Chapter 42
Deep Brain Stimulation in the Management of Neuropsychiatric Conditions in Children

DBS in Paediatric Neuropsychiatric Diseases

Luciano Furlanetti, Asfand Baig Mirza, Kantharuby Tambirajoo, and Keyoumars Ashkan

Abbreviations

AB	aggressive behaviour and self-harm
ALIC	anterior limb of the internal capsule
BNST	bed nucleus of stria terminalis
cg25	Broadman's area 25
CM	centromedian nucleus of the thalamus
DBS	deep brain stimulation
ED	eating disorder
GPi	globus pallidus internus [am = anteromedial, pv = posteroventral]
GTS	Gilles de la Tourette syndrome

L. Furlanetti (✉)
Department of Basic and Clinical Neuroscience, King's College London, London, UK

King's Health Partners Academic Health Sciences Centre, London, UK

A. B. Mirza · K. Tambirajoo · K. Ashkan
King's Health Partners Academic Health Sciences Centre, London, UK

Department of Neurosurgery, King's College Hospital NHS Foundation Trust, London, UK

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ITP	inferior thalamic peduncle
NAc	nucleus accumbens
OCD	obsessive compulsive disorder
pHyp	posterior hypothalamus
slMFB	superolateral branch of the medial forebrain bundle
STN	subthalamic nucleus
TRD	treatment resistant depression
VC/VS	ventral internal capsule/ventral striatum

42.1 Introduction

Psychiatric disorders remain refractory to treatment for a significant number of patients despite significant advances in pharmacological and non-pharmacological management strategies. Neurosurgery has provided an alternative option for patients with refractory psychiatric indications, where ablative therapy, including anterior cingulotomy, capsulotomy, limbic leucotomy were proven to be highly effective [1]. More recently, the advantages conferred by non-destructive, reversible and adjustable deep brain stimulation (DBS) therapy has favoured it over ablative procedures as the first choice option in most neurosurgical units worldwide.

Psychosurgery has had a highly controversial background, stemming from historical misuse and technological abuse in diverse patient populations with lack of ethical and regulatory oversight for ambiguous indications associated with considerable morbidity [2]. Because of that, current approach to neuromodulation with DBS in psychiatry has had to largely follow a structured ethical and regulatory route whilst advances in neuroimaging, stereotactic methods and neurosurgical tools have reduced the surgical risks.

Nonetheless, DBS therapy at present remains investigational for most psychiatric conditions with a lack of large-scale controlled studies to assess its efficacy and outcomes. At least partly this is related to the heterogenous symptoms and complex anatomy and biology of psychiatric disorders which make such studies difficult. This is even more evident in the paediatric population, where the stakes are significantly higher and where modulating the developing brain raises additional concerns. This chapter sets out to delineate the current evidence for DBS use in psychiatric conditions, highlighting the work done thus far in the paediatric population.

42.2 Scientific Evidences

A comprehensive review of the literature has recently detailed the state of art of potential applications of DBS in the management of complex neuropsychiatric conditions in adults and children [3]. Out of over seventy peer-reviewed studies reported so far, only 11 included patients under the age of 18 years. Among paediatric patients, the indications for surgery included GTS, AB and ED (Table 42.1)

Table 42.1 Deep brain stimulation for neuropsychiatric disorders in children

Author/Year	Study design	No. of patients	Age, years at surgery (range)	Indication	DBS target (s)	Uni/ Bilateral	Results (% improvement, mean)	Follow-up (mean, months)
Servello et al. (2009)	Observational, open label	35	17–57	GTS	Thalamus; GPi-pv; ALIC/NAc	Bilateral	50.3% (YGTSS)	3–24
Motlagh et al. (2013)	Open-label prospective	8	16–48	GTS	Thalamus, Gpi-am, GPi-pv	Bilateral	45% (YGTSS)	69
Nair et al. (2014)	Observational cohort	4	15–43	GTS	GPi-am	Bilateral	82.1% (YGTSS)	42.5
Sachdev et al. (2014)	Observational cohort	17	17–51	GTS	GPi-am	Bilateral	44.8% (YGTSS)	24.1
Johnson et al. (2019)	Multicentric, retrospective	110	14–61	GTS	CM, GPi-am, GPi-pv, NAc/ALIC	Bilateral	46.7% (YGTSS)	33.7
Martinez-Ramirez et al. (2019)	Multicentric, prospective	185	13–58	GTS	CM, GPi-am, GPi-pv, NAc/ALIC	Bilateral	45.1% (YGTSS)	12
Zhang et al. (2013)	Observational cohort	6	13–17	Anorexia	NAc	Bilateral	+28% (BMI 12.2 to 15.6)	1
Wu et al. (2012)	Observational cohort	4	16–17	Anorexia	NAc	Bilateral	+65%, (BMI 11.9 to 19.6)	38
Torres et al. (2013)	Observational cohort study	6	17–48	AB/DRE	pHyp	Bilateral	47% (ICAP); 30% reduction in DRE	6–82
Benedetti-Isaac et al. (2015)	Observational cohort study	9	16–33	AB/DRE	pHyp	Bilateral	65% (OAS); 89.6% seizure reduction	2–48
Tambirajoo & Furlanetti et al. (2020)	Observational cohort study	4	11–16	Lesch-Nyhan	amGPi/pmGPi	Bilateral	60.5% (BPI-frequency) 64% (BPI-severity)	22–98

GTS Gilles de la Tourette Syndrome, *GPi* globus pallidus internus, *am* anteromedial, *pv* posteroventral, *cm* centromedian nucleus of the Thalamus, *ALIC* anterior limb of the internal capsule, *NAc* Nucleus Accumbens, *YGTSS* Yale Global Tic Severity Scale, *AB* aggressive behaviour and self-harm, *OAS* Overt Aggression Scale, *pHyp* posterior hypothalamus, *DRE* drug resistant epilepsy, *ICAP* Inventory for Client and Agency Planning (maladaptative behaviour index), *N/A* not available, *BPI* Behaviour Problems Inventory

[4–14]. Despite of the large number of published works on the management of TRD and OCD with DBS among adult patients, consistent studies evaluating this approach in children are still lacking. The various brain targets approached for the treatment of the psychiatric conditions in children included the GPi, the ALIC or (VC/VS), the NAc, different nuclei of the Thalamus and the pHyp. The main findings and evidences available in favour or against DBS in the management of psychiatric conditions in patients under 18 years of age are discussed below.

42.2.1 Gilles de la Tourette Syndrome

42.2.1.1 Background

GTS is characterised by motor and vocal tics with a disease onset usually occurring before 18 years of age [15]. The onset of tic symptoms often begins in childhood, reaches a peak during the prepubertal period before gradually decreasing in the adolescence. Approximately 75% of children with GTS will experience a significant improvement in their symptoms by adulthood [15]. Children with severe and debilitating symptoms often have impaired quality of life (QoL) which is complicated by the presence of other psychiatric co-morbidities such as attention deficit/hyperactive disorder (ADHD), OCD, anxiety, depression and AB [16].

42.2.1.2 Surgical Management

Vanderwalle et al. 1999 reported the first three cases of DBS for GTS, using the centromedian nucleus—substantia periventricularis—nucleus ventro-oralis internus complex (CM-Spv-Voi) target, which was based on the stereotactic target used for ablative procedures introduced by Hassler and Dieckmann [17]. Multiple targets are currently in use including the dorsomedial nucleus of the thalamus, ventral anterior and ventrolateral motor part of thalamus, GPi (anteromedial part [am] and posteroventrolateral part [pl]), NAc and the ALIC. A pooled analysis of studies demonstrated that DBS for GTS had the highest efficiency amongst the psychiatric diseases [18].

Most of the studies for DBS in GTS have been conducted in adults with moderate to good clinical outcomes [19–26]. The first case series in 1999 of 3 patients aged 28–45 years had a 70–90% reduction in tic frequency and intensity over a follow up of 1–5 years [17]. A systematic review and meta-analysis of 57 studies involving 156 cases with a median age of 30.0 years ± 9.8 years (15–60 years) demonstrated a 52.68% reduction in the Yale Global Tic Severity Scale (YGTSS) scores [27]. No significant difference was seen in score reduction between the

different targets used. Overall vocal tic control was better than motor control [27]. Another long term study of post-DBS clinical outcomes in 110 patients in 13 centres demonstrated a median time of 13 months to achieve a 40% improvement in tics associated with a significant improvement in obsessive-compulsive behaviour with no appreciable differences across brain targets [8]. A prospective DBS database and registry of 185 patients in 31 centres with a mean age of 29 years (13–58 years) showed significant improvements in YGTCC score, motor and phonic tics [9]. There was a 35.4% incidence of adverse events (AE), with 3% rate of infections and 6% rate of dysarthria [9]. Another study reported on 15% risk of apathy exclusively seen with thalamic stimulation [28].

42.2.1.3 DBS for GTS in Paediatric Patients

The European Society for the study of Tourette Syndrome (ESSTS) initial guidelines in 2011 recommended that DBS should be reserved for resistant disease with well managed co-morbidities, an age limit of above 25 years, with the operation to be carried out in an experienced multi-disciplinary unit [21]. The updated guidelines in 2014 removed the 25-year-old age limit but recommended that ethical review should be sought for patients aged less than 18 years with careful and robust data collection [29]. A meta-analysis specifically looking at safety and efficacy of DBS in 58 children and young adults (mean age 17.9 ± 2.7 years, range 12–21 years) demonstrated an average of 57.5% ± 24.6% improvement in the YGTSS across the studies [30]. The presence of co-morbid depression correlated negatively with outcome and 25% experienced side effects, the majority of which were classed minor in nature. A single case report of a 15-year-old patient with extremely refractory GTS with associated OCD demonstrated an 81% improvement in YGTCC score and complete resolution of the OCD symptoms at 1 year after stimulation of ALIC/bed nucleus of stria terminalis (BNST), emphasising that young age should not be a contraindication for stimulation therapy in well selected patients [31]. Nevertheless, the application of DBS for OCD in the paediatric population is sparsely reported, since many children with OCD can spontaneously remit as they grow up [32, 33]. Also, the combination of pharmacotherapy and cognitive behavioural therapy can achieve remission rates as high as 50% [32, 33].

In the field of neuropsychiatric disorders, GTS represents the largest experience in terms of application of DBS as a treatment option in children. Since the first published case report over 20 years ago, there is now some evidence to support DBS as an effective and safe option for the treatment of medically refractory GTS in selected children and young adults. However, GTS is associated with high remission rates by early adulthood unlike movement disorders such as primary dystonia. Therefore, arguments for use of DBS in children for diseases that will have an eventual decrease in severity will need to include a rationale for possible persistence and for marked disability during symptomatic periods [34]. Uncontrolled GTS, especially if

associated with other comorbidities such as OCD, in a child may hinder social and educational development, irrespective of possible remission later in childhood and DBS offers the possibility of symptom control during this critical time [34]. However, the risk-benefit ratio of DBS needs to be considered in the light of symptom severity and adverse effect of alternative treatment [28]. Large prospective studies with long-term follow-up are needed for a better understanding of the impact of neuromodulation at different targets on the course of the disease in children.

42.2.2 Eating Disorders

42.2.2.1 Background

Even though early treatment of adolescents with anorexia nervosa (AN) is successful in 30–60% of patients, management of patients with symptom duration of longer than 3 years is more challenging [35]. Outcomes are poor with a high mortality rate in those with an established disease despite the best available psychological treatments [36]. Patients with severe AN are extremely aversive to eating and weight gain with pathologically rewarding behaviours of food restriction and other weight-loss behaviours [37]. AN has a strong association as a comorbidity with other psychiatric disorders and has shown improvement in outcomes after DBS for concomitant OCD or TRD [37, 38].

42.2.2.2 Surgical Management

Blomstedt et al. (2017) reported a female patient with TRD and AN who had DBS of BST with resultant subjective improvement in food and eating anxiety without any significant effects on the BMI [39]. Another paper reports of a female patient with refractory OCD and AN who underwent VC/VS-DBS with subjective improvement in AN symptoms with neuromodulation [40]. A single case report of a female patient with restrictive AN and chronic recurrent depression who underwent subgenual cingulate stimulation resulted in a BMI sustained above 19.1 for 2 years with no further interventions or hospitalisation required for the AN [41].

A pilot study looking at DBS in AN specifically was carried out in six patients using the subcallosal cingulate as the target [42]. Fifty per cent of patients maintained BMI greater than at baseline at 9 months with a similar number reporting improved QoL. One adverse event (Seizure) was attributed to metabolic disturbances [42]. A one-year follow-up open label trial of 16 patients (aged 20–60 years) with an average BMI of 13.83 and 88% incidence of co-morbid mood disorders, anxiety disorders or both demonstrated significant improvements in depression, anxiety and affective regulation with subcallosal cingulate stimulation [43]. Interestingly, significant changes in glucose metabolism in key AN-related

structures were noted at 6- and 12-months post stimulation. 44% had serious AEs related to the underlying illness and two patients requested device removal or deactivation during the study [43]. Another study of two adult patients with intractable AN who underwent stimulation of the NAc reported improved BMI at 1 year with no AE [44].

42.2.2.3 DBS for Eating Disorders in Children

Wu et al. specifically focused on the role of DBS in paediatric AN [11]. They undertook a study in four female patients aged 16–17 years with an average baseline BMI of 11.9, using the NAc as the target. Three patients had OCD and the fourth had generalised anxiety disorder. Significant increase in BMI was seen in all four patients with an average 65% increase in body weight after a mean follow-up of 38 months [11].

Despite the promising initial results, including in the paediatric age group, DBS in AN is high-risk and remains investigational with a current lack of consensus on the optimal target [38]. Severe chronic malnutrition leads to an increased risk of surgical complications and longer-term clinical outcomes are currently unknown. An ongoing longitudinal study is presently investigating the feasibility and efficacy of NAc-DBS in severe and enduring AN with a further aim to assess any subsequent neural changes and to develop an ethical gold standard to guide treatment applications [45]. What is already clear though is the need for multimodal therapy in this difficult to treat disorder where DBS's success will be highly dependent on other measures, including pre-surgical weight optimisation, psychological input and metabolic resuscitation.

On the other end of the eating disorders spectrum lies binge eating and obesity. To date, only few studies have reported the use of neuromodulation in the management of obesity with conflicting results. Pre-clinical and clinical studies have shown that neuromodulation of the lateral hypothalamic area (LHA) can result in weight loss [46–48]. Hamani et al. reported a loss of 12 kg in 5 months in a patient treated with LHA-DBS [48]. By turning off stimulation, the patient reverted to binging and weight gain [48]. However, Franco et al. showed LHA to be ineffective in improving anthropometric measures in a cohort of four obese patients with Prader-Willi Syndrome [49]. Four other case reports have investigated the role of neuromodulation of the NAc in the management of obesity (total of six patients) [50, 51]. Despite evidence of weight loss with NAc-DBS, one patient committed suicide and another decided to have the DBS system removed after 13 months [50]. Authors caution other groups regarding the high risk and complexity of these patients due to the associated psychiatric comorbidities, such as refractory depression, anxiety and personality disorders, and the need for well-designed studies, strict enrolment criteria and close psychiatric monitoring in trials addressing DBS management in morbidly obese patients [50].

In patients with refractory eating disorders, DBS appears to be feasible and of some advantage. Six clinical studies, including prospective trials, [42, 43, 52] reported on the safety and efficacy of DBS treatment of anorexia. Two other papers focused on or included paediatric patients in their analysis, showing a mean increase in BMI ranging from 28% to 65% with no additional risks compared to older patients with AN undergoing surgery [10, 11].

The mechanism of action of DBS in eating disorders is unclear and there remains scope for optimisation, an area worthy of further exploration given the high rate of morbidity and mortality associated with AN. Pre-clinical and clinical studies have shown that the mechanisms of reward and neural networks involved in eating disorders overlap, to some extent, at key structures along the fronto-striatal and mesolimbic pathways with circuits responsible for other neuropsychiatric disorders, such as depression, OCD and addiction [53, 54]. The ventral tegmental area sends mesolimbic and mesocortical dopaminergic projections to the NAc and to the prefrontal cortex via medial forebrain bundle [53, 54]. During the last decades, different structures of this network, such as slMFB, ALIC, NAc and cg25, have been targeted using ablative or neuromodulation techniques in the management of various neuropsychiatric conditions [53]. Therefore, further understanding of the underlying mechanisms of the diseases will allow a more personalized treatment, choosing the correct target for the correct individual patient.

42.2.3 Aggressive Behaviour and Self-Harm

42.2.3.1 Background

Self-harm behaviour is usually caused by perinatal insults, brain malformations and/or genetic syndromes, and is usually associated with mental and cognitive impairment, hyperkinesia, destructiveness of objects and aggressiveness [12, 13]. This dramatic condition is often refractory to medical treatment, precludes proper care and makes the use of restraining measures necessary in order to avoid harm to the patient and carers.

42.2.3.2 Surgical Management

Historically, stereotactic surgical procedures have been employed in an attempt to alleviate these symptoms, such as cingulotomy, amygdalotomy, dorsomedial thalamotomy and, [13] also the posteromedial hypothalamotomy as proposed by Sano et al. [55] Lesion of the pHyp was shown to be effective, to some extent, in 95% of the patients, with results considered “satisfactory” in up to 84% of the cases [55]. More recently, three groups reported on the use of bilateral DBS of the pHyp in a total of 22 patients with self-harm behaviour, refractory epilepsy and severe

cognitive impairment [12, 13, 56]. Franzini et al. reported an overall 65% improvement of the Overt Aggression Scale (OAS) and 50% improvement of epilepsy in two out of seven adult patients.

The ethical consideration on surgery for behavioural disorders limit the widespread application. Nonetheless the current evidence does suggest clinical benefit in carefully selected patients, including children, with severe self-harm refractory behaviour such as in Lesch-Nyhan syndrome [57].

42.2.3.3 DBS for Aggressive Behaviour and Self-Harm in Children

Torres et al. (2013) and Benedetti-Isaac et al. (2015) also included paediatric patients in their series, reporting dramatic behavioural improvement in eight out of ten patients with long-term follow-up (mean, 44 months) [12, 13]. Tambirajoo et al. 2020 recently published the long-term clinical outcomes and connectivity profiles in four children undergoing GPi-DBS for Lesch-Nyhan syndrome [58]. Bilateral DBS of the posteroventral (motor) and anteromedial (cognitive/behavioural) GPi using four electrodes led to clinical improvement of self-harm behaviour and motor control, which was not only dependent on the position of the active contacts within the GPi itself, but also strongly correlated with specific connectivity patterns between the basal ganglia and distant cortical brain regions. These findings shed light on the underlying mechanisms of DBS in the treatment of this complex condition and, in line with the literature, indicate a potential benefit of DBS in the management of drug-refractory aggressive behaviour in selected cases.

42.2.4 Autism Spectrum Disorder

ASD consists of a group of neurodevelopmental conditions altering cognitive and behavioural function, with an estimated prevalence of 1% worldwide [59]. The DSM-5 defines autism spectrum with high functioning patients capable of living on their own at one end, and those with severe symptoms at the other. Core to the definition of ASD are: (1) early-onset difficulties in social interaction and communication, (2) repetitive, restricted behaviours and interests [60]. Patients in the low functioning end of the ASD spectrum very often present with self-injurious behaviour, poor social interaction and other potentially life-threatening psychiatric features [59, 61]. Although medical management may improve some of these symptoms, a considerable subset of the patients turns out to be refractory to conservative treatment. Recently, reports have emerged on the use of DBS as an adjuvant tool in the management of a total of four severe refractory ASD patients, mainly as an attempt to decrease aggressivity and self-harm [62–64]. The basolateral nucleus of the amygdale (BLn) was targeted in two patients, [63, 64] the GPi in one patient and both the GPi and the ALIC in the other [62]. The authors concluded that

neuromodulation of the BLn may be an effective adjuvant tool for the management of self-harm behaviour and aggression, whereas the GPi or ALIC could be a target for the treatment of OCD-like symptoms in these patients. Nevertheless, clearly further long-term controlled trials are needed to better understand the role of surgical management in ASD.

42.3 Complications

The rates of serious surgical complications of DBS for psychiatric diseases are low, and in general comparable to those seen with DBS for movement disorders [28]. The most serious reported AE in psychiatric patients submitted to DBS were intracranial haemorrhage and suicide/suicidality. However, since psychiatric patients are usually younger, the risk of intracranial haemorrhage is expected to be lower [28]. On the other hand, Saleh et al. (2015) has shown higher suicidality rate (5.9%), increased in not only patients with TRD but also those with OCD and GTS [28] OCD patients had a high rate of postoperative mood changes [28]. Hardware related complications and infection occurred in 14.3% and 7.7% of the patients with higher infection rates in the GTS group. Of particular relevance to the paediatric patients, the infection risks tend to be higher compared to the adult patients. We recently reported a surgical site infection rate of around 10% in 129 patients undergoing DBS for dystonia with a mean age of 10.8 y (range 3.0–18.75) at a mean follow up of 3.3y (range 0.5–10.3). However, the DBS infection rate was 4.7% in the under 7-year-old cases [65]. Specific strategies are therefore required to reduce and manage these risks.

42.4 Perspectives and Challenges

A number of ethical considerations arise when considering DBS in psychiatric conditions. The selection of potential participants is important for optimising efficacy and safety. Although limited standardised criteria exist at present, [29] selection criteria should include patients who are physically, emotionally and cognitively capable of understanding and undergoing surgery [66]. This is particularly important in the children and will require specific frameworks and pathways. The presence of a stable social environment and the family members is also imperative. Informed consent can be challenging but with the inherent risks that DBS surgery carries, it is crucial that a comprehensive informed consent is obtained. As DBS procedures are often considered as “last resort” options, desperation on a patient or carer’s part can undermine the informed consent process due to possibly unreasonable high expectations clouding the appreciation of the various treatment options

and alternatives [67]. Pre-surgical expectation management and goal setting are therefore critical to achieve good patient satisfaction, both at the short and long term, highly relevant to the paediatric patients and their carers [68].

Interest in neuromodulation in the management of neuropsychiatric disorders continues to grow and remains an area of active research. Three main factors have been expressed as potential causes of failure of important clinical trials evaluating DBS in the management of neuropsychiatric disorders, and should be addressed in future prospective studies: a) premature evaluation endpoints; b) variable surgical protocols and selection of ideal brain targets; c) heterogeneous patient selection and lack of biomarkers predictive of favourable outcome [69–71]. Although current data available may support surgical intervention for the treatment of some refractory psychiatric conditions in the paediatric population, large long-term randomised trials are rare and thus the threshold for surgical neuromodulation in a child must remain high. A multidisciplinary approach to assessment and treatment by an experienced team is paramount if surgery is being considered. High quality research to further explore the ideal brain targets for specific indications, incorporating the ethical concerns and the potential influence of DBS therapy on the developing brain and vice versa, is needed. Well-designed translational neuromodulation research and functional connectivity analysis using cutting-edge imaging technology might shed light on the brain networks involved, the plasticity of the developing brain and the underlying mechanisms of neuropsychiatric disorders in paediatric patients paving the way towards personalised neuromodulation [8, 70, 72–74].

42.5 Final Remarks

The application of DBS for psychiatric indications has progressed at a steady pace in the adult population and at a much slower pace in the paediatric population. Despite of its approved use as an adjuvant strategy in the management of OCD, and encouraging results reported in the treatment of GTS and TRD, DBS for psychiatric disorders in paediatric patients remains largely investigational. The stakes are much higher in children and adolescents. Future multidisciplinary studies in children should be done in a long-term trial setting with strict and robust criteria and conduct to minimise the effect of harm and maximise the data and evidence on efficacy and safety of DBS therapy. A move towards personalising DBS therapy and exploration of new stimulation techniques will provide new frontiers and possibilities in this growing field.

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