (Kleiner-Fisman *et al.* 2006), dystonia (Holloway *et al.* 2006) and chronic pain (Bittar *et al.* 2005). This is the first meta-analysis of the procedure in psychiatric conditions. By combining the effects of small and possibly underpowered studies, such an approach can help to establish the true efficacy of an intervention such as DBS, where large studies may be impractical. In addition, given the logistical and ethical difficulties of undertaking RCTs in this area, it is important to maximize the use of existing RCT evidence. The controversy that surrounds DBS in some quarters makes it all the more important to establish a firm evidence base for the procedure. Although we were only able to combine results from five studies on OCD, we did demonstrate a statistically significant mean reduction in the YBOCS score of around 9. However, this finding has to be tempered by the fact that, in terms of clinical significance, this represents partial, rather than full, remission. The patients included in these studies all had severe treatment-resistant OCD and these results may therefore not be generalizable to patients with mild to moderate symptoms even if this were ever contemplated. In addition, there were no significant effects on co-morbid depression and anxiety in the small number of studies where this was measured.

Furthermore, the procedure was associated with significant adverse effects. Although many events were transient, in over a third of patients (16 out of a total of 44 patients included in the studies) they were classed by study authors as serious. In 15 patients, adverse effects were permanent, irrespective of whether these were minor or significant.

One area of concern when DBS has been applied to Parkinson's disease has been a post-operative decline in cognitive function including verbal learning and memory (Parsons *et al.* 2006). We were unable to demonstrate a similar effect in performance scores with stimulation across subjects with OCD, but this may have been due to the small study numbers, especially as we could not combine these results in a meta-analysis (Mallet *et al.* 2008; Denys *et al.* 2010).

There are several limitations to this study. The most obvious is that we were only able to find and combine data from studies on OCD and were not able to include other conditions such as major depression or anorexia nervosa. Although all the included studies were

https://doi.org/10.1017/S0033291714000981 Published online by Cambridge University Press

Table 2. *Main adverse effects*

Adverse event	Transient	Permanent
Surgery related		
Wound infection at incision	1	2 requiring device removal
Other serious events (haemorrhage, further capsulotomy)	0	2
Tiredness	4	0
Feeling of numbness at incision site	7	0
Device-related discomfort	11	2
Stimulation related		
Hypomanic symptoms	13	0
Cold shivers	2	0
Stomach aches	4	0
Dizziness	2	0
Taste reduction	3	0
Feeling that the face is asymmetric	2	0
Increased libido	0	8
Nausea	2	0
Difficulty falling asleep	3	0
Micturition problems, enuresis, polyuria	0	4
Forgetfulness	1	6
Difficulty finding words	0	3
Paraesthesias	5	0
Other		
Increase in depressive or anxious symptoms	6	0
Increase in obsessive symptoms	2	0
Headaches	6	0

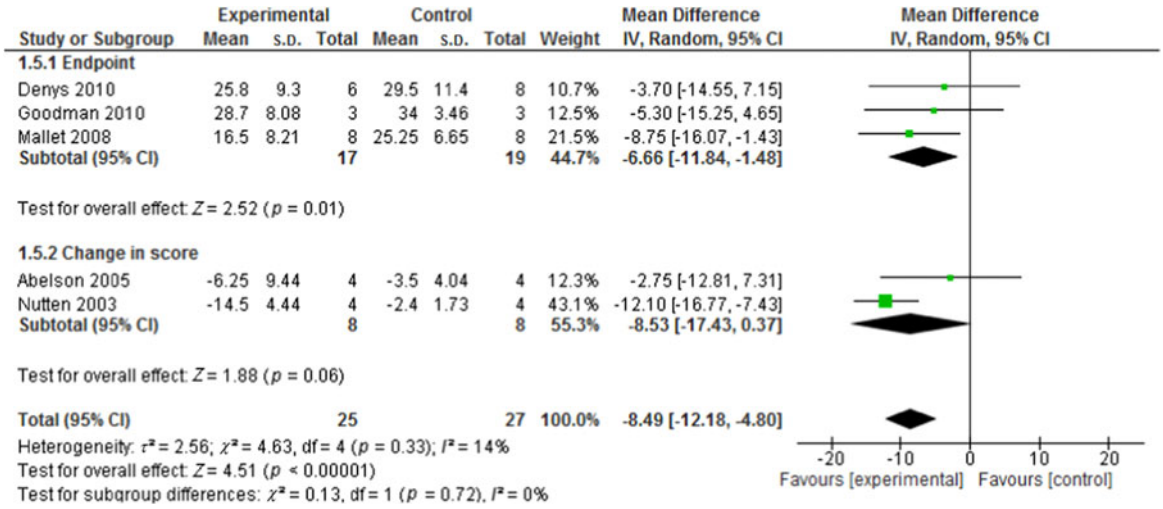

Fig. 2. Obsessive symptoms: Yale–Brown Obsessive Compulsive Scale (YBOCS) total scores. CI, Confidence interval; S.D., standard deviation; df, degrees of freedom.

described as being double-blinded, it is possible that patients may have been aware of their treatment allocation as many report that they can feel the stimulation. Support for this concern comes from the frequency of adverse side-effects by patients on active treatment. There was no loss to follow-up after randomization in any of the studies. However, in several trials, not all patients were included in the randomized phase because of participant refusal, or for clinical reasons (Table 1). This may limit the generalizability of the findings. Some of the cross-over studies did not specify whether the results came from the

https://doi.org/10.1017/S0033291714000981 Published online by Cambridge University Press

first or subsequent phases of the study (Nuttin *et al.* 2003; Abelson *et al.* 2005). However, we found similar results when we restricted analyses to the first phase of parallel-group RCTs with a cross-over design, where this was not an issue (Mallet *et al.* 2008; Denys *et al.* 2010; Goodman *et al.* 2010). In addition, sensitivity analyses of the effect of substituting second-phase results for those of the first phase, when these were available, made no difference to the results. There were insufficient studies to investigate the effect of different intervention sites. Several studies reported the proportion of responders after treatment but only one compared the response rates between active and sham treatment (Mallet *et al.* 2008). This gave a non-significant result although it is possible that this may be explained by the small number of subjects. The limited data on co-morbid depression and anxiety in people with OCD may have meant our meta-analyses were also underpowered to detect a significant difference between sham and active treatments for these outcomes. Finally, DBS has probably been performed in many more patients than the numbers reported to date, with the consequent additional possibility of reporting bias.

In conclusion, DBS may show promise for severe treatment-resistant OCD but there are insufficient randomized controlled data in the case of other psychiatric conditions. Even in the case of OCD, the risks and burdens of the procedure are finely balanced with the perceived benefits. In addition, not all participants consented to randomization, thereby potentially limiting the generalizability of any benefit. This intervention should therefore be considered as an experimental treatment in adults for severe, medically refractory conditions (Kringelbach & Aziz, 2009). Further research is indicated with respect to psychiatric conditions other than OCD, along with research on patient selection and management, target location and mechanisms of action (de Koning *et al.* 2011). This should include double-blind trials with a longer sham stimulation period, the determination of demographic and clinical predictors of response and remission, and the role of adjunctive medication and psychotherapies in improving recovery (Holtzheimer *et al.* 2012).

Declaration of Interest

None.

References

Abelson JL, Curtis GC, Sagher O, Albucher RC, Harrigan M, Taylor SF, Martis B, Giordani B (2005). Deep brain stimulation for refractory obsessive-compulsive disorder. *Biological Psychiatry* **57**, 510–516.

Abramowitz JS, Taylor S, McKay D (2009). Obsessive-compulsive disorder. *Lancet* **374**, 491–499.

Aouizerate B, Rotgé J-Y, Martin-Guehl C, Cuny E, Rougier A, Guehl D, Burbaud P, Bioulac B, Tignol J (2006). A systematic review of psychosurgical treatments for obsessive-compulsive disorder: does deep brain stimulation represent the future trend in psychosurgery. *Clinical Neuropsychiatry* **3**, 391–403.

APA (2000). *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. DSM-IV-TR*. American Psychiatric Association: Washington, DC.

Benabid AL, Pollak P, Gervason C, Hoffmann D, Gao DM, Hommel M, Perret JE, de Rougemont J (1991). Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. *Lancet* **337**, 403–406.

Benazzouz A, Piallat B, Pollak P, Benabid AL (1995). Responses of substantia nigra pars reticulata and globus pallidus complex to high frequency stimulation of the subthalamic nucleus in rats: electrophysiological data. *Neuroscience Letters* **189**, 77–80.

Bittar RG, Kar-Purkayastha I, Owen SL, Bear RE, Green A, Wang S, Aziz TZ (2005). Deep brain stimulation for pain relief: a meta-analysis. *Journal of Clinical Neuroscience* **12**, 515–519.

Bloch MH, Landeros-Weisenberger A, Kelmendi B, Coric V, Bracken MB, Leckman JF (2006). A systematic review: antipsychotic augmentation with treatment refractory obsessive-compulsive disorder. *Molecular Psychiatry* **11**, 622–632.

Cho DY, Lee WY, Chen CC (2008). Limbic leukotomy for intractable major affective disorders, a 7-year follow-up study using nine comprehensive psychiatric test evaluations. *Journal of Clinical Neuroscience* **15**, 138–142.

D'Astous M, Cottin S, Roy M, Picard C, Cantin L (2013). Bilateral stereotactic anterior capsulotomy for obsessive-compulsive disorder, long-term follow-up. *Journal of Neurology, Neurosurgery and Psychiatry* **84**, 1208–1213.

de Koning PP, Figee M, van den Munckhof P, Schuurman PR, Denys D (2011). Current status of deep brain stimulation for obsessive-compulsive disorder: a clinical review of different targets. *Current Psychiatry Reports* **13**, 274–282.

Denys D, Mantione M, Figee M, van den Munckhof P, Koerselman F, Westenberg H, Bosch A, Schuurman R (2010). Deep brain stimulation of the nucleus accumbens for treatment-refractory obsessive-compulsive disorder. *Archives of General Psychiatry* **67**, 1061–1068.

Goodman WK, Foote KD, Greenberg BD, Ricciuti N, Bauer R, Ward H, Shapira NA, Wu SS, Hill CL, Rasmussen SA, Okun MS (2010). Deep brain stimulation for intractable obsessive compulsive disorder: pilot study using a blinded, staggered-onset design. *Biological Psychiatry* **67**, 535–542.

Greenberg BD, Gabriels LA, Malone DA Jr, Rezai AR, Friehs GM, Okun MS, Shapira NA, Foote KD, Cosyns PR, Kubu CS, Malloy PF, Salloway SP, Giftakis JE, Rise MT, Machado AG, Baker KB,

https://doi.org/10.1017/S0033291714000981 Published online by Cambridge University Press

Stypulkowski PH, Goodman WK, Rasmussen SA, Nuttin BJ (2010). Deep brain stimulation of the ventral internal capsule/ventral striatum for obsessive-compulsive disorder: worldwide experience. *Molecular Psychiatry* **15**, 64–79.

Grimley Evans J, Malouf R, Huppert F, van Niekerk JK (2006). Dehydroepiandrosterone (DHEA) supplementation for cognitive function in healthy elderly people. *Cochrane Database of Systematic Reviews*. Issue 4, Art. No. CD006221.

Hariz MI, Hariz GM (2013). Therapeutic stimulation versus ablation. *Handbook of Clinical Neurology* **116**, 63–71.

Higgins JPT, Green S (eds) (2011). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* [updated March 2011]. The Cochrane Collaboration.

Holloway KL, Baron MS, Brown R, Cifu DX, Carne W, Ramakrishnan V (2006). Deep brain stimulation for dystonia: a meta-analysis. *Neuromodulation* **9**, 253–261.

Holtzheimer PE, Kelley ME, Gross RE, Filkowski MM, Garlow SJ, Barrocas A, Wint D, Craighead MC, Kozarsky J, Chismar R, Moreines JL, Mewes K, Posse PR, Gutman DA, Mayberg HS (2012). Subcallosal cingulate deep brain stimulation for treatment-resistant unipolar and bipolar depression. *Archives of General Psychiatry* **69**, 150–158.

Iremonger KJ, Anderson TR, Hu B, Kiss ZH (2006). Cellular mechanisms preventing sustained activation of cortex during subcortical high-frequency stimulation. *Journal of Neurophysiology* **96**, 613–621.

Jung HH, Kim CH, Chang JH, Park YG, Chung SS, Chang JW (2006). Bilateral anterior cingulotomy for refractory obsessive-compulsive disorder: long-term follow-up results. *Stereotactic and Functional Neurosurgery* **84**, 184–189.

Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry* **62**, 593–602.

Kleiner-Fisman G, Herzog J, Fisman DN, Tamma F, Lyons KE, Pahwa R, Lang AE, Deuschl G (2006). Subthalamic nucleus deep brain stimulation: summary and meta-analysis of outcomes. *Movement Disorders* **21** (Suppl. 14), S290–S304.

Kringelbach ML, Aziz TZ (2009). Deep brain stimulation: avoiding the errors of psychosurgery. *Journal of the American Medical Association* **301**, 1705–1707.

Kubu CS, Malone DA, Chelune G, Malloy P, Rezai AR, Frazier T, Machado A, Rasmussen S, Friehs G, Greenberg BD (2013). Neuropsychological outcome after deep brain stimulation in the ventral capsule/ventral striatum for highly refractory obsessive-compulsive disorder or major depression. *Stereotactic and Functional Neurosurgery* **91**, 374–378.

Loo C, Trollor J, Alonzo A, Rendina N, Kavess R (2010). Mental health legislation and psychiatric treatments in NSW: electroconvulsive therapy and deep brain stimulation. *Australasian Psychiatry* **18**, 417–425.

Lozano AM, Mayberg HS, Giacobbe P, Hamani C, Craddock RC, Kennedy SH (2008). Subcallosal cingulate gyrus deep brain stimulation for treatment-resistant depression. *Biological Psychiatry* **64**, 461–467.

Mallet L, Polosan M, Jaafari N, Baup N, Welter ML, Fontaine D, du Montcel ST, Yelnik J, Chereau I, Arbus C, Raoul S, Aouizerate B, Damier P, Chabardes S, Czernecki V, Ardouin C, Krebs MO, Bardinet E, Chaynes P, Burbaud P, Cornu P, Derost P, Bougerol T, Bataille B, Mattei V, Dormont D, Devaux B, Verin M, Houeto JL, Pollak P, Benabid AL, Agid Y, Krack P, Millet B, Pelissolo A (2008). Subthalamic nucleus stimulation in severe obsessive-compulsive disorder. *New England Journal of Medicine* **359**, 2121–2134.

McIntyre CC, Savasta M, Kerkerian-Le Goff L, Vitek JL (2004). Uncovering the mechanism(s) of action of deep brain stimulation: activation, inhibition, or both. *Clinical Neurophysiology* **115**, 1239–1248.

Medtronic (2014). *About Deep Brain Stimulation for Psychiatric Disorders* (https://professional.medtronic.com/pt/neuro/dbs-pd/edu/about/index.htm#tabs-1). Accessed 19 March 2014.

Nuttin BJ, Gabriels LA, Cosyns PR, Meyerson BA, Andreewitch S, Sunaert SG, Maes AF, Dupont PJ, Gybels JM, Gielen F, Demeulemeester HG (2003). Long-term electrical capsular stimulation in patients with obsessive-compulsive disorder. *Neurosurgery* **52**, 1263–1272; discussion 1272–1274.

Parsons TD, Rogers SA, Braaten AJ, Woods SP, Tröster AI (2006). Cognitive sequelae of subthalamic nucleus deep brain stimulation in Parkinson's disease: a meta-analysis. *Lancet Neurology* **5**, 578–588.

Perlmutter JS, Mink JW (2006). Deep brain stimulation. *Annual Review of Neuroscience* **29**, 229–257.

Schlaepfer TE, Bewernick BH (2013). Deep brain stimulation for major depression. *Handbook of Clinical Neurology* **116**, 235–243.

Schlaepfer TE, Lieb K (2005). Deep brain stimulation for treatment of refractory depression. *Lancet* **366**, 1420–1422.

Shah DB, Pesiridou A, Baltuch GH, Malone DA, O'Reardon JP (2008). Functional neurosurgery in the treatment of severe obsessive compulsive disorder and major depression: overview of disease circuits and therapeutic targeting for the clinician. *Psychiatry (Edgmont)* **5**, 24–33.

Torres AR, Prince MJ, Bebbington PE, Bhugra D, Brugha TS, Farrell M, Jenkins R, Lewis G, Meltzer H, Singleton N (2006). Obsessive-compulsive disorder: prevalence, comorbidity, impact, and help-seeking in the British National Psychiatric Morbidity Survey of 2000. *American Journal of Psychiatry* **163**, 1978–1985.

Wu H, Van Dyck-Lippens PJ, Santegoeds R, van Kuyck K, Gabriels L, Lin G, Pan G, Li Y, Li D, Zhan S, Sun B, Nuttin B (2013). Deep-brain stimulation for anorexia nervosa. *World Neurosurgery* **80**, S29.e1–S29.e10.