

TITLE PAGE

Title: STATE OF THE ART: NOVEL APPLICATIONS FOR DEEP BRAIN STIMULATION

Running title: Novel applications for DBS

Holly A Roy, MRCS

Alexander L Green, FRCS

Tipu Z Aziz, FMedSci

Nuffield Department of Surgical Sciences, Oxford University, Oxford UK

Neurosurgery Department, Oxford University Hospitals, Oxford, UK

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Corresponding Author:

Holly A Roy

Oxford Department of Functional Neurosurgery, Level 6, West Wing, John Radcliffe Hospital, Headley Way, OX3 9DU

Email: roy.hollyann@gmail.com

Abstract

(1) Objectives, stating the hypothesis of the study; (2) Materials and Methods, including the means for problem solving, the subjects (number and relevant characteristics), the intervention studied, and briefly, the statistical analysis; ¹ Results, including the outcome of the study and statistical significance; and (4) Conclusions, stating the outcome importance.

(1) Objectives: Deep brain stimulation is a rapidly developing field of neurosurgery with potential therapeutic applications that are relevant to conditions traditionally viewed as neurological, psychiatric and general medical disorders. Our objective, in this review, is to highlight some of the emerging applications of deep brain stimulation within three distinct but overlapping spheres, namely trauma, neuropsychiatry and autonomic physiology. (2) Review methods. An extensive literature review was carried out in Medline, to identify relevant studies and review articles describing applications of DBS in the areas of trauma, neuropsychiatry and autonomic neuroscience. ¹ Results: A wide range of applications of DBS in these spheres was identified, some having only been tested in one or two cases, others much more well studied. (4) Conclusions: We have identified various avenues for DBS to be applied for patient benefit in cases relevant to trauma, neuropsychiatry and autonomic neuroscience. Further developments in DBS technology and clinical trial design will enable these novel applications to be effectively and rigorously assessed and utilised most effectively.

Key Words

Deep brain stimulation

Brain injury

Depression

Bladder control

Spinal cord injury

Introduction

There has been a dramatic increase in the number of novel applications of DBS proposed and tested in recent years. Running a basic Pubmed search using the search terms ‘DBS’ or ‘deep brain stimulation’ and restricting the publication year to 1995 revealed 3 English language papers describing DBS in humans, two on DBS for pain ² ³ and one on DBS for Parkinson’s disease ⁴ . Repeating the same search with the publication year restricted to 2005 produced a total of 206 English language papers covering 9 different subject categories relating to DBS including Parkinson’s disease and other movement disorders (109), DBS methods including clinical and technological papers (51), neuropsychiatry (13), pain (8), epilepsy (8), local field potentials and DBS related neurophysiology (7), autonomic effects of DBS ¹, trauma and vegetative state (2), and neurodegenerative conditions other than movement disorders (1), as well as 4 general papers which did not fit into any of the above categories. Repeating the same search again for publication year restricted to 2015 gave 608 English language papers covering 10 categories: Parkinson’s disease and other movement disorders (229), DBS methods including clinical and technological papers (222), neuropsychiatry (66), pain (10), epilepsy (16), local field potentials and DBS related neurophysiology (32), autonomic effects of DBS (2), trauma and vegetative state (0) and neurodegenerative conditions other than movement disorders ¹, and general & ethical (21). The growth in almost all subject areas is remarkable over the past two decades. Improved neuroscience techniques including task-based

and resting state functional MRI, high resolution diffusion tensor imaging and optogenetic techniques are rapidly increasing both functional and neuroanatomical understanding of neurological and neuropsychiatric disorders. With this expansion, and with the growing the acceptability of DBS as a valid and important technology, an explosion in the proposed applications of DBS has occurred. Particularly and encouraging is the steady growth in technical and engineering-based studies which are essential for equipping the field for progress. In this review, we examine emerging areas where DBS is being actively studied and tested in human trials, and analyse some of the factors that may drive or restrict further development for DBS as a whole. In particular, we focus on developments in three areas of DBS surgery- trauma, neuropsychiatry and autonomic physiology. Although neuropsychiatry has received considerable attention in the literature, trauma and autonomic indications for DBS have been less well studied and reviewed, which is why we have chosen to describe them in depth here.

Trauma and acquired injury

Trauma is a common and devastating condition. In 2010, there were 2.5 million traumatic brain injuries (TBIs) in the US alone, with the highest rate of deaths in the over 65 and 15-24 year age group (National Vital Statistics Mortality Data, Centres for disease control and prevention). The incidence of TBI is set to increase by 2020 ⁵ and there is growing interest in how to reduce the rate of TBI and improve outcomes for sufferers. Moreover, as many as 3 million people worldwide are living with

disability following spinal cord injury (SCI) ⁶ , including paralysis and loss of pelvic organ function. Most of the applications of DBS for traumatic brain and spinal injury focus on restoring function in the damaged brain or spinal cord by modulating behaviour of circuits to compensate for altered network activity following trauma, although some techniques ⁷ are being developed to ameliorate the neurotoxic effects of traumatic injury itself. Furthermore, DBS is being explored as a treatment for other sequelae of traumatic injuries, such as neuropathic pain following limb amputation or nerve avulsion, post-traumatic tremor, and post-traumatic stress disorder (PTSD).

Traumatic brain injury

Due to improved emergency care and neuro-critical care, amongst other factors, survival rates after severe traumatic brain injury are improving. However, one consequence of this is an increased number of individuals with poor functional outcome including vegetative state (complete unawareness of self or surroundings with no evidence of purposeful behaviour) and minimally conscious state (definite behavioural evidence of consciousness). In a case series of 25 subjects with post-traumatic vegetative state, Cohadaon et al describe “definite improvement” in 13 following centrum medianum-parafascicularis complex DBS, but emphasise the fact that all of these patients remained severely disabled and that some of the improvement may have been unrelated to DBS ⁸ . Yamamoto et al (2005) ⁹ report outcomes following DBS of the thalamic centro-median parafascicular complex in 19 cases of vegetative state and 5 cases of minimally conscious state. They also describe DBS of the mesencephalic reticular formation (nucleus cuneiformis) in 2 cases of vegetative state. A strong temporary arousal response occurred at the onset of stimulation in all

patients, which was not associated with purposeful vocalisation or activity. In 8 patients, emergence from the vegetative state occurred. Furthermore, all cases with minimally conscious state became able to communicate purposefully after DBS. The main shortcoming of this study is the lack of a control or comparison group, thus it is not clear to what extent DBS altered the natural progression of selected patients, however the results are promising in that they are linked with a degree of improvement.

A case report published in 2007 describes significant improvements associated with thalamic DBS in cognitive behavioural measures, oral function and limb function in a patient with chronic severe TBI and who was in a minimally conscious state for 6 years with no earlier response to other therapy ¹⁰. The patient was selected for the trial because despite inability to communicate, functional MRI revealed the existence of bihemispheric cerebral language networks, suggesting that the neural systems required to support communication and language were present, at least to some extent, and that lack of communication could be due to global reduction in neuronal activity as a result of damage to midbrain and thalamic structures. Electrodes were targeted to the central thalamus, and improvements were not observed until a considerable period of time after electrode implantation and onset of stimulation (160 days after implantation). After titration testing, a crossover design was implemented whereby assessors of clinical function were not aware of whether the patient had DBS turned on or off. The group found that the patient received the maximum score on the arousal subscale more often when the DBS was turned on than turned off and that limb control and oral feeding scores were also higher when DBS was turned on.

Object naming ability and performance in the CRS-R Motor and Communication subscale scores did not significantly change with stimulation.

In another trial, this time including 4 patients who had chronic severe disabilities following TBI due to automobile crashes, but who were “awake, alert and able to follow commands”, the effect of nucleus accumbens/internal capsule DBS was tested¹¹. Post-hoc t-tests after 2 years’ follow-up showed that there was an improvement on the functional composite score (combining results from the Mayo-Portland Adaptability Inventory-4 and the Functional Independence Measure- essentially representing cognitive, emotional and self-care including mobility, toileting, transfers and social cognition). The target (NAcc/IC) was selected because of its extensive safety history due to use for other indications including OCD, and because it is known to modulate the behaviour of frontal lobe networks which were thought to underpin the majority of deficits experienced by patients following traumatic brain injury.

An additional target for DBS following traumatic brain injury has been proposed based on animal studies. Stimulation of the septo-hippocampal system after TBI improves spatial learning and restores normal object exploration, particularly if the stimulation occurs in the theta frequency band^{12 13} or is delivered as theta burst stimulation¹⁴. Theta burst stimulation is thought to improve learning either by inducing long-term potentiation or by evoking theta oscillations, which facilitate memory formation¹⁴. As far as we are aware hippocampal stimulation has not been attempted in human subjects following traumatic brain injury, although indirect stimulation of the hippocampus during DBS for other indications has been shown to have an effect on memory, such as a case of high frequency stimulation of the

hypothalamic/fornix for obesity which improved verbal memory via likely action on the hippocampus ¹⁵ .

It is still early days for DBS purposed to improve brain function in subjects following traumatic brain injury. The highly heterogeneous nature of TBI makes subject and target selection for trial purposes highly complex. However, existing results have shown that DBS may bring benefits, particularly to patients in a minimally conscious state, and in the future, potentially to those with specific cognitive impairments including memory problems following TBI.

Spinal cord trauma

There has been an expansion of research into the use of neuro-electric technologies to restore motor function after spinal cord injury. Around half of spinal cord injuries are incomplete, meaning that some motor and sensory function below the level of injury remains ¹⁶ . The use of closed-loop stimulation systems to decode cortical (or subcortical) signals about intended movement, and control movements of a prosthesis (brain-machine interfaces) or trigger electrical stimulation to drive a desired movement in peripheral organs such as the limbs (functional electrical stimulation) is already a reality, as demonstrated by the BrainGate system. This system was a 100-electrode array implanted into M1 of a patient with a transected cervical cord. By decoding neural signals within M1 the system could be activated by imagined limb movements and used to control both a neural cursor and basic movements of a prosthetic limb ¹⁷ . Although proposed systems such as the BrainGate for SCI do not involve direct brain stimulation, the recording component often involves invasive

brain electrodes, and is therefore a close companion of DBS, particularly as closed loop DBS devices are currently under development. Respiratory and lower urinary tract control driven by subcortical sensors and developed based on autonomic research carried out in the context of DBS may be possibilities for the future in the field of spinal cord injury.

Furthermore, there is some evidence that DBS itself may potentially be of therapeutic benefit following spinal cord injury. Low frequency stimulation of the raphe nucleus and the periaqueductal grey area after thoracic spinal contusion in rats has been shown to reduce astrogliosis in the injured area ^{7, 18}, improve white matter integrity and improve motor co-ordination and sensory processing. The authors suggest that the nucleus raphe magnus may be a “repair control centre”; activated during traumatic injury and responsible for releasing substances important for neurorepair. Whether or not this target will prove beneficial for human subjects after spinal cord injury has not yet been shown; nor whether the NRM also improves neuronal repair following traumatic brain injury, however these are clearly avenues for future investigation.

Post-traumatic pain

Post-traumatic neuropathic pain can occur from a variety of traumatic aetiologies, commonly trauma during surgery (such as chronic limb pain following amputation, or failed back surgery syndrome), or an accident producing nerve trauma such as brachial plexus avulsion. Incidence of chronic pain in these groups can be as high as 76% in brachial plexus avulsion ¹⁹, 10-40% following lumbar disc surgery ^{20 21 22} and

60% in the form of phantom pain after limb amputation^{23, 24} producing a significant burden of disease. In a proportion of these patients, the pain is refractory to pharmacological therapy, which can also have serious side-effects including cognitive impairment. DBS has been reported to be efficacious in a number of cases of such medication-refractory traumatic pain syndromes.

Historically, DBS for chronic pain has been performed since the 1950s, and a number of more recent open-labelled studies have demonstrated moderate efficacy. Recognised targets include the ventral posterior lateral thalamic nucleus (VPL) and the periaqueductal grey/periventricular grey area (PAG/PVG). A study published in 1969 demonstrated that electrical stimulation of the dorsolateral part of the central grey region of the rat produced reversible analgesia²⁵, and in the 1970s, the first experimental studies of temporarily²⁶ or permanently implanted²⁷ electrodes within the PAG/PVG for chronic pain described analgesic effects. In parallel to this, the effects of alternative stimulation sites including the sensory thalamus were also explored²⁸. Since these early studies, DBS for chronic pain, including post-traumatic pain, has been reported by various groups. For example, Rasche et al (2006)²⁹ reported the results of a series of 56 patients who received DBS for chronic pain, some of whom had pain of traumatic origin, including 13 with failed back surgery syndrome, 4 with phantom limb pain and 12 with pain following spinal cord injury. The best results were obtained for patients with failed back surgery syndrome, where 9/13 experienced greater than or equal to 50% pain relief at long term follow up (range 2-8 years for successful outcomes). There was a mixed outcome for the small number of subjects (n = 4) with phantom limb pain. In this small group, all of whom received VPL/PVG DBS, two out of four experienced more than 50% pain relief, but

one of these did not want to keep the DBS system implanted. Better outcomes for DBS for phantom limb pain were reported in a case series of 11 patients implanted with VPL DBS for neuropathic limb pain (pain aetiology was either phantom limb pain after amputation or deafferentation pain after brachial plexus avulsion) ³⁰ . In this group, there was an improvement of visual analogue pain score of $69.6\% \pm 29.6\%$ 12 months after surgery, which was statistically significant. There were also significant improvements in the University of Washington Neuropathic Pain Score (UWNPS) and the Brief Pain Inventory (BPI) 12 months post-operatively, and non-significant improvements in SF-36 score. The authors noted that patients with amputation pain responded better than those with brachial plexus avulsion. Another open label single centre study reported improvements in 89% of amputees receiving DBS at the VPL, PVG or both for chronic neuropathic pain ³¹ . However, two US open-label trials to support application for FDA approval of DBS for chronic pain were closed without the criterion for success of therapy being met overall. In the first trial of the Medtronic 3380 lead, 46% of internalised patients had greater than or equal to 50% pain relief at 12 months follow up, however, the second trial using the Medtronic 3386 lead identified only 16.2% of patients with greater than or equal to 50% pain relief at follow up ³² . The explanation for variability in outcomes of different trials is not clear, particularly the poor outcomes reported in the second Medtronic trial. However, important methodological differences exist between trials in crucial issues of patient selection, pre-operative opioid reduction and assessment of outcome. Blinding and sham stimulation are generally absent from reports of DBS for chronic pain and it seems important to have a trial in a selected aetiology group using these key methodological features. Further efforts to evaluate the efficacy of DBS for post-

traumatic pain in specific patient groups in the hands of an experienced neurosurgeon and multidisciplinary team, with carefully planned trial methodology, is imperative.

Acquired brain injury tremor

DBS for tremor associated with acquired brain injury has been reported in a number of case reports and small case series ³³⁻³⁶. In one series of 8 patients with tremor following acquired brain injury either in the form of a haematoma, ischaemic stroke or traumatic brain injury, DBS of the ventro-oralis posterior (VOP)/zona incerta (ZI) region produced a mean tremor reduction of 80.75%, based on the Bain tremor rating ³³. The efficacy of this treatment may be a result of activity within preserved white matter tracts between the stimulation target and cortical areas responsible for movement control ³⁷.

Acquired dystonia

While pallidal DBS is well established for primary dystonia, there is relatively less work published regarding DBS for children with acquired dystonias. These can occur as part of cerebral palsy, usually secondary to perinatal brain damage due to hypoxic ischaemic encephalopathy, periventricular leukomalacia, kernicterus or basal ganglia strokes ³⁸. Small studies have reported modest but clear improvements in selected paediatric patients with acquired dystonia following pallidal DBS in terms of motor score (improvements in the region of 30 - 40% have been reported), disability score

and quality of life ^{39 40} . Furthermore, a recent study described no negative effects on cognition but improved function on a perceptual reasoning test in a cohort of children following pallidal DBS for secondary dystonia ⁴¹ .

Post-traumatic stress disorder

Post-traumatic stress disorder is a disabling condition in which an individual who has had a previously traumatic experience repeatedly re-experiences symptoms of trauma, often in the form of nightmares, intrusive thoughts and flashbacks, along with symptoms of avoidance, mood disturbance, hyperarousal, sleep impairment ^{42 43} . In severe cases, sufferers may be unable to have normal interpersonal interactions or hold down a regular job due to the severity and intensity of flashbacks and other PTSD symptoms. PTSD can be refractory to pharmacotherapy in up to 30% of patients ⁴⁴ . The development of PTSD is likely to involve both fear and memory neurocircuitry ⁴³ including the amygdala, which is involved in creating an association between a stimulus and fear. The amygdala is also central to the process of extinction, whereby a stimulus no longer evokes a fear reaction. Both fear conditioning and extinction are influenced by inputs from the medial prefrontal cortex ⁴⁵ . Deep brain stimulation within the right amygdala of the rat has been shown to reduce hypervigilance to a trauma-associated object relative to sham DBS and paroxetine, despite paroxetine being more effective at reducing generalized anxiety ⁴⁶ . Following these observations, in a single subject with severe PTSD, amygdala DBS targeted to the basolateral nucleus of the amygdala produced a remarkable improvement in

nightmare intensity and sleep quality ⁴⁵ . It is likely that further studies of DBS in PTSD will follow in the future.

Neuropsychiatric conditions

There has been an increase in the interest in the use of DBS for the treatment of neuropsychiatric conditions. These disorders involving mood, memory, personality and behaviour are major challenges for the medical profession and often refractory to pharmacotherapy, thus representing an important avenue for the development of DBS.

Treatment resistant depression

For over a decade, treatment resistant depression (TRD), defined as the presence of major depressive disorder and failure to respond to at least four different classes of anti-depressant (including augmentation with lithium, anticonvulsants, atypical antipsychotics and antidepressants) electroconvulsive therapy and evidence based psychotherapy, has been investigated for its responsiveness to DBS. A number of neuroanatomical DBS targets have been described including the ventral capsule/ventral striatum (VC/VS), the subcallosal cingulate ⁴⁷ , the nucleus accumbens ⁴⁸ , medial forebrain bundle, inferior thalamic peduncle and the lateral habenula ^{49,50} . Generally, response to DBS is taken to be equal to or more than 50% improvement in the Hamilton Depression Rating Score (HDRS), while remission is taken to be a score of “non-depressed” on the HDRS scale. The stimulation target associated with the most extensively reported outcomes is probably the subcallosal cingulate, otherwise known as the subgenual cingulate or Brodmann’s area 25 ⁵¹.

Reasons for initial interest in this area as a target included observations that reduced metabolic activity in this region was reported in patients with major depressive disorder who responded to anti-depressant therapy, but not those who were unresponsive to anti-depressant therapy ^{52, 53} . Furthermore, the subgenual cingulate appeared to be connected to a number of other important regions linked with depression ⁵⁴ . In small open label trials, DBS of the subcallosal cingulate has indeed been shown to be safe and efficacious ^{55 56 57} . Furthermore, an open label trial including a sham lead in phase has also shown good results ⁵⁸ , and ongoing DBS in patients with successfully treated treatment resistant depression also appears to protect against remission ⁵⁹ . However, the BROADEN trial, an important controlled, blinded trial of subcallosal DBS for TRD carried out by St Jude Medical was discontinued, as it failed a futility test, raising important questions about the efficacy of the treatment and the best way to assess outcome.

DBS of the VC/VS has also been investigated with apparent beneficial effects ⁶⁰ with no major adverse neuropsychological effects ⁶¹ however, this too was associated with a discontinued clinical trial, again due to perceived lack of efficacy of the treatment compared with sham stimulation ⁶² .

However, despite apparent lack of efficacy in the large industry sponsored trials, research continues. Alternative targets are actively under investigation including DBS at the inferior thalamic peduncle (ITP) and median forebrain peduncle ⁵⁰ and furthermore, research into the mechanism of action of existing DBS targets for TRD is taking place, with the aim of better defining stimulation targets and providing ways of optimising target selection based on individual anatomy. For example, in patients

with subcallosal cingulate DBS, analysing the structural connectivity of contacts producing the best behavioural outcomes compared with non-best (but nevertheless positive) outcomes showed that the best outcomes were associated with connectivity to three white matter pathways: forceps minor, left uncinate fasciculus (both innervating the ventromedial prefrontal cortex) and the left cingulum bundle (passing to the cingulate cortex), whereas the non-best pathways only involved the cingulate ⁶³. The anatomical specificity that may be achieved through tractography-based approaches is likely to improve outcomes and help researchers identify optimal stimulation targets on a case-by-case basis.

Obsessive compulsive disorder

Obsessive compulsive disorder is a disabling psychiatric disorder which has a prevalence of around 2-3% ⁶⁴. It is associated with unwanted ideas, images and compulsions, which lead to the performance of repetitive and stereotyped mental or behavioural acts. Of the population diagnosed with OCD, 10% may be completely medication refractory, and as many as 10-40% may remain severely disabled despite treatment ⁶⁵⁻⁶⁸. Historically, lesional surgery such as cingulotomy and anterior capsulotomy has been a last-resort option for patients with severe refractory OCD, but the procedure is irreversible and associated with a risk of adverse effects ⁶⁹. OCD is thought to be associated with neural circuit abnormalities in cortico-striato-thalamo-cortical loops that implicate the thalamus, striatum and amygdala, and cortical regions including the prefrontal cortex, dorsolateral prefrontal cortex, orbitofrontal cortex, anterior cingulate cortex and the ventromedial prefrontal cortex ⁶⁹. High frequency DBS, aimed at modulating activity within this circuit, was first described in 1999 ⁷⁰,

and in 2009, the US FDA released a humanitarian device exemption for DBS for OCD

(<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm149529.htm>), based on evidence from 26 patients with severe, medication refractory OCD, across 4 sites who had an average 40% symptom reduction over a 12 month period. A number of targets have been trialled including the anterior limb of the internal capsule (ALIC), the nucleus accumbens, ventral caudate, ventral capsule & ventral striatum (VC/VS), the STN and the inferior thalamic peduncle (ITP), and successful outcomes may be linked to a reduction in high pre-operative fronto-striatal connectivity ⁷¹ . A recent meta-analysis of studies of DBS for OCD ⁷² included data from 31 studies (116 patients), of which six studies (45 patients) were double blind sham controlled studies. The meta-analysis found that there was a global improvement on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) of 45.1%, global response of 60% and that the incidence of severe adverse effects was less than for the comparable ablative techniques, capsulotomy or cingulotomy. Although follow-up durations differed between studies, all of the trials that included a sham stimulation arm reported a significant benefit resulting from active stimulation compared with sham stimulation ⁷² . Adverse effects included intracranial haemorrhage in 3 patients, 5 patients with infections of the scalp or abdominal wound, which were controlled with antibiotics, and 1 tonic-clonic seizure. Hypomanic symptoms were the most common adverse effect (n = 23) and some autonomic side effects were also described including enuresis (n = 3), weight changes (n = 6), sleep difficulties (n = 4), flushing (n = 12) dizziness and nausea (n = 7). Interestingly although many studies did not report quality of life outcomes, those which did provide this data appeared to show that QOL measures continued to improve years after the implantation of DBS and that QOL

improvements were seen even in those patients who were classified as non-responders. This point is of critical importance, which could easily have escaped unnoticed if study design had been limited to narrow outcome criteria or short follow-up durations.

Tourette's Syndrome

Tourette's syndrome is a neuropsychiatric condition that affects roughly 1% of the population globally ⁶⁸. It develops in childhood and is associated with multiple motor tics and also vocal tics. There is also a high incidence of comorbid neuropsychiatric conditions such as ADHD, OCD and deliberate self-injury behaviours. Although the neural basis of Tourette's syndrome is not fully understood, one hypothesis implicates dysfunctional striatal circuitry whereby the GPi and SNr receive excessive inhibition, resulting in thalamic disinhibition and the resultant brief motor tic ^{73, 74}. Based on this concept, a number of targets have been investigated including the thalamic centromedian-parafascicular complex (CN/Pf) which receives output from basal ganglia circuits ⁷⁴, the subthalamic nucleus, the nucleus accumbens and the globus pallidus interna (GPi). In a study which included 18 patients with up to 6 years' follow up, Porta et al (2012) ⁷⁵ reported a significant improvement in tics as well as the incidence of OCD and depression after CM/Pf DBS. More recently, a randomised double blind cross-over trial of GPi DBS reported a significant improvement in tics during the on stimulation blinded phase of the trial relative to the off stimulation phase ⁷⁶, and a further improvement in the incidence of tics and an improvement quality of life measures during the open label phase. Only one study has attempted to compare the CM thalamic and GPi targets in terms of both tic reduction and

improvement of psychiatric co-morbidities and this study found the GPi to be the most advantageous in this regard ⁷⁷ .

Alzheimer's Disease

Although Alzheimer's disease (AD) has been traditionally viewed as a structural disorder with clear pathological features, there are associated functional changes, including deficits in memory and cognition. It is a possibility that functional deterioration could be reversed or slowed by DBS to enhance performance in selected functional circuits. A phase I trial of DBS in the fornix/hypothalamus (electrodes were implanted in the hypothalamus but also made contact with the anterior border of the fornix) in 6 patients with mild AD demonstrated a turnaround in the pattern of reduced glucose utilisation relative to controls typically seen in AD, and the rate of decline in mini mental state (MMSE) score appeared to decrease ⁷⁸ . Furthermore, in a different report describing the same patient cohort, improved functional connectivity in fronto-temporo-parieto-striatal-thalamic and fronto-temporo-parieto-hippocampal networks were observed at 12 months post DBS and metabolic changes in related cortical regions correlated with better memory, cognitive and quality of life outcomes ⁷⁹ . Furthermore, at one-year follow up, hippocampal atrophy was significantly less in the DBS group than in a matched AD group who did not receive DBS ⁸⁰ . The long-term follow-up and safety outcomes from this cohort will be of great interest.

Addiction, obesity and eating disorders

“Limbic” circuits have been targeted in the search for DBS for addiction and eating disorders. As the brain’s “reward centre”, the NAc is thought to be a promising target for DBS for addiction, and has been shown to have a significantly reduced volume relative to controls in male heroin addicts ⁸¹ . Case reports have described cessation of addiction in heroin addiction ^{82, 83} and alcohol addiction ⁸⁴ following NAc DBS, and in a long term follow up study, Muller et al reported outcomes for 5 patients who underwent DBS of the NAc for alcohol addiction. Of these, all patients reported complete absence of cravings for alcohol and two out of five became completely abstinent at long-term follow up, while the other 3 significantly reduced their alcohol intake ⁸⁵ .

Anorexia nervosa is a potentially life-threatening eating disorder, associated with a fear of weight gain and “refusal to maintain a body weight at or above the minimally normal weight for age and height” (DSM-IV). This is classified as restricting type or binge-eating/purging type. In a phase I prospective study of six patients with chronic anorexia nervosa, Lispman et al (2013) ⁸⁶ reported improved BMI in three patients at 3 months post surgery and improvements in mood and affective symptoms in four subjects. There was one serious adverse event reported in the trial (a seizure thought to be due to severe metabolic derangements during programming). PET imaging showed a reduction in cingulate, medial frontal and insular metabolic activity and increase in parietal lobe activity after treatment. A case report also describes improved BMI in a single patient after DBS of the subgenual cingulate for anorexia nervosa ⁸⁷ . DBS of the NAcc ^{88, 89} and VC/VS has also been shown to be beneficial in a patient with anorexia nervosa and symptoms of OCD ⁹⁰ .

Morbid obesity has also been a subject of interest in relation to DBS. The costs and risks of bariatric surgery are not negligible and various neural stimulation targets for obesity treatment have been described, including the lateral hypothalamus and ventral hypothalamus, important centres for the control of appetite and feeding behaviour, and the nucleus accumbens based on evidence that dysregulation of reward circuitry is involved in obesity ^{91,92}. There is limited published evidence about the outcome of DBS for obesity in humans: Whiting et al (2013) ⁹³ published a small series of 3 patients and described DBS of the lateral hypothalamus as safe, with ‘weight loss trends’ observed when monopolar stimulation was specifically set at contacts demonstrated to increase metabolic rate. A single subject was treated with bilateral hypothalamic electrodes ¹⁵ with no effect on weight, and further trials are underway.

Autonomic

The autonomic nervous system (ANS) is involved in the regulation of physiologic and homeostatic parameters relating particularly to the visceral organs and the co-ordination of physiological responses to threat. Blood pressure and heart rate, respiration, pupillomotor reactivity, sexual function, gastrointestinal secretions and motility, and urine storage and micturition are all under a degree of autonomic nervous system control. Furthermore, there is close integration between the autonomic nervous system and other neural functions such as emotion and cognition ⁹⁴, and thus brain regions that are known to be important for autonomic control are

also implicated in emotional functions, such as the amygdala in fear conditioning and PTSD.

Many autonomic functions are maintained via peripheral nervous system feedback loops, often with a central nervous system component. Collectively, the network of brain areas involved in maintaining and regulating the autonomic nervous system is known as the ‘central autonomic network’ and important progress in our understanding of the anatomy and function of the CAN in the human have been made in recent years due to developments in neuroimaging techniques^{95 96}. Modulation of activity within the CAN at specifically selected anatomic targets, using DBS, offers a possible means of altering or modifying autonomic functions, and carefully observed studies of autonomic side effects arising from DBS for other indications, have made it possible to experimentally test the effects of DBS on the autonomic nervous system⁹⁷. However, these results have to be interpreted in the light of the underlying pathology of the patients in which the electrodes have been implanted- for example, many of the observations will be described here based on data from STN DBS in patients with PD- it is not clear whether STN DBS would have similar effects in healthy control subjects and it is probable that the reported effects are significantly modulated by the disease state. Nevertheless, emerging patterns of autonomic changes following DBS have implications for sufferers of a range of cardiovascular, respiratory, gastrointestinal and genitourinary disorders that implicate ANS functioning, in addition to patients with primary dysautonomias, and conditions such as Parkinson’s disease and multiple system atrophy (MSA) that impair the performance of organs regulated primarily by the autonomic nervous system. The scope is vast and for patients with severe and life-threatening or life-impairing disturbances of the

autonomic nervous system, the risks of deep brain stimulation may be acceptable when weighed against the symptoms and implications of their condition.

Generalised autonomic changes following DBS

Deep brain stimulation of the subthalamic nucleus (STN) in Parkinson's disease has been shown to have measurable effects on autonomic nervous system activity, both intra-operatively and following implantation. Thornton et al (2002) ⁹⁸ showed that high frequency stimulation of the STN produces a physiological effect similar to that during exercise. According to a microstimulation study by Benedetti et al (2004) ⁹⁹, consistent autonomic effects were achieved with dorsal STN stimulation regardless of whether the patient was aware of, or blinded to, the onset of stimulation. By contrast, stimulation of the ventral STN produced variable autonomic effects that were modulated by patient awareness of stimulation, and on 3 occasions, was accompanied by additional emotional response. The authors hypothesise that the dorsal STN autonomic effect may be directly related to central command, while the ventral STN effects may be inter-related with emotional and associative responses via the limbic system. In one study, which investigated motor and non-motor effects during intra-operative exploration of the STN in subjects with PD ¹⁰⁰, autonomic effects were described at 19.6% of target points evaluated, occurring in 15 of the 17 patients included in the study. The authors described two groups of symptoms which occurred in association with one another: (1) those of a subjective character, producing feelings of stress, anguish or anxiety; chest congestion, faintness or abdominal discomfort; and a sensation of warmth or cold, and (2) those of a more objective nature, including mydriasis, sweating and flushing, either unilateral or bilateral; and tachycardia and

increased blood pressure. There was no lateralisation associated with these symptoms, however, they were commonly evoked when the stimulating electrode was well-placed for improving motor symptoms, and the effects increased with increasing voltage. The authors suggested that the effects could have been caused by current spread to local autonomic structures connected with the hypothalamus, such as the median forebrain bundle, zona incerta or Forel's fields; or by stimulation of the limbic subdivision of the STN, thought to be connected with other autonomic structures including the anterior cingulate cortex. The close association with motor improvement and autonomic adverse effects in this study may support the former hypothesis.

Similarly, studies in patients with PD to investigate post-operative effects of STN DBS on autonomic variables have demonstrated various autonomic effects resulting from STN stimulation. A study of 19 PD subjects found improvements in symptoms of dyshidrosis based on a semi-structured questionnaire, but no change in the sympathetic skin response recorded from the palm and the sole of the foot before and after DBS ¹⁰¹. Halim et al (2010) ¹⁰² carried out structured questionnaires in 11 PD subjects with STN DBS. 3 out of 11 subjects reported improvements in autonomic symptoms following DBS; improvements in sweating were reported by all three subjects, urinary symptoms by two and bowel symptoms by one. All 3 subjects had early onset PD, while the 8 subjects who did not report autonomic improvement had late onset PD.

STN DBS has been shown to produce symptomatic improvements in gastrointestinal symptoms associated with PD, including constipation, sialorrhoea, dysphagia and difficulty with defecation, and also leads to normalisation of recorded

electrophysiological signals as recorded by electrogastrography ¹⁰³, which may be related to changes in the autonomic nervous system in general.

Cardiovascular system

Although generalised autonomic changes appear to follow STN DBS, the evidence is less clear as to whether cardiovascular autonomic variables improve in patients who have had STN DBS. Holmberg et al (2005) ¹⁰⁴ compared changes in cardiac autonomic reflexes over a 1-year period between a group of PD subjects receiving pharmacological treatment only and another group who had undergone STN DBS. They found no significant difference in the cardiovascular autonomic score change relative to baseline between the two groups, and moreover in the STN group, there was an increase in the number of patients displaying pathological responses to tilt testing. However, in a more recent study which compared heart rate variability during sleep in the ‘off’ and ‘on’ stimulation states in 8 patients ¹⁰⁵, STN DBS significantly increased the sympathetic component of the autonomic response, based on an increase in the LF/HF ratio with DBS ‘on’ compared with DBS ‘off’. Furthermore, cerebrovascular reactivity, which is thought to be linked to orthostatic hypotension and is reduced in PD as a result of impaired sympathetic innervation, was shown to improve with STN DBS ¹⁰⁶.

DBS of the PAG for chronic pain has also been shown to have major effects on the cardiovascular system. The PAG is a horseshoe-shaped grey-matter structure which encircles the cerebral aqueduct in the midbrain ¹⁰⁷. It is arranged into longitudinal columns that represent functionally distinct regions ¹⁰⁸. Stimulation of the lateral

PAG with excitatory amino acids elicits defensive ('fight or flight') reactions associated with tachycardia, raised arterial blood pressure and distribution of peripheral blood flow towards the limbs ^{109 110}, while stimulation of the ventrolateral PAG column elicits quiescence, as would be expected after social defeat, associated with reduced arterial blood pressure and bradycardia ^{111 112}. Similar effects have been reproduced in stimulation experiments in humans with implanted deep brain stimulation systems ¹¹³. While eliciting a passive coping response or a 'fight or flight' response is not necessarily desirable or useful therapeutically, the ability to reliably modulate blood pressure using PAG stimulation may have important therapeutic benefits for patients with refractory hypertension. Reduction in VAS score with rostral PAG DBS correlated with the reduction of blood pressure achieved by PAG stimulation during 9 six-minute testing sessions ¹¹³, and a case report describes a subject treated with PAG stimulation for chronic pain whose blood pressure dropped so significantly that his anti-hypertensive medications could be stopped ¹¹⁴. PAG DBS has also been shown to oppose the postural drop in blood pressure associated with standing from sitting in patients with chronic pain and clinical orthostatic hypotension or orthostatic intolerance ¹¹⁵ and to modulate the balance of parasympathetic and sympathetic nervous system activity as measured by heart rate variability ¹¹⁶.

Respiratory system

Like cardiovascular function, the effects of STN DBS on respiratory function are not completely clear. In a group of 10 subjects with STN DBS, there was a significant increase in peak expiratory flow rate with DBS turned on, which correlated with the

overall energy product (a numerical value based on the product of pulse width, voltage and frequency of stimulation), with no effect of DBS on FEV1 or FVC ¹¹⁷ . Furthermore, a case of respiratory dyskinesia was successfully treated by bilateral STN DBS ¹¹⁸ . However, these positive effect on respiratory function should be balanced against the findings of Chalif et al, who found that patients with STN DBS reported symptoms of dyspnoea following chronic stimulation ¹¹⁹, suggesting that the long-term symptomatic changes following STN DBS may be different to the short term ON/OFF effects.

PAG DBS also has an effect on respiratory function. In a group of ten patients with PAG DBS, peak expiratory flow rate increased by a mean 13.4% with PAG stimulation ON vs OFF ¹¹⁷ , although there was no significant change in forced vital capacity (FVC) or FEV1/FVC ratio in the same group of subjects. Different anatomical columns of the PAG region are differentially involved in the response to respiratory challenge, with the lateral PAG responsible for the sensorimotor aspects of breathlessness and the ventrolateral PAG activated during the anticipation of a breathing challenge ¹²⁰ . Column-specific targeting may therefore be necessary if PVG/PAG stimulation is to prove effective in the management of respiratory disorders such as asthma.

Lower urinary tract symptoms

Urinary incontinence and voiding difficulties are conditions that can severely affect quality of life. Urinary problems develop as a consequence of many neurological

conditions including spinal cord injury, cerebrovascular events, multiple sclerosis, Parkinson's disease and vascular and neoplastic lesions affecting the brain's bladder control system.

Improvements in lower urinary tract symptoms in PD patients after STN DBS have been shown in a number of studies. In a small study with five participants STN DBS was shown to increase bladder volume at normal desire to void, as well as increasing bladder capacity, and the bladder volume threshold for detrusor overactivity ¹²¹. The majority of subsequent studies corroborate this early observation, finding that STN stimulation in human subjects with PD, at clinically therapeutic stimulation parameters, increases sensory thresholds during bladder filling ¹²²⁻¹²⁴, facilitating a larger bladder capacity and enabling greater volume to be held in the bladder before the onset of detrusor overactivity. At an extreme end of the spectrum, two patients were reported to have gone into urinary retention after STN DBS implantation ¹²⁵. The only exception is a report by Winge et al 2007 ¹²⁶, where no urodynamic changes were reported with STN DBS ON compared with STN DBS OFF, and the reason for this difference is not clear, although it may be that differences in stimulation parameters or electrode location (not published in all studies), or patient factors, influenced the results. A PET study demonstrated that STN DBS appeared to modulate afferent bladder information transmission from the periaqueductal grey area to the posterior thalamus and this was proposed as a possible mechanism of action for the improved urinary storage following STN DBS ¹²³.

There is no doubt that this fairly consistent "side effect" of STN stimulation on urinary function brings serendipitous benefits to sufferers of Parkinson's disease who

have had DBS for their movement disorder. However, it is likely that this effect is specific to Parkinson's disease sufferers, 'normalising' a neurophysiological imbalance unique to PD that affects bladder control. For many other patients with bladder disorders, STN DBS may not offer hope of improvement. Other DBS targets for bladder control have also been investigated. The PAG, which is well recognised to be an important link in the brain-bladder system, receiving afferent information about bladder fullness and contextual information from forebrain regions, may act as a switch to change between voiding and storage modes (see Griffiths & Fowler 2013 for a review) ¹²⁷. In the human, it has been shown that DBS of the PAG increases maximal bladder capacity but not bladder volumes at earlier stages of filling, consistent with the theory that PAG activity is critical at the storage-voiding switch ¹²⁸. Perhaps for patients with urgency incontinence, a DBS system which stimulated this region intermittently, when subjects experienced a sensation of urinary urgency, could prevent leakage and allow the patient enough time to reach a toilet facility- for this a "closed loop" type model of DBS would be the optimal design, if appropriate physiological signals within the PAG could be identified as consistent with urinary urgency.

Interestingly, other modes of DBS have also been shown to affect bladder function. In a single subject with Parkinson's disease, pedunculo pontine nucleus (PPN) DBS produced new onset detrusor overactivity after electrode implantation ¹²⁹. Since the PPN is located close to the brainstem pontine micturition and storage centres, it is probable that both effects reported were due to different activity at one of these critical bladder centres. The effects of thalamic DBS, tested in patients with essential tremor (ET), reduced bladder capacity and sensory thresholds during bladder filling

¹³⁰ . Pallidal DBS in dystonia sufferers reduced detrusor overactivity, reduced the urine flow rate and increased the post-void residual, without affecting bladder filling parameters ¹³¹ , suggesting that the pallidum may have a role in co-ordinating urinary voiding. Interestingly, one patient with traumatic brain injury who received NAcc/IC DBS with the goal of improving frontal lobe functioning to reduce overall disability caused by TBI was able to stop taking tolterodine for urinary urgency because he became able to “self-initiate toileting” ¹¹ . It is hopeful that these early studies may lead to new treatment options for patients with severe incontinence or voiding difficulties, either as an independent neuromodulation device, or, for individuals with bladder disorders secondary to peripheral nerve or spinal injuries, as part of a system coupled to a functional electrical stimulation device to link brain signals to bladder contractions.

TRIALS AND TECHNOLOGY: THE KEY TO PROGRESS

Technological innovation has underpinned and paralleled developments in the clinical applications of DBS. In this final section, we discuss some important factors involved in recent and future developments including animal models, trials and technology.

One of the critical factors that has both enabled and restrained development of DBS technology is animal models. Availability of a good animal model, for example as in the case of Parkinson’s disease, has enabled lesion/stimulation targets to be tested and verified before human trials of DBS began ^{132 133} . Animal models for other conditions, particularly neuropsychiatric, are less optimal but nevertheless still important for advancing knowledge about the condition. Coupling of animal models

with powerful techniques such as optogenetics have been particularly useful in selecting and refining certain stimulation targets ^{134, 135} .

Clinical trials are essential for establishing a new indication for DBS, demonstrating efficacy of anatomical targets and stimulation parameters for given patient groups. Anatomical sites for DBS that have the support of clear trial evidence are most likely to receive health authority approval, licensing and funding. However, for ethical and practical reasons, DBS trials can be difficult to run, and this can therefore represent a major hurdle in the development of the field. One explanation for the challenging nature of DBS trials is that, as described above, animal models for neuropsychiatric conditions are not always adequate. This means that questions about precise targeting, stimulation parameters and patient selection often have to be answered through human studies, which in some circumstances is ethically questionable. However, improvements in structural and functional MRI ¹³⁶, along with parallel developments in MEG, EEG and intracranial recordings using subdural grids and implanted DBS electrodes, have greatly increased our ability to determine effective targets by highlighting aberrant circuit activity in different conditions. We believe that including a “control” design, either by using an N-of-1 paradigm ¹³⁷ or by incorporating a sham stimulation arm ¹³⁸ , ensuring double-blinding wherever possible ¹⁰ , using a well-selected range of primary and secondary outcome measures including quality of life ¹³⁹ and ensuring a long follow up duration ⁷² are all important elements to the ideal trial.

Stereotactic and functional neurosurgery has been characterised by innovative thinking in the past ¹⁴⁰ . New ideas and innovations will inevitably change the nature

of the field in the future. For example, adaptive stimulation for Parkinson's disease, using a brain computer interface to trigger STN DBS onset when beta oscillations within the STN exceed a threshold, and to stop stimulation when oscillations fall below the threshold, has been shown to be clinically more effective and more energy efficient than continuous DBS ¹⁴¹ . Intermittent DBS is also being investigated for conditions with non-continuous symptomatology, such as Tourette syndrome ⁶⁸ , and neural oscillations are being studied to identify pathological signatures, such as the beta band in PD and the theta band in treatment resistant depression ¹⁴² . Furthermore, directional DBS lead types are becoming available which permit greater flexibility over the shape of the volume of activated tissue to avoid unwanted side effects due to current spread to adjacent white matter tracts ¹⁴³ .

Finally, in addition to advancements in DBS technology that will improve the efficiency and effectiveness of DBS, and the range of conditions that can be treated, we anticipate changes in technology that will allow systems to become easier to program and use. For example, systems that can be programmed remotely will enable changes to be made without the patient travelling to clinic to physically meet a member of the DBS team. Changes such as these, in combination with improved efficiency and longer battery life, may make DBS technology more accessible including to those in less economically developed countries, where at the moment, high treatment costs and poor access to tertiary centres makes DBS an unrealistic option for many people who would benefit from it.

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