**POST-OPERATIVE EXTERNALIZATION OF DEEP BRAIN STIMULATION LEADS DOES NOT INCREASE INFECTION RISK**

Running title: Externalization of DBS leads and infection

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## Authorship statement

A.M. conceived the study, collected, analysed and interpreted the data, and drafted the manuscript. F.Bg. analysed and interpreted the data and critically appraised the manuscript. F.Bs. and M.U. collected and data and critically appraised the manuscript. F.M. interpreted the data and critically appraised the manuscript. E.A.C.P. conceived the study, interpreted the data and critically appraised the manuscript. All authors approved the final manuscript.

## Conflicts of interest

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# Abstract

## Objectives

Externalization of deep brain stimulation (DBS) leads is performed to allow electrophysiological recording from implanted electrodes as well as assessment of clinical response to trial stimulation before implantable pulse generator (IPG) insertion. Hypothetically, lead externalization provides a route for inoculation and subsequent infection of hardware, though this has not been established definitively in the literature. We sought to determine if lead externalization affects the risk of infection in DBS surgery.

## Materials and methods

We present our centre’s experience of lead externalization and surgical site infection in DBS surgery for movement disorders. Patients were divided into two cohorts: one in which leads were not externalized and IPGs were implanted at the time of electrode insertion, and one in which leads were externalized for six days while patients underwent electrophysiological recording from DBS electrodes for research. We compare baseline characteristics of these two cohorts and their surgical site infection rates.

## Results

Infective complications were experienced by 3/82 (3.7%) patients overall with one (1.2%) requiring complete hardware removal. These occurred in 1/36 (2.7%) in the externalized cohort and 2/46 (4.3%) in the non-externalized cohort. The incidence of infection between the two cohorts was not significantly different (*p* = 1, 2-tailed Fisher’s exact test). This lack of significant difference persisted when baseline variation between the cohorts in age, hardware manufacturer and indication for DBS were corrected by excluding patients implanted for dystonia, none of whom underwent externalization. We present and discuss in detail each of the three cases of infection.

## Conclusions

Our data suggest that externalization of leads does not increase the risk of infective complications in DBS surgery. Lead externalization is a safe procedure which can provide a substrate for unique neurophysiological studies to advance knowledge and therapy of disorders treated with DBS.

Key words: deep brain stimulation; lead externalization; surgical wound infection; postoperative complications; neurophysiology

# Introduction

Over the past three decades, deep brain stimulation (DBS) has become a routine and effective surgical treatment for many indications including movement disorders, epilepsy, chronic pain and psychiatric disease. Many centres perform DBS surgery in a ‘staged’ fashion in which the first stage of electrode insertion and the second stage of implantable pulse generator (IPG) placement are performed in separate surgical sessions often days apart 1. In such staged surgery, it is possible for the intracranial leads to be connected to extension leads that are externalized through the scalp to allow recording of local field potentials (LFPs) from target brain structures or delivery of electrical stimulation through the electrodes using an external pulse generator in the interval between the first and second stages. In addition to therapeutically motivated trialling of stimulation in the early post-operative period 2, externalization of DBS leads has provided a unique and rich substrate for neurophysiological research into the pathophysiology of neurological and psychiatric disorders 3-5. It has also allowed studies into the clinical effects of experimental stimulators delivering stimulation in novel paradigms such as closed-loop adaptive stimulation in Parkinson’s disease 6-8.

One hypothetical concern with externalization is the creation of a potential route via the externalized leads for implanted hardware to become inoculated with micro-organisms and subsequently infected. In order to address this issue, we report here an analysis of our centre’s experience of surgical site infections (SSIs) from DBS surgery and examine two patient cohorts undergoing DBS implantation with and without lead externalization. We also review the literature on infections in relation to lead externalization.

# Materials and methods

## Patients

We retrospectively identified patients who underwent *de novo* DBS implantation surgery between September 2016 and October 2019 by a single surgeon (E.A.C.P.) at St George’s Hospital, London, UK, who had at least 6 months of post-operative follow-up. Relevant patient details were recorded in clinical records, including demographics, indication, pre- and post-operative clinical assessments, comorbidities and medication history. All patients were deemed by a multidisciplinary team of neurosurgeons, neurologists, specialist nurses and neuropsychologists as suitable for the procedure. From May 2018 onwards, patients with a diagnosis of Parkinson’s disease and isolated tremor syndromes were offered to participate in research studies involving LFP recording from the target brain structures. Upon signing written consent for taking part in research, they underwent externalization of leads between electrode and IPG implantation for LFP recording. A control group of patients undergoing DBS surgery but not externalized was implanted with the electrodes and IPG in the same surgical session (see Surgical technique). All patients provided written informed consent to the procedure and participation in the research where applicable after local institutional approval.

## Surgical technique

All DBS implantations were performed as two-stage procedures: stage 1 involved stereotactic implantation of the intracranial leads using direct image-guided targeting with or without externalization of extension leads, while stage 2 consisted of connection of the intracranial leads to a subcutaneous, prepectoral IPG via tunnelled extension leads. Patients all underwent planning 1.5 T or 3 T magnetic resonance imaging (MRI) in the weeks prior to stage 1 surgery, based on which frontal trajectories to the target structures (bilateral subthalamic nucleus for Parkinson’s disease, bilateral ventral intermediate thalamus and caudal zona incerta for tremor, bilateral globus pallidus pars interna or subthalamic nucleus for dystonia) were planned on dedicated software (Neuroinspire™, Renishaw, Gloucestershire, UK). Stage 1 surgery was performed awake under local anaesthesia with additional intravenous remifentanyl sedation as required and intra-operative neurologist-led assessment until February 2018 and then, in most cases, ‘asleep’ under general anaesthesia. All but one of the patients with externalized leads received stage 1 surgery under general anaesthesia as externalization was only performed from May 2018 onwards.

A Cosman-Roberts-Wells stereotactic frame (Integra LifeSciences, Burlington, MA, USA) was attached to the skull with the base ring approximately parallel to the infraorbitomeatal line. A stereotactic computed tomography (CT) scan was performed with the CT localizer attached to the frame. This was co-registered with the pre-operative MRI on the planning software and the planned trajectories expressed in stereotactic space to yield the required frame parameters. Patients were then transferred to the operating theatre. The hair was triple washed, first with chlorhexidine gluconate cleanser, then warm sterile water, and finally with 0.5% alcoholic chlorhexidine gluconate solution preparation before sterile draping around the stereotactic frame. Prophylactic intravenous cefuroxime 1.5 g was administered immediately prior to the start of surgery.

Electrodes were implanted stereotactically using the frame via bilateral 3 cm linear frontal incisions with minimal hair shave, and craniostomies with a frame-mounted 2.7 mm diameter twist drill, taking care to avoid CSF egress and pneumocephalus with continuous irrigation. Leads were secured adjacent to the craniostomy with titanium two-hole plates and screws. The right sided lead was tunnelled to the left frontal incision. In patients not undergoing externalization, the proximal connectors of the cranial leads were secured in a protective silicone ‘boot’ and placed in a left parietal subgaleal pocket. In those undergoing externalization, the cranial leads were coiled subgaleally and connected to extension leads which were tunnelled and externalized from the left temporal scalp and secured at the exit site with 2-0 silk purse string sutures. A further stereotactic CT was performed at this stage and fused with the pre-operative imaging to verify electrode position. Patients not undergoing externalization returned to the operating theatre and proceeded immediately to stage 2 under general anaesthesia after stereotactic base ring removal. Patients with externalized leads remained as inpatients and participated in research studies with LFP recording from the electrodes between stages 1 and 2 9-11, and proceeded to stage 2 surgery six days after stage 1. Antibiotics were not routinely administered between surgical stages, only at induction for each operation.

In stage 2 surgery, all patients were administered general anaesthesia. The skin was prepared and draped aseptically with alcoholic povidone-iodine solution from the scalp to the chest. In externalized patients, the extension leads were cut flush to the scalp after purse string suture removal before skin preparation. During surgery the remaining extension leads were disconnected from the electrodes, extracted and discarded. New sterile extension leads were connected and tunnelled subcutaneously, first to a 2 cm left inferior parietal incision and then to a left infraclavicular subcutaneous pocket above the prepectoral fascia where they were connected to the IPG. All scalp wounds were sutured with interrupted 2-0 Vicryl (Ethicon, Cornelia, GA, USA) to the galea and 3-0 continuous polyamide (nylon) monofilament to the skin. The IPG site incision was closed with interrupted 2-0 Vicryl subcutaneously and 3-0 Monocryl (Ethicon, Cornelia, GA, USA) subcuticular sutures with buried knots at each incision end. No antibiotics were administered into the IPG pocket. Implanted hardware included Medtronic (Minneapolis, MN, USA) 3389 leads with Activa PC or Activa RC IPG, Boston Scientific (Marlborough, MA, USA) Vercise (DB-2201) and Vercise Cartesia (DB-2202) leads with Gevia RC or Vercise PC IPG, and the St Jude Medical (Abbott Laboratories, Lake Bluff, IL, USA) Infinity system with either 0.5 mm or 1.5 mm spaced directional leads and Infinity 7 IPG, and in each specific case depended on indication, surgical target(s), and clinician and patient preference.

## Infective complications

We defined infective complications based on the guidance on SSIs provided by Public Health England 12, itself derived from SSI definitions established by the US Centres for Disease Control and Prevention 13. We were guided by the criteria for superficial and deep incisional infections, but also included in our definition cases of skin erosion in relation to the hardware in the absence of other features of infection. Where possible, microbiological specimens were obtained from superficial or intra-operative sources.

## Statistical analysis

Demographic and clinical factors between the two cohorts were compared with two-tailed t-tests for continuous variables and Fisher’s exact tests to compare proportions of categorical variables (with Freeman-Halton extension where there were more than two categories) at a significance level of 0.05.

# Results

During the 38-month period of the study, 82 patients received new DBS implants of whom 36 patients underwent lead externalization. Patient details and demographics of externalized and non-externalized cohorts are summarized in Table 1 (groups A and B, respectively). Three patients overall (3.7%) experienced infective complications post-operatively as detailed in Figure 1. Of these, only one was in the externalized group (2.8%; see Case 3 below) and was managed with surgical washout and superficial debridement and antibiotics with preservation of all hardware. The other two patients with infections were in the cohort that had undergone electrode and IPG implantation in the same surgical session (4.3%) and eventually required either partial or complete removal of hardware. Thus, there was no significant difference in the proportion of patients experiencing infection in the externalized and non-externalized cohorts (*p* = 1, 2-tailed Fisher’s exact test).

There were significant differences between the two cohorts in age, proportion of implantations performed asleep versus awake, indication for DBS and hardware manufacturer, and duration of follow-up (see Table 1). The externalized cohort did not include any subjects with dystonia, who tend to be younger than patients with Parkinson’s disease and tremor. We therefore repeated the analyses with dystonia patients excluded from the non-externalized group (group C in Table 1) in order to have two more comparable cohorts. This offset the discrepancies between the externalized and non-externalized groups in age, indication for DBS and hardware manufacturer, though significant differences remained in asleep versus awake surgery and duration of follow-up. Group C included 35 patients and one case of infection (2.9%), which again was not significantly different from the externalized cohort (*p* = 1, 2-tailed Fisher’s exact test).

Given the remaining discrepancy between groups A and C in the proportion of implantations performed awake, we examined this factor separately. We divided the Parkinson’s disease and tremor patients, whether externalized or not, into asleep surgery and awake surgery cohorts with 26 and 45 subjects, respectively. There was one case of infection in each group, which again did not represent a statistically significant difference (*p* = 1, 2-tailed Fisher’s exact test).

We describe each of the three cases of infection in further detail below.

**Case 1**

**A 68-year old woman with idiopathic Parkinson’s disease underwent bilateral subthalamic nucleus DBS in which intracranial electrode insertion was performed awake (Boston Scientific Vercise Cartesia leads and Vercise PC IPG). Stages 1 and 2 were performed in the same session without externalization of the leads and with an uncomplicated perioperative course. Her past medical history included carcinoma of the right breast treated with wide local excision and chemo-radiotherapy eight years prior. She presented six months following surgery with erosion of the skin around the left parietal surgical wound, having been treated by her general practitioner with oral antibiotics for intermittent wound discharge over the preceding two weeks. On assessment, there were a few millimetres of exposed lead through the eroded left parietal incision but no other signs of active infection. She underwent urgent wound debridement, washout and closure with preservation of hardware. Intra-operative microbiology samples cultured serratia marcescens. She received 24 hours of post-operative intravenous antibiotics followed by a 7-day course orally. Six months later, there was recurrent skin erosion at the same site overlying the left extension lead. The wound was surgically debrided and washed out, and the left extension lead replaced. Intra-operative swabs again cultured serratia marcescens and a 7-day course of initially intravenous then oral ciprofloxacin was completed. Three months later, she was found to have a discharging sinus at the medial edge of the left pectoral incision. The wound was surgically explored and the IPG removed from the pocket, cleaned with iodine solution and repositioned laterally in a new subcutaneous pocket. Serratia marcescens was again isolated and treated with oral ciprofloxacin as per sensitivities. Three months later, the IPG and extension leads were removed due to erythema at the IPG site. The IPG pocket was found to be purulent and serratia marcescens was again cultured and treated with four weeks of intravenous ertapenem. Despite antibiotics, recurrent erythema and erosion developed at the left parietal wound after one month and both cranial leads were eventually removed, leaving no remaining hardware in situ. A further three weeks of intravenous ertapenem were administered. Six months after completion of antibiotic treatment she underwent implantation of a new system. Surgical stages 1 and 2 were performed under general anaesthesia in the same session without externalization with the IPG implanted in right chest wall. There have been no further complications fourteen months after recurrent implantation.**

**Case 2**

A 69-year old woman underwent bilateral subthalamic nucleus DBS for cervical dystonia without lead externalization (Boston Scientific Vercise leads and Gevia IPG). Operative stages 1 (performed asleep) and 2 were completed under general anaesthesia in the same session with an uncomplicated perioperative course. Four months after surgery she experienced two weeks of erythema, oedema and pruritus of the left parietal incision site and over the extension leads in the neck over sternocleidomastoid, which was persistent despite a course of oral flucloxacillin. She underwent debridement of the left parietal wound and removal of the extension leads with the brain leads re-tunnelled from left to right parietal scalp. The IPG was removed from the left pectoral site, thoroughly cleaned with antiseptic iodine solution and scrubbed, and was repositioned, unconnected, into a new left abdominal subcutaneous pocket. Intra-operative specimens cultured a scanty growth of staphylococcus aureus and she received a further fourteen days of flucloxacillin. Six months later, she underwent revision surgery to re-establish a working DBS system. The IPG was retrieved from the abdominal site, placed into a new right pectoral subcutaneous pocket, and connected to the electrodes with new tunnelled extension leads via a new right inferior parietal incision. Nine months after this revision surgery there have been no further issues.

**Case 3**

A 61-year old man with a past medical history of type 2 diabetes mellitus, hypertension, obstructive sleep apnoea, and severe obesity awaiting bariatric surgery (body mass index 48) was implanted with bilateral DBS electrodes targeting ventral intermediate thalamus and zona incerta for dystonic tremor affecting the upper limbs and head (St Jude Medical Infinity system with 1.5 mm spaced directional electrodes and Infinity 7 IPG). Implantation surgery was staged and stage 1 was performed awake for anaesthetic reasons. Extension leads were externalized for six days prior to IPG insertion, with LFP recording for research performed on days four and five. There were no immediate complications during his hospital admission for the procedure. He presented again 16 days following stage 2 surgery with four days of purulent discharge from his right frontal surgical wound for which his general practitioner had started oral flucloxacillin empirically. On assessment, the right frontal wound was erythematous and dehiscent, and he was systemically well with normal inflammatory markers. During surgical exploration of the wound, no evidence of infection was seen deep to the galea. Washout, debridement of dehiscent tissue and primary closure was carried out and all hardware was preserved. Intra-operative wound swabs cultured coagulase negative staphylococci, which was treated with two weeks of intravenous flucloxacillin. One year after treatment there have been no further infective issues and all original hardware remains in situ.

# Discussion

Surgical site infection (SSI) is recognized as one of main complications of DBS surgery and often necessitates removal of hardware with associated additional morbidity, withdrawal of therapeutic benefit, need for additional surgery and costs associated with discarded contaminated implants, hospital admission and prolonged antibiotic therapy 14. Case series have reported infection rates per patient of 0–25%, and comprehensive meta-analyses of these have reproducibly estimated the mean value in a narrow range from 4.7% to 6.1% 15-17. A further, more recent meta-analysis examining the rate of wound complications necessitating hardware removal determined a rate of 3.8% per patient 18, though this may underestimate the true infection rate given that a significant proportion of infections may be managed without explantation (e.g. see case 3) 19. Examination of even more recent case series published within the last three years yields similar figures of between 0% and 10.9% with the proviso of significant heterogeneity in the way infection was defined (e.g. the inclusion of skin erosion without signs of infection), denominators used (e.g. patients, procedures or implants), duration of follow-up, inclusion of revision surgery in addition to primary implants, surgical technique, anti-infection measures trialled during the studies, and patient factors 14, 18, 20-42.

One single study to date has implicated lead externalization as a risk factor for infection in DBS surgery 43. The authors of this investigation compared their series of patients in whom DBS leads were externalized for three to five days following electrode implantation to the majority of their patients in whom the entire system was implanted in the same surgical session. They demonstrated that externalization was associated with a significant increase in the infection risk from 4.2% to 15.3%.

We present here our centre’s experience of SSIs in two cohorts of patients with and without a period of lead externalization. We demonstrate a favourable overall infection rate of 3.7%. Furthermore, in our cohort, lead externalization did not significantly increase the risk of infection. Our study is notable as we could compare directly two cohorts, with and without externalization, operated in a single department using otherwise the same technique by a single surgeon. However, its pragmatic, observational nature precludes strict control of several other factors between the cohorts such as age, underlying diagnosis, awake versus asleep surgery, implanted hardware, and duration of follow-up. We attempted to address this and reduced the baseline differences between our two cohorts by excluding subjects with dystonia from the non-externalized group, which again did not reveal a significant difference in infection risk. Given remaining differences between the two cohorts in proportions who underwent asleep versus awake surgery, we examined this factor separately and found no difference in the infection risk between asleep and awake cohorts regardless of externalization status.

Other studies that have addressed this question include one which found no statistically significant difference in infection rate between one surgical centre in which leads were routinely externalized and a different centre in which externalization was not performed by the same surgeon operating at two centres 44. However, uncontrolled differences in environment and practice between the two centres beyond lead externalization alone may have influenced the observed infection rates. A subsequent systematic review of articles published in 2009 or earlier examined the issue by comparing pooled data from 23 case series in which patients underwent a period of lead externalization to nine in which primary internalization of leads was performed. This meta-analysis did not reveal any significant difference in the proportion of patients experiencing infection 16. Four further case series since have reported corroborating findings. Sixel-Doring and colleagues 45 did not find a significant difference in infections in relation to externalization in a series of 85 patients including 43 with externalized leads, although their reported wound complication rate was unusually high at 25%. Similarly, Pepper and colleagues reported no significant difference in infection rate in 100 externalized versus 23 non-externalized patients 46. In a further large series of 105 patients reported by Rosa and colleagues, all of whom underwent lead externalization for LFP recording, the overall infection risk compared favourably to the literature at 2.8% 23. One additional study reported only three infections or skin erosions in 161 patients, including 72 in whom leads were externalized, of which at least two occurred in non-externalized patients, though no formal comparison of externalized and non-externalized patients was made 47. A recent systematic review and meta-analysis of infection rates in DBS surgery with externalization, incorporating 23 studies and 1354 patients, calculated a pooled patient infection risk of 6.9% which was comparable with historical infection rates in non-externalized patients 48. An additional meta-analysis of the three studies 43, 44, 46 which compared infection rates in an externalized cohort versus a non-externalized control group, revealed similar figures (5.2% versus 6.0%, respectively) but was deemed inadequately powered to demonstrate conclusively the absence of a statistically significant difference. The authors likewise concluded that infection rates with and without externalization are comparable.

We describe above our three cases of infection in detail. We achieved salvage of hardware fully in one case and partially in another, while the remaining patient eventually required complete hardware removal. Our practice is to treat superficial infections with short (1-2 week) courses of antibiotics and sparing of hardware where possible. If infection recurs, as in Case 1, then our experience is that complete hardware removal is often inevitable, even after prolonged antibiotic therapy, though we acknowledge the reported success of others with partial hardware removal and long (up to 6-week) intravenous antibiotic courses 49. While the presence of diabetes in case 3 is a well-recognized risk factor for SSI 50 and obesity may have also contributed, no common factor is evident in the three reported cases. Implant-related SSIs may occur up to twelve months after initial implantation 12, therefore our inclusion of patients with at least six months of post-operative follow-up may underestimate the true infection risk. In this regard, sixteen of the 82 patients included in the analysis (eleven of whom are in the externalized cohort) have yet to complete twelve months of post-operative follow-up at the time of writing. The majority of infections, however, present well within six months of implantation 46, 49, 51 so any underestimation is likely to be minor, though some skin erosions have been reported to occur in a much more delayed fashion 30, 52. Furthermore, our study’s overall low infection rate limits the statistical power of our analyses in detecting small but significant differences between our cohorts.

# Conclusions

Our data indicate that externalization of extension leads in staged DBS surgery does not increase the risk of surgical site infection in our hands. Lead externalization either for clinical reasons, or in our practice for research in the form of LFP recording, can therefore be a safe procedure with the potential to provide unique neurophysiological data for the development of more effective neuromodulation therapies and a better understanding of fundamental mechanisms of disorders treated with DBS.

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# Figure Legend

## Figure 1

Bar chart showing number of infected and overall number of patients in externalized (A) and non-externalized (B) groups, as well as the non-externalized group excluding patients implanted for dystonia (C). The proportion of patients with infections was not significantly different between groups A and B, nor between groups A and C (p = 1, Fisher’s exact test).