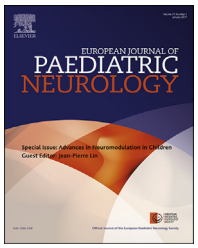
ELSEVIER

Official Journal of the European Paediatric Neurology Society



Review article

Deep brain stimulation for childhood dystonia: Is 'where' as important as in 'whom'?

Daniel E. Lumsden [a,b,*], *Margaret Kaminska* [a], *Keyoumars Ashkan* [c], *Richard Selway* [c], *Jean-Pierre Lin* [a]

[a] *Complex Motor Disorder Service, Evelina London Children's Hospital, Guy's and St Thomas' NHS Foundation Trust, London, UK*

[b] *Division of Imaging Sciences and Biomedical Engineering, King's College London, London, UK*

[c] *Functional Neurosurgery, Department of Neurosurgery, Clinical Neurosciences, King's College Hospital, London, UK*

Keywords:
Dystonia
Childhood
Basal ganglia
Electrode
Deep brain stimulation

ABSTRACT

Deep brain stimulation (DBS) has become a mainstay of dystonia management in adulthood. Typically targeting electrode placement in the GPi, sustained improvement in dystonic symptoms are anticipated in adults with isolated genetic dystonias. Dystonia in childhood is more commonly a symptomatic condition, with dystonia frequently expressed on the background of a structurally abnormal brain. Outcomes following DBS in this setting are much more variable, the reasons for which have yet to be elucidated. Much of the focus on improving outcomes following DBS in dystonia management has been on the importance of patient selection, with, until recently, little discussion of the choice of target. In this review, we advance the argument that patient selection for DBS in childhood cannot be made separate from the choice of target nuclei. The anatomy of common DBS targets is considered, and factors influencing their choice for electrode insertion are discussed. We propose an "ABC" for DBS in childhood dystonia is proposed: Appropriate Child selected; Best nuclei chosen for electrode insertion; Correct position within that nucleus.

Contents

* *Corresponding author*. Complex Motor Disorder Service, Evelina Children's Hospital, Guy's and St Thomas' NHS Foundation Trust, Westminister Bridge Road, London, SE1 7EH, UK. Fax: +44 20 7188 0851.
E-mail address: Daniel.lumsden@gstt.nhs.uk (D.E. Lumsden).

http://dx.doi.org/10.1016/j.ejpn.2016.10.002

1. Introduction

Dystonia is a disorder of movement and posture characterized by "*sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both*".[1] Dystonia in childhood is most commonly a symptomatic condition, arising due to an acquired perturbation of the motor network, e.g. following a hypoxic ischaemic insult.[2] In contrast, dystonia presenting first in adulthood is often an isolated finding, in the absence of other neurological abnormalities. Childhood dystonia is frequently refractory to pharmacological management, and adverse reactions to anti-dystonic medication may limit their use.[3]

Deep brain stimulation (DBS) has been used in the management of dystonia for almost 20 years.[4] The technique involves implantation of electrodes into the deep substance of the brain, connected to an implanted pulse generator delivering high-frequency electrical stimulation to the targeted brain region. DBS has most frequently been used in the management of isolated, presumably monogenic dystonias, previously termed "primary dystonias".[5,6] In this group, profound improvements in dystonia severity have been reported and beneficial effects sustained for several years.[7–12] Isolated dystonia has been shown to be responsive to DBS in childhood,[13–17] with shorter disease duration appearing to correlate with a better response.[18–21] Other factors predicting outcome have been suggested in this patient group, though evidence is less compelling, with the possible exception of the beneficial effect of DYT1 positive status.[5,6,19,22] Symptomatic (formerly "secondary") dystonia is known to be less responsive to DBS, the reasons for which remain unclear.[5,6,21,23] Some exceptions to this rule have been found, e.g. the markedly positive response to DBS seen in tardive dystonia/dyskinesia.[5,24,25]

The focus on improving outcomes for DBS in the management of dystonia has largely been the importance of patient selection.[6,26] The issue of electrode placement has been less studied, posing the question whether where the electrode is placed may be as important as whom the electrode is placed in? Currently established anatomical targets for DBS in the management of dystonia will be reviewed, examining the influence of choice of target nuclei and precise placement within each nuclei on outcome following surgery.

2. Anatomical targets for DBS in dystonia – the basal ganglia and thalamus

Dystonia has traditionally been considered a disease of the basal ganglia and thalami, though more recently it has been emphasized that dystonia arises as a consequence of disruptions across a much broader whole-brain network, including regions of the cerebral cortices, brainstem and cerebellum.[27–31]

The basal ganglia are a group of subcortical grey matter nuclei, the major input nuclei being the striatum (caudate and putamen) and subthalamic nucleus (STN), and the major output nuclei being the substantia nigra pars reticulate (SNr). A simplified representation of the connections between these nuclei is shown in Fig. 1. Whilst it is increasingly recognized as an over simplification, the most influential model of the intrinsic structure of the basal ganglia is that of the "direct" and "indirect" pathways proposed by Albin and colleagues.[32] This model suggests that the output of the basal ganglia (inhibitory connections from the SNr/GPi to thalamus) is determined by the balance of activity in the direct pathway (inhibitory connection from striatum to GPi/SNr) which promotes thalamic activity, and indirect pathway (connection from striatum relayed to SNr/GPi through GPe and STN) which inhibits thalamic activity. In this model, dystonia can be thought of as arising due to a relative *excess* activity in the direct pathway. It is now appreciated that intrinsic connectivity of the basal ganglia is much more complex, with much greater interconnectivity between nuclei, and the so-called "hyper direct" pathway between cortex and STN.[33–35]

The basal ganglia form part of a loop running from the cortex through the basal ganglia to the thalamus and then passing back up to the cortex – the cortico-striato-pallido-

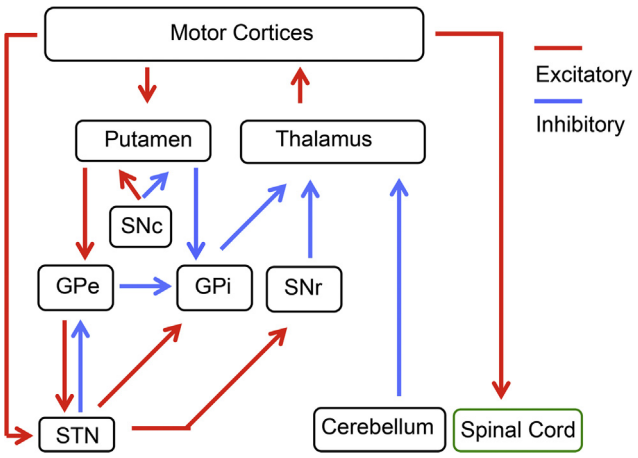


Fig. 1 – A simplified representation of the connections of the basal ganglia, thalamus and cerebellum. Excitatory connections are represented by red arrows, inhibitory connections by blue arrows. Abbreviations: "GPe" – Globus Pallidus Externa, "GPi" – Globus Pallidus Interna, "SNc" – Substantia Nigra Pars compacta, "SNr" – Substantia Nigra Pars Reticulata, "STN" – Subthalamic Nucleus". (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)