**Cognitive function in children with primary dystonia**

**before and after deep brain stimulation.**

**Tamsin Owen, DClinPsya, c, Hortensia Gimeno, MSc(OT)a,d, Richard Selwayb, FRCS (SN); Jean-Pierre Lina, MRCP(UK) PhD**

a Complex Motor Disorders Service, Paediatric Neurosciences, Evelina Children’s Hospital, Guy’s & St Thomas’ NHS Foundation Trust, London, UK.

bFunctional Neurosurgery, King’s College Hospital NHS Foundation Trust, London, UK.

C Department of Clinical Psychology, Royal Holloway, University of London, UK.

d Department of Psychology, Institute of Psychiatry, King’s College London, UK.

\* Corresponding Author: Dr Tamsin Owen, Complex Motor Disorders Service, Paediatric Neurosciences, Evelina Children’s Hospital, Guy’s & St Thomas’ NHS Foundation Trust, London, UK. Tel: +44 207 188 8533. Fax: +44 207 188 0851. Email: tamsin.owen@gstt.nhs.uk; tamsin.owen@rhul.ac.uk

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**ABSTRACT**

Background: Dystonia is characterised by involuntary movements (twisting, writhing and jerking) and postures. The effects of deep brain stimulation (DBS) surgery on the motor aspect of primary dystonias have been well reported, however, there is a paucity of research investigating its impact on cognitive function, particularly in childhood dystonia. We performed a follow-up of cognitive function in children with primary dystonia following DBS pallidal surgery.

Methods: Cognitive function was measured in a cohort of 13 children with primary or primary plus dystonia who had undergone DBS surgery using a retrospective case series design. Baseline pre-DBS neuropsychological measures were compared to scores obtained at least one year following DBS. Cognitive function was assessed using standardised measures of intellectual ability and memory.

Results: All children demonstrated improvements with regard to dystonia reduction, as measured by the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS). Overall, cognition remained stable following DBS in the majority of the cohort. Individual case analysis revealed improvements in some domains of cognitive function in eight members of the cohort and a deterioration of certain domains in four.

Conclusion: Cognition largely remained stable in children with primary/ primary plus dystonia following DBS surgery, although further research with a larger sample is necessary to explore this statistically. Notwithstanding the limitations of a small size, this preliminary data has potentially positive implications for the impact of DBS on cognitive functioning within a paediatric population.

**INTRODUCTION**

Dystonia is a movement disorder characterised by involuntary, sustained muscle contractions resulting in twisting, repetitive movements and abnormal postures1, 2. Primary dystonia is described when dystonia is often the only motor feature, there is no neurodegeneration or measurable neurometabolic abnormality and the patient’s brain is anatomically intact3. There are many genetic mutations associated with primary dystonia, the most common being the DYT1 mutation4. The term “Primary-Plus” syndrome is used to describe subgroups of patients with an idiopathic dystonia occurring alongside features of a movement disorder (e.g. dystonia-myoclonus syndrome seen in patients with epsilonsarcogly can gene mutations)5.

Primary dystonia usually begins in childhood and often yields a poor response to pharmaceutical treatment. Over the past decade, the use of deep brain stimulation (DBS) of the internal globus pallidus (GPi) has been used to successfully manage dystonia, across the lifespan 6,7, 8. Children with primary dystonia have been shown to make a significant improvement in their motor scores, as measured by the BFMDRS, both at 6 and 12 months following DBS surgery4. The importance of the duration of the condition has also been highlighted; with the response to pallidal DBS declining with the proportion of life lived with dystonia4.

With regard to DBS, neuropsychological assessment has been recommended as part of the overall surgical process, to determine the impact of the DBS surgery on cognitive functioning9. It has been highlighted that the basal ganglia, the target of DBS therapy, has as influential an effect on cognition as it does on movement10. For example, the basal ganglia have been identified as playing an important role in various problem-solving tasks, via its interaction with the prefrontal cortex11. The crucial role of the basal ganglia in working memory function has also been demonstrated and the GPi, in particular, have been identified as playing a key role in working memory gating functions12. Due to the important role the basal ganglia play in supporting cognition, and the fact that DBS modulates its functional output, examining the impact DBS has on cognition, in addition to movement, is felt to be valuable.

To date, the exploration of the cognitive implications of DBS surgery has largely been limited to adult populations and findings have been mixed, with some studies demonstrating no cognitive change, some demonstrating improvements and some a decline in cognitive functioning, particularly in the context of STN DBS for Parkinson’s disease13. There have been no studies to date relating to cognitive function in individuals specifically with primary-plus dystonia following DBS.

Jahanshahi et al. 14 recently concluded that GPi DBS in adults with primary dystonia did not have an adverse effect on the main domains of cognitive function. Similarly, an evaluation of 22 adults with primary dystonia by Pillion et al.15, found no change in cognition 12 months post DBS surgery on the majority of cognitive tests administered. This was with the exception of a mild but significant improvement on the Raven Progressive Matrices (a measure of non-verbal performance), the Wechsler Adult Intelligence Scale-Revised Similarities subtest (a measure of verbal comprehension ability), free recall and a reduction of non-perseverative errors on the Wisconsin. Halbig et al.16 also found a mild improvement post DBS surgery on Form A of the Trail Making test, a measure of executive function. This improvement was thought to be partially explained by an improvement in motor ability.

Conversely, in a study of four patients with cervical dystonia who underwent bilateral stimulation of the subthalmic nucleus (STN), Kleiner-Fisman et al.17 found that the entire sample showed a non-significant decline with regard to certain executive functions. A significant deterioration was seen in one patient with regard to their verbal memory and in the visual memory of a further two patients. Kiss18 also reported a significant decline in phonemic verbal fluency in one adult patient and in the verbal memory ability in another following GPi DBS. It was noted by the authors that these changes did not affect the day-to-day functioning of these patients.

Little is known about the impact of DBS surgery on the cognitive functioning of children. Indeed, the importance of assessing the non-motor impacts of dystonia management within a paediatric population was highlighted in a recent study by Cialone and Mink19 who reported a decline in school function during treatment with trihexyphenidyl in children between eight and 15 years of age, with a diagnosis of DYT1 dystonia. However, research is yet to systematically assess the impact of DBS surgery on cognitive functioning in children with primary dystonia. This is important due to the developing nature of the child’s brain, and is needed in order to broaden the evidence-base for this population. Our objective was to assess global cognitive ability and memory in a group of children with primary dystonia who have undergone bilateral pallidal DBS.

**METHOD**

**Design:**

The study used a retrospective case series design involving 13 children and young people who had undergone bilateral pallidal DBS for the management of primary/ primary plus dystonia. All patients were under the care of a tertiary hospital specialist complex movement disorder service. The assessments were performed routinely as part of the services’ clinical protocol and were conducted between 2007 and 2013.

**Participants:**

All patients under the care of the service with a confirmed diagnosis of primary dystonia and at least one year follow up data post-DBS were included in this study (n=13). Six patients had DYT1 negative dystonia, four were DYT1 positive, three had primary plus syndrome (of these two had DYT11 positive dystonia and one had primary plus syndrome with parkinsonism features – unknown diagnosis). Patients were diagnosed by the Consultant Paediatric Neurologist and, where possible, the diagnosis was confirmed by genetic testing. The mean age of participants at the time of surgery was 11.5 years (SD = 3.5; range = 6 to 18 years). Seven patients were male and six were female. For the purposes of anonymity, each patient has been allocated case numbers ranging from 1 to 13.

DBS surgery was performed under general anaesthetic using MRI-guided postero-latero-ventral globus pallidus targeting4.

**Measures:**

Cognitive functioning was assessed using standardised measures. For each child, the measures used depended on their age and ability to physically and verbally access the materials. The measures used were:

1. **Non-verbal intellectual abilities:** The Perceptual Reasoning Index subtests of the Wechsler Scales of Intelligence IV: (WISC-IV)20 and Wechsler Abbreviated Scales of Intelligence (WASI) 21 (Block Design, Matrix Reasoning, Picture Concepts, and Picture Completion) were used to measure non-verbal intelligence, including visuo-spatial, abstract, and conceptual reasoning skills.
2. **Verbal intellectual abilities:** The Verbal Comprehension Index subtests of the WISC-IV20 and WASI21 (Vocabulary, Similarities, Comprehension) were used to measure understanding of verbal concepts, social rules, and vocabulary.
3. **Memory:** Immediate and delayed verbal and visual recall were assessed using Faces, Dot Locations, Stories and Word Pairs [subtests of the Children’s Memory Scale (CMS) 22 and Wechsler Memory Scales (WMS)]23. Working memory, the ability to mentally retain and manipulate verbal information, was measured using the Working Memory Index subtests (Digit Span and Letter-Number Sequencing) of the WISC-IV20.
4. **Processing Speed:** The Processing Speed Index subtests of the WISC-IV20 (Coding, Symbol Search and Cancellation) were used to measure the speed with which an individual processes and responds to visual information.

**Procedure:**

All patients were assessed by a clinical psychologist as part of a routine baseline assessment prior to DBS surgery and then at post-DBS clinical follow-up. Follow-up times varied from one year to three years post-surgery. The variation in follow-up times was due to the fact that there was approximately a two year period where the team did not have full access to clinical psychology support and some assessments were subsequently delayed. For patients who experienced significant difficulties with their hand function (n=3), Picture Completion was substituted for Block Design and Cancellation was substituted for Coding on administration of the WISC-IV. This is due to the fact that these subtests require less hand function ability. One case in the cohort was non-verbal and it was not, therefore, possible to administer assessments with a verbal component. Due to the impact of movements on fatigue, patients were given regular breaks during testing.

 The WMS and WASI are both normed on adult populations and were administered to the young people over the ages of 16 (n=2). One patient was administered an abbreviated assessment (WASI) due to assessment time constraints and therefore did not complete working memory or processing speed assessments.

**Data analysis:**
Due to the small sample size, powered statistics were not used and data is reported descriptively. Where possible, results are reported as index scores, alongside their confidence intervals and these are discussed individually. In cases where there was significant subtest scatter within the indices (i.e. too much variation between the individual subtests that comprise each index), it was not possible to calculate the index scores. Scores were deemed to have remained stable if they stayed within the expected confidence interval post-surgery.

**RESULTS**

**Demographic Information**

Demographic and assessment details are presented in Table 1. Previous investigations have confirmed and reported on a reduction in dystonia within this cohort of children4.

**Table 1: Cohort demographic and assessment details.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Case | ***Gender*** | ***Diagnosis*** | ***Age at disease onset (yrs)*** | ***Age at DBS surgery (yrs)*** | ***Follow-up point (yrs)*** | ***Interpretable Index Scores*** |
| 1 | M | DYT1 positive | 8 | 11 | 1 | WMI, VisImm |
| 2 | M | DYT1 negative | 11 | 13 | 1 | VCI, PRI, WMI, PSI, VisImm, VisDel, VerbDel. |
| 3 | M | DYT1 positive | 11 | 14 | 2 | VCI, PRI, WMI, PSI, VisDel, VerbImm, VerbDel |
| 4 | M | DYT1 negative | 9 | 18 | 1 | VCI, PRI |
| 5 | M | DYT1 positive | 10 | 13 | 1 | VCI, PRI, WMI, PSI, VisImm |
| 6 | F | DYT1 positive | 6 | 8 | 3 | VCI, PRI, WMI, PSI, VisImm, VisDel, VerbImm, VerbDel |
| 7 | F | DYT1 negative | 14 | 16 | 1 | VCI, PRI, VisImm, VisDel, VerbImm, VerbDel |
| 8 | M | Primary Plus (DYT11 positive) | < 2  | 12 | 1 | VCI, PRI, WMI, PSI, VisImm, VisDel, VerbImm, VerbDel |
| 9 | F | Primary Plus (DYT11 positive) | < 2 | 9 | 1 | PRI |
| 10 | F | Primary Plus (dystonia with parkinsonism features) | 7 | 10 | 1 | PRI |
| 11 | F | DYT1 negative | < 2 | 12 | 1 | VCI, PSI, VisImm, VisDel, VerbImm, VerbDel |
| 12 | M | DTY1 negative | 4 | 6 | 1 | VCI, PRI, WMI, PSI |
| 13 | F | DYT1 negative | < 2 | 7 | 1 | PRI, WMI |

**Medication**

Details of changes in medication are presented in Table 2. . Only 5 of the 13 patients were taking medication for the management of their movement disorder prior to surgery. Of these 5 patients, 1 had no change in medication at one year follow up. Due to a reduction in the severity of motor symptoms, two patients had a partial reduction in medication and 3 patients were able to completely cease medication relating to the management of motor symptoms following surgery.

**Table 2: Medication prescribed prior to and following DBS Surgery**

|  |  |  |
| --- | --- | --- |
| **Case** | **Medication Pre DBS Surgery** | **Medication Post DBS Surgery** |
| 1 | Sinemet (4.97mg/kg/day)  | Sinemet (4.04 mg/kg/day)  |
| 2 | Diazepam (0.05 mg/kg/day) | None |
| 3 | Sinemet (4 mg/kg/day)Chloral hydrate (10.68 mg/kg/day)Trihexyphenidyl (0.64 mg/kg/day)  | Toparimate (0.79 mg/kg/day) |
| 4 | Trihexyphenidyl (0.18 mg/kg/day)Flucloxacillin (0.04 mg/kg/day) | Flucloxacillin (0.04 mg/kg/day) |
| 5 | None | None |
| 6 | Trihexyphenidyl (0.16 mg/kg/day) | None |
| 7 | None | None |
| 8 | None | None |
| 9 | None  | None |
| 10 | Baclofen (0.41 mg/kg/day)Trihexyphenidyl (0.71 mg/kg//day) | Trihexyphenidyl (0.69 mg/kg/day) |
| 11 | None | None |
| 12 | None | None |
| 13 | None | None |

**Results of Cognitive Testing**

**Global Cognitive Function (WISC IV)**

There was a spread across the range of individual diagnoses regarding those patients whose cognition remained stable, those who showed improvements and those who declined. As such, results are discussed as a broad cohort rather than by specific aetiology.

*Verbal Comprehension Index (VCI)*

Four out of the thirteen cases did not have an interpretable VCI due to a significant difference between the subtest scaled scores that make up the index. Of the remaining nine cases, four had a VCI which remained stable and within the same confidence interval as prior to surgery. Of the remaining five patients, four showed an improvement in VCI outside the expected confidence interval, and one showed deterioration outside the expected confidence interval. The patient who deteriorated (case 6) had a reduction in medication following surgery.

*Perceptual Reasoning Index (PRI)*

Two out of the 13 cases did not have an interpretable PRI. Of the remaining 11 cases, seven had a PRI which remained stable and within the same confidence interval as prior to surgery. Three had a PRI which improved outside the expected confidence intervals after DBS surgery. Two of the three who improved (cases 2 and 3) had a reduction in medication following surgery. The remaining case showed a deterioration in their PRI outside the expected confidence interval following the surgery and this individual (case 6) also had a reduction in medication.

*Working Memory Index (WMI)*

The subtests that make up the WMI were administered to 12 out of the 13 patients. Of these, eight had an interpretable WMI. Of these patients, six had a WMI which remained stable and within the same confidence interval as that prior to surgery and two showed an improvement outside the expected confidence intervals. Both of these (cases 2 and 3) had a reduction in medication following surgery.

*Processing Speed Index (PSI)*

The subtests that make up the PSI were administered to 12 out of the 13 patients. Five did not have an interpretable PSI. Four patients had a PSI which remained stable and within the same confidence intervals as prior to surgery. Two patients showed an improvement outside the expected confidence intervals and one showed a deterioration. One of the patients who showed an improvement (case 6) had a reduction in their medication following surgery.

**Memory Function (CMS)**

*Visual Immediate Memory Index*Six out of the 13 cases did not have an interpretable Visual Immediate Memory Index score. Of the remaining seven cases, six remained stable with regard to their visual immediate memory and within the expected confidence intervals after DBS surgery, and one showed an improvement. The individual that showed an improvement (case 2) had a reduction in medication following surgery.

*Visual Delayed Memory Index*Seven out of the 13 cases did not have an interpretable Visual Delayed Memory Index score. Of the remaining six cases, four remained the same and within the expected confidence intervals post-surgery, one showed an improvement and one declined. The individual who declined (case 6) had a reduction in medication following surgery.

*Verbal Immediate Memory Index*Eight out of the 13 cases did not have an interpretable Verbal Immediate Memory Index score due to a significant difference between the subtest scaled scores that make up the index. Of the remaining five cases, three had Verbal Immediate Memory Index Scores that remained stable after surgery, one improved and one declined.

*Verbal Delayed Memory Index*Seven out of the 13 cases did not have an interpretable Verbal Delayed Memory Index score. Of the remaining six cases, Verbal Delayed Memory Index stayed the same and within the expected confidence intervals post-surgery in four patients. It showed an improvement in one patient and a decline in another.

**Table 3: Pre- and post WICS IV and CMS index scores and confidence intervals\*.**

|  |
| --- |
| **Index** |
| **Case** | **VCI** | **PRI** | **WMI** | **PSI** | **VisIm** | **VisDel** | **VerbIm** | **VerbDel** |
|  | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post |
| **1****DYT1+** | - | - | - | - | 83*77-92* | 88*81-97* | - | - | 106*92-120* | 100*84-116* | - | - | - | - | - | - |
| **2****DYT1-** | 95*89-102* | 91*85-98* | 102*94-109* | 125*115-131* | 91*84-99* | 107*99-114* | 73*67-85* | 7872-90 | 109*93-125* | 131*103-147* | 109*94-123* | 122*107-136* | *-* | - | 94*85-102* | 97*88-106* |
| **3****DYT1+** | 121*113-127* | 116*108-122* | 94*87-102* | 96*89-104* | 86*79-95* | 99*91-107* | 65*60-78* | 62*58-76* | - | - | 103*83-118* | 100*85-115* | 88*78-98* | 82*71-93* | 88*79-97* | 88*78-98* |
| **4****DYT1-** | 102*96-108* | 108*102-113* | 97*91-103* | 106*100-111* | - | - | - | - | - | - | - | - | - | - | - | - |
| **5****DYT1+** | 116*108-122* | 132*123-137* | 119*110-125* | 110*102-117* | 91*84-99* | 94*87-102* | 103*94-112* | 123*111-129* | 131*115-137* | 109-*93-125* | - | - | - | - | - | - |
| **6****DYT1+** | 99*96-102* | 91*85-98* | 110*102-117* | 98*91-106* | 86*79-95* | 88*81-97* | 73*67-85* | 91*83-101* | 115*100-130* | 112*99-126* | 118*103-133* | 88*77-99* | 94*82-106* | 82*71-93* | 103*88-113* | 88*77-99* |
| **7****DYT1-** | 123*114-129* | 133*126-137* | 107*100-113* | 112*106-117* | - | - | - | - | 115*102-123* | 112*100-120* | 122*108-128* | 125*111-131* | 130*121-135* | 130*121-135* | 117*106-124* | 124*112-130* |
| **8****1o plus** | 112*105-118* | 126*118-131* | 110*102-117* | 108*100-115* | 91*84-99* | 88*81-97* | 109*99-117* | 109*96-114* | 103*87-119* | 103*87-119* | 106*88-124* | 125*110-140* | 125*115-135* | 137*127-147* | 118*107-124* | 134*125-143* |
| **9****1o plus** | - | - | 71*66-81* | 71*66-81* | - | - | - | - | - | - | - | - | - | - | - | - |
| **10****1o plus** | - | - | 53*49-64* | 57*53-68* | - | - | - | - | - | - | - | - | - | - | - | - |
| **11****DYT1-** | 79*73-87* | 83*77-91* | - | - | - | - | 83*76-94* | 83*79-94* | 103*87-117* | 115*99-131* | 100*86-114* | 109*94-124* | 91*81-101* | 69*59-79* | 84*75-96* | 66*57-75* |
| **12****DYT1-** | 63*58-72* | 93*89-102* | 84*78-93* | 82*76-91* | 8377-92 | 77*71-86* | 8578-96 | 75*69-87* | - | - | - | - | - | - | - | - |
| **13****DYT1-** | - | - | 71*66-81* | 92*85-100* | 83*77-92* | 83*77-92* | - | - | - | - | - | - | - | - | - | - |

\*Confidence intervals are displayed in italics. “-“ denotes the fact that the Index scores were not interpretable or the scale was not administered.

**DISCUSSION**

This pilot study examined the cognitive profiles of children and young people with primary and primary-plus dystonia who had undergone DBS surgery and is the first study to systematically assess cognition following DBS exclusively within a childhood primary-dystonia population. All children demonstrated improvements with regard to dystonia reduction and cognitive profiles were largely found to remain stable before and after surgery. This has important implications for the impact of DBS on non-motor functioning and tentatively suggests that it did not impact negatively on cognitive function in a small sample of children, although more research is necessary to clarify this.

Ten patients’ scores either remained stable or improved following DBS surgery across the range of cognitive tests. The finding that patient’s scores remained stable supports previous research from Pillion et al.15 who found similar results in an adult population, and it is important that this has now been demonstrated with a child population. Consistent with the findings of Pillion et al. 15 in adults, improvements in this study were most likely to be seen in verbal comprehension and perceptual reasoning skills.

Three patients showed a deterioration across certain domains of function following DBS surgery. One child (case 6) declined in their performance across three different areas; verbal comprehension, perceptual reasoning and visual delayed memory. One child (case 12) declined in their processing speed performance and one (case 13) deteriorated in their immediate and delayed verbal memory. One possible variable influencing this deterioration could be because all children reported experiencing either fatigue or distractibility at the time of the follow up assessment, and felt this may have affected their performance. The deteriorations seen in visual memory support the findings of Kleiner-Fisman et al.17 who also found a decline in the visual memory of two adult patients following DBS surgery. The patients in the current study who experienced a deterioration in aspects of their memory anecdotally reported that they had not noted any memory difficulties in their day-to-day lives since having the surgery and their parents concurred with this. These cases where a decline was seen suggest that more research is warranted to review these children over an extended period of time to better judge whether this decline is consistent over time and what impact any decline has on quality of life and participation.

Improvement in cognitive ability may relate to a number of different variables. Firstly, a reduction in medication may contribute to improved cognitive performance. As previously mentioned the potential detrimental impact of trihexyphenidyl on academic performance in childrenhas been reported19 and demonstrates the impact of medication on cognition. Of the five patients in the current study who had a medication reduction, four experienced improvement in certain domains of function. It is possible that medication reduction was accountable for improved function in these cases. It is also of note; however, that one of the patients who had a reduction in medication also experienced a decline across certain domains of function and the possible reasons for this is discussed above.

Improvement in cognitive function may also be attributable to improvements in movements which can allow for increased physical access to testing materials and subsequently improves the time in which patients can respond on timed tasks. Similar improvements in cognitive performance relating to an increase in access to testing materials have also been reported following DBS in children with neurodegeneration with brain iron accumulation, which is a severely progressive dystonia associated with the PANK2 mutation24. Such an increase in access would have a particular impact on timed processing speed tasks. It could also be hypothesised that a reduction in dystonia may lead to improved attention and concentration and therefore enable patients to better engage with both their education in general, and cognitive testing. Exploring possible reasons for improvements in cognitive function post-DBS, with a particular focus on medication reduction, would be a useful area for future research.

The primary limitation to this study is the small sample size and the fact that assessment data was not available for every participant in the sample. While all patients in the sample have a diagnosis of primary dystonia, heterogeneity still exists in terms of the specific individual diagnoses within this group. These limitations clearly create a challenge in terms of being able to make reliable generalisations. While this is inevitable when the prevalence of primary (genetically confirmed) dystonia within the child population is low, caution must, nevertheless, be used when interpreting the findings. As a further area for investigation, it would be important to further separate the primary and primary plus dystonias cohort into the specific diagnoses that exist within this population.

The movements experienced by the children also affect the overall validity of the assessment administered. This is particularly true of any timed subtests involving motor control, such as the PSI of the WISC IV. Again, results must be interpreted with caution as these test results are likely to reflect speed of motor control rather than speed of cognitive processing. Lastly, post-surgery follow-up cognitive assessments were repeated at different time intervals, which makes it difficult to make direct and reliable comparisons between patients, though this is reflective of the context of routine clinical practice in which the study took place.

The current study examined the impact of DBS surgery on cognition in children. Results from this study are largely suggestive of preserved in children with primary dystonia after DBS surgery. This provides initial information to tentatively suggest that GPi DBS within this population has no adverse effect on cognition. On an individual level, some improvements were noted, which may be attributable to medication reduction made possible by the motor benefits of DBS surgery. These findings are particularly important in light of the possible negative impact of other dystonia managements on academic function in children19.

There is a need for further research to explore these initial findings and broaden our understanding of cognition after DBS within the paediatric primary dystonia population. An outstanding question in paediatric DBS research is to what extent, if any, the stimulation of a basal ganglia structure produces changes in cognition due to a direct stimulation of the executive/cognitive system within this structure. This has been the focus of some attention in patients with Parkinson's disease undergoing DBS of the subthalamic nucleus (STN), and a relationship has been identified between cognitive decline and both the position of the active contact within the STN and whether the electrode traversed the caudate nucleus or not25. Future research strategies within paediatric DBS for dystonia will, therefore, need to focus on the influence of the electrode position within the target structure, as well as the trajectory of the electrode and basal ganglia structures traversed.

Lastly, access to a larger, multi-centre sample would enable more in depth exploration of improvements and declines in certain areas of cognition and any clinical significance of these changes. Such research should also be extended to include children with secondary dystonia who have also undergone DBS surgery. This information could be used to support families and schools in planning and monitoring changes in education provision following DBS surgery.

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**Author Roles:**

Tamsin Owen: 1) Research Project: A. Conception, B. Organization, C. Execution; 2) Result Analysis: A. Design, B. Execution, C. Review and Critique; 3) Manuscript Preparation: A. Writing of the first draft

Hortensia Gimeno: 1) Research Project: A. Conception, B. Organization ; 2) Result Analysis: C. Review and Critique; 3) Manuscript Preparation: B. Review and Critique

Richard Selway: 3) Manuscript Preparation: B. Review and Critique

Jean Pierre Lin: 1) Research Project: A. Conception; 2) Result Analysis: C. Review and Critique; 3) Manuscript Preparation: B. Review and Critique

**References**

1. Fahn S, Marsden CD, Calne DB. Classification and investigation of dystonias. In: Marsden CD, Fahn, S editors. Movement Disorders 2. London: Butterworths, 1987: 332-58.
2. Fahn S, Bressman S, Marsden CD. Classification of dystonia.  *Adv Neurol* 1998; **78**: 1-10.
3. Fasano A, Elia AE, Albanese A. Early onset primary torsion dystonia. In: Fernández-Alvarez E, Arzimanoglou A, Tolosa E. Paediatric Movement Disorders: Progress in understanding. Surrey, 2005: John Libbey Eurotext: 31-55.
4. Lumsden DK, Kaminksa M, Gimeno, H, Tustin, K, Baker, L, Perides, S, Ashkan,

K, Selway, R, Lin, J-P. Proportion of life lived with dystonia adversely correlates with response to Deep Brain Stimulation in primary and secondary childhood dystonia. *Developmental Medicine and Child Neurology* 2013; **55**: 1-8. doi: 10.1111/dmcn.12117.

1. Phukan J, Albanese A, Gasser T, Warner T. Primary dystonia and dystonia-plus syndromes: clinical characteristics, diagnosis, and pathogenesis. Lancet Neurol 2011; 10:1074-85.
2. Cif L, El Fertit H, Vayssière, Hemm S, Gaudin D, Serrat S, Coubes P. Deep brain stimulation in paediatric dystonia*.* In: Fernández -Alvarez E, Arzimanoglou A, Tolosa E. Paediatric Movement Disorders: Progress in understanding. Surrey, 2005: John Libbey Eurotext: 77-85.
3. Haridas A, Tagliati M, Osborn I, Isaias I, Gologorsky, Bressman SB, Weisz D, Alterman RL. Pallidal deep brain stimulation for primary dystonia in children. *Neurosurgery* 2011*;* **68**: 738-743. doi: 10.1227/NEU.0b013e3182077396.
4. Gimeno H, Lumsden D, Gordon A, Tustin K, Ashkan K, Selway R, Lin JP. Improvement in upper limb function in children with dystonia following deep brain stimulation. *European Journal of Paediatric Neurology* 2013; **17:** 353-60. [doi:10.1016/j.ejpn.2012.12.007](http://dx.doi.org/10.1016/j.ejpn.2012.12.007).
5. Jahanshahi M, Czernecki V, Zurowski M. Neuropsychological, neuropsychiatric and quality of life issues in DBS for dystonia.  *Movement Disorders* 2010; **26**: 68-83. doi: 10.1002/mds.23511.
6. Kozio L, Ely Budding D.Subcortical structures and cognition: Implications for neuropsychological assessment. New York, 2010: Springer: 44.
7. Middleton FA. Fundamental and clinical evidence for basal ganglia influences on cognition. In: Bedard M, Agid Y, Chouinard S, Fahn S, Korczyn A editors. Mental and behavioural dysfunction in movement disorders. Totowa, NJ: Humana Press Inc, 2003: 13-34.
8. McNab F, Klinberg T. Prefrontal cortex and basal ganglia control access to working memory. *Nature Neuroscience,* 11, 103-107. doi: 10.1523/jneurosci.1513-10.2010.
9. Massano J, Garrett, C. Deep brain stimulation and cognitive decline in Parkinson’s Disease: A Clinical Review. *Front Neurol.* 2012; **3**: 66. doi: 10.3389/fneur.2012.00066.
10. Jahanshahi M, Torkamani M, Beigi M, Wilkinson L, Page D, Madeley L, Hariz M, Zrinzo L, Limous P. Pallidal stimulation for primary generalised dystonia: effect on cognition, mood and quality of life. *Journal of Neurology* 2013; **261**:164-173. doi: 10.1007/s00415-013-7161-2.
11. Pillion B, Ardouin C, Dujardin K, Vittini P, Pelissolo A, Cottencin O, Vercueil L, Houeto JL, Krystkowiac P, Agid Y, Destée, A Pollak P, Vidailhet M. Preservation of cognitive function in dystonia treated by pallidal stimulation. *Neurology* 2006; **66**: 1556-1558.
12. Halbig TD, Gruber D, Kopp UA, Schneider GH, Trottenberg T, Kupsch A. Pallidal stimulation in dystonia: effects on cognition, mood and quality of life. *J Neurol Neurosurg Psychiatry* 2005;**76**:1713-1716.
13. Kleiner-Fisman G, Liang GS, Moberg PJ, Ruocco AC, Hurtig HI, Baltuch, GH, Jaggi JL, Stern MB. Subthalmic nucleus deep brain stimulation for severe idiopathic dystonia: impact on severity, neuropsychological status, and quality of life. *J Neurosurgery* 2007; **107**: 29-36.
14. Kiss ZH. Bilateral pallidal stimulation – long term motor and cognitive effects in primary generalised dystonia. *Nat Clin Pract Neurol* 2007; **3**: 482-483.
15. Cialone J, Mink J. Globus pallidus deep brain stimulation provides benefit and allows medication reduction in young children. *DevMed Child Neurol* 2012; **54**(suppl 4):39–40.
16. Wechsler D. Wechsler Intelligence Scale for Children, Fourth Edition. London, UK: Pearson Education Ltd, 2004.
17. Wechsler D. Wechsler Abbreviated Scale of Intelligence. London, UK: Pearson Education Ltd, 1999.
18. Cohen M. Children’s Memory Scale. London, UK: Pearson Education Ltd, 1997.
19. Wechsler D. Wechsler Memory Scale. London, UK: Pearson Education Ltd, 1998.
20. Mahoney R, Selway R, Lin JP.  [Cognitive functioning in children with pantothenate-kinase-associated neurodegeneration undergoing deep brain stimulation.](http://www.biomedexperts.com/Abstract/Abstract.aspx?recordid=21166667)  *Developmental Medicine & Child Neurology* 2011; **53**: 275-279. doi: 10.1111/j.1469-8749.2010.03815.
21. Witt K, Granert O, Volkmann J, Flak D, van Eimeren T, Deuschl G. Relation of lead trajectory and electrode position to neuropsychological outcomes of subthalamic neurostimulation in Parkinson’s disease: Results from a randomized trial. *Brain* 2013; **136**: 2109-2119.