The Rationale for the Dentate Nucleus as a Target for Deep Brain Stimulation in Dystono-Dyskinetic Syndromes

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Abstract

Purpose: To discuss the potential of Deep Brain Stimulation (DBS) of the dentate nucleus as a treatment for dystono-dyskinetic syndromes.

Methods: An extensive literature review has been carried out, covering the anatomy and physiology of the dentate nucleus and the experimental evidence for its involvement in the pathophysiology of dystonia and dyskinesia.

Results: Evidence from animal models and from functional imaging in humans is strongly in favor of involvement of the dentate nucleus in dystono-dyskinetic syndromes. Results of previous surgical series of dentate nucleus stimulation have been promising but precise descriptions of the movement disorders being treated are lacking and outcome measures have generally not been well defined.

Conclusion: In the light of new evidence regarding the involvement of the dentate nucleus in dystono-dyskinetic syndromes, we present a review of the current literature and discuss why we believe the question of dentate nucleus stimulation deserves to be re-visited.

Keywords: Dentate nucleus; Deep brain stimulation; Dystonia; Spasticity; Dyskinesia; Hypertonia

Introduction

The idea that stimulation of the dentate nucleus could be used as a treatment for movement disorders is not new. Irving Cooper began implanting surface electrodes to stimulate the cortex of the anterior lobe of the cerebellum for cerebral palsy at the beginning of the 1970's and the first reported stimulation of the dentate nucleus itself for spasticity was carried out in 1972 but dentate nucleus lesioning and stimulation for the treatment of spasticity have fallen out of use over the last 30 years, having been superseded principally by baclofen and botulinum toxin [1,2]. Dystonia, defined as a neurological movement disorder in which sustained muscle contractions cause twisting and repetitive movements or abnormal postures, and dyskinesia, defined as difficulty or distortion in performing voluntary movement, often occur together, giving the clinical picture of dystonia-dyskinesia, or Dystono-Dyskinetic Syndrome (DDS). Pure dystonia (extrapyramidal hypertonia) can be present without dyskinesia but more commonly the two symptoms co-exist.

Dystono-dyskinetic syndromes vary in severity from writer's cramp to a life-threatening dystonia storm and have essentially two components increased tone (the "pure dystonia" component) and involuntary movement (the dyskinetic component, which can be either a kinesia or hyperkinesias, depending on the integrity of the dopaminergic pathways) both of which are manifestations of damage to the extrapyramidal system. Damage to the pyramidal tract also causes increased tone, manifest as spasticity, and movement disorder, manifest as focal motor deficit, and may co-exist with DDS. The combination of pyramidal and extrapyramidal movement disorders presents a particularly difficult therapeutic challenge. In some ways it is perhaps slightly artificial to try to separate disorders of the pyramidal and extrapyramidal systems because the one cannot function normally without the other, but it is a useful concept from a therapeutic point of view because the management of each is different. Movement disorders can be divided into four broad categories...
as follows: pure dystonia (extrapyramidal tone disorder); pure dystono-dyskinetic syndrome (extrapyramidal tone and movement disorder); mixed extrapyramidal and pyramidal tone and movement disorder either with predominantly extrapyramidal symptoms or with predominantly pyramidal symptoms; pure pyramidal tone and movement disorder. The different types of movement disorder are distinguished primarily by the history and clinical examination but investigations such as MRI, functional imaging, Single Photon Emission Computed Tomography (SPECT), electrophysiology, and genetic testing where appropriate, can also be helpful.

So why revisit the question of dentate nucleus stimulation in the context of DDS? The evidence from MRI and functional imaging that there is a link between dystonia and the basal ganglia is incontrovertible but there is now mounting evidence of a similar nature linking dystonia with cerebellar dysfunction and indeed it seems likely that there is more than one underlying pathophysiological mechanism. Animal models also suggest a link between the cerebellum and dystono-dyskinetic disorders. Injection of a glutamate antagonist into the cerebellar vermis in normal mice induces dystonia postures but the same procedure in transgenic mice without Purkinje cells does not result in dystonia, implying that activation of Purkinje cells is important in the pathophysiology [3]. In a mouse model of paroxysmal dyskinesia, surgical removal of the cerebellum has been shown to worsen ataxia but eliminate dyskinesia, supporting the hypothesis that abnormal cerebellar output contributes to paroxysmal dyskinesia [4]. Increased metabolic activity has been demonstrated in the cerebellum in humans in DYT1 dystonia, writer’s cramp, cervical Dystonia and Myoclonus Dystonia (DYT11) [5-9]. The evidence suggests that there is an abnormal increase in cerebellar output in dystonia, therefore both primary and secondary dentate nucleus dysfunction could potentially manifest as a dystono-dyskinetic syndrome. It is an attractive idea that modulation of dentate nucleus function by DBS would be able to correct for abnormal cerebellar output and therefore control the symptoms resulting from it. Pallidus stimulation can be a highly effective treatment for dyskinesia [10] but hypertonia, i.e. the pure dystonia component tends to respond less well. Other nuclei can be targeted but outcomes in the purer forms of dystonia can be disappointing. For a significant number of patients with movement disorders, currently available treatments do not make a significant impact on their symptoms. Global dystonia without dyskinesia, post-stroke hemidystonia, some mitochondrial cytopathies and post-anoxic dystonia can all respond poorly to both DBS and medical therapy. A more effective treatment for hypertonia is needed. It is possible that dentate nucleus stimulation may be able to ameliorate both dyskinesia and hypertonia and could therefore be an effective treatment for mixed extrapyramidal and pyramidal movement disorders.

Anatomy and Physiology of the Dentate Nucleus

Demole et al. [11] described the microgyric (dorsomedial) and macrogyric (rostrolateral) regions of the dentate nucleus. Corresponding to the parvocellular and magnocellular regions later described by Korneliussen et al. [12] (Figure 1). These regions are now known to be functionally distinct, with the rostral part of the nucleus being motor and the caudal part being non-motor [13]. The connections of the two anatomically distinct regions of the dentate are different. Efferent fibers from the motor dentate terminate in the nucleus ventralis intermedialis lateral is of the thalamus (the “VIM” of neurosurgeons) and in the later caudal parvocellular red nucleus, as well as in the reticular formation. A mesencephalo-olivary-cerebellar loop connects the motor dentate to the dorsal lamina of the principal olivary nucleus via the red nucleus. There is also a direct GABAergic connection between the dentate and the contralateral inferior olivary nucleus [14]. The cortical projections of the motor dentate are principally to the contralateral primary motor area and the premotor area and are organized somatotopy. Efferent fibers from the non-motor dentate terminate in the nucleus ventralis intermedialis medialis of the thalamus and in the dorsomedial parvocellular red nucleus; there are also direct and indirect connections with the ventral lamina of the principal oliva. The cortical projections of the non-motor dentate are principally to the prefrontal cortex and the parietal cortex. It appears that all regions of the cerebral cortex receiving dentate input project back to it via the pontine nuclei and the cerebellar cortex, forming multiple dentato-thalamo-cortico-ponto-cerebellar loops [13]. There are also reciprocal connections between the dentate nucleus and the cerebellar cortex. Descending fibers from the dentate nucleus project directly to the ipsilateral and contralateral reticular formation and from there to the spinal cord [15,16]. The connections of the dentate nucleus with the reticular formation are important because they are the principal means by which the cerebellum can influence muscle tone. Two of the three main descending tracts involved in the control of muscle tone originate in the reticular formation the dorsal reticulospinal tract (inhibitory) and the medial reticulospinal tract (excitatory). The projections of the reticular formation to the spinal cord are bilateral [17-20]. An indirect connection between the dentate nucleus and the vestibulospinal tract via the interstitial nucleus of Cajal exists in cats but it is not known whether a similar connection exists in man. The Cortico Spinal Tract (CST) may also have a role to play in the regulation of muscle tone, although damage to the CST in isolation does not result in spasticity [21,22].

Recent evidence has demonstrated a disynaptic connection between the dentate and the striatum via the thalamus and a trisynaptic connection between the dentate and the globus pallidus externus via the striatum and the thalamus in the macaque monkey [23]. These connections are predominantly contralateral but there is also an ipsilateral component. There are no direct connections between the left and right dentate nuclei but there are indirect connections via the cerebral cortex, the cerebellar cortex, the basal ganglia, the hypothalamus and the reticular formation. It is therefore possible that the left and right dentate nuclei can communicate via the corpus callosum, the cerebellar commissure and the bilateral projections to the diencephalon and brainstem. These pathways may underlie the observation of bilateral dentate and cerebellar cortex activation on functional MRI during unilateral motor tasks. The dentate is one
of only two folded nuclei in the central nervous system, the other being the inferior olivary nucleus, which is involved in mediating excitatory input to the dentate nucleus from the cerebral cortex [24]. The shape of the dentate has been likened to a "crumpled purse", with its opening facing ventromedially and rostral [25]. The complexity of the morphology of the nucleus is important from the point of view of surgical targeting and can be explained in part by its embryology. The dentate is first visible at around 11 weeks in humans and initially lies along a dorsoventral axis. The axis changes by 45 degrees at around 14 weeks so that it becomes dorsomedial-ventrolateral. Gyri begin along a dorsoventral axis. The axis changes by 45 degrees at around 14 weeks so that it becomes dorsomedial-ventrolateral. Gyri begin to form in the dorsomedial lamina at around 20 weeks and in the ventrolateral lamina at around 23 weeks. By 28 weeks the microgyric and macrogyric regions are discernable and the nucleus resembles that of an adult [26,27].

The dentate nucleus measures approximately 9 mm to 20 mm in width, 7 mm to 20 mm in height and 13 mm to 23 mm in length [28]. It is estimated that Purkinje cells outnumber Deep Cerebellar Nuclei (DCN) cells by somewhere between 3 to 6:1 implying a degree of convergence of cerebellar cortical output [29,30]. All the DCN nuclei contain glutamatergic and GABAergic cell populations [31]. The glutamatergic cells in the DCN project mainly to the ventrolateral thalamus [32], the red nuclei [33], the vestibular nuclei [34], and the pontine nuclei [35], whereas the GABAergic cells project to the inferior olive and to targets thought to be within the DCN [36].

There is considerable evidence from neurophysiological studies that dystono-dyskinesia result from reduced inhibition of the cerebral cortex [37]. Is it possible that cortical disinhibition could result from cerebellar dysfunction? Cerebellar lesions are usually associated with hypotonia, due to reduced excitatory output from the DCN, leading to reduced excitatory input to the cerebral cortex via the thalamus, but dystono-dyskinetic syndromes are associated with hypertonia. The theory that there is abnormal activation of the DCN in dystono-dyskinetic syndromes is in keeping with our current understanding of the connections between the cerebellum and the cortex (Figure 2), whereby abnormally high levels of output from the dentate would have a net excitatory effect on the cerebral cortex because dentate input to the thalamus is excitatory. What is not known is whether pallidal output can be modulated by dentothalamic fibers at a subcortical level, for example presynaptically or within the thalamus itself, as shown by the dotted arrows in (Figure 3). Cerebellar and pallidal thalamic territories are adjacent but anatomically distinct and direct connections between them have not been demonstrated. Figure 3 illustrates possible subcortical connections between the cerebellothalamic and pallidothalamic pathways. If dentothalamic fibers are able to influence the pallidothalamic pathway then, under normal circumstances, the cerebellum would exert an inhibitory influence because of the GABAergic output of the cerebellar cortex. If, however, there is hyperactivity or desynchronous discharge in the dentate nucleus then this could potentially lead to increased activity in the pallidal thalamic territory (nucleus ventralis oral is, VO) and set up abnormal/desynchronous discharges in the pallido-thalamo-cortico-striato-sub thalamic circuit (illustrated by the thick red and blue arrows in Figure 3) resulting in hypertension and dyskinesia. VIM stimulation can be used to treat dystono-dyskinetic syndromes, either in isolation or in combination with GPI stimulation. The VIM is a very small and irregularly-shaped target and indeed not significantly larger than a DBS electrode. The size of the VIM and the proximity of VO make it likely that VIM stimulation also exerts an effect on the pallidal thalamic territory and is thereby able to modulate pallidal input to the cortex and the activity in the pallido-thalamo-cortico-striato-sub thalamic circuit. By extension, dentate nucleus stimulation should be able to modulate the pallido-thalamo-cortico-striato-sub thalamic circuit indirectly. Subcortical/intrathalamic connections between the dentothalamic and pallidothalamic tracts would be consistent with the proposed 'motor network' model of dystono-dyskinetic disorders, although experimental evidence for such connections is lacking at the present time [38].

MRI and functional imaging in dystono-dyskinetic syndromes

Not only is the dentate nucleus a rather awkward shape for DBS in terms of target selection and electrode placement, it is also rather difficult to see on conventional MRI sequences. In the past, atlas co-ordinates have been used for electrode implantation but this method can be susceptible to significant error and we believe that direct MRI based target selection is the technique of choice [39].
extent, each nucleus is part of a network involved in motor control, in man remains poorly understood. The concept of a “target” in on T2 imaging. The anatomical basis for the control of movement to define the target on the basis that the dentate is more clearly visible likely to be fusion of 3D T1 and T2 MR Images, using the T2 image useful for targeting purposes. The best compromise for targeting is image would be distorted and so the technique is unlikely to prove SWI sequences but there would still be concern that the resulting concern in the context of functional neurosurgery because it would affected carriers had increased metabolic activity in the midbrain, cerebellum (region corresponding to the dentate nucleus) and thalamus during movement. They concluded that a functional imbalance in the cortico-striato-pallido-thalamo-cortical loop may mediate DYT1 dystonia. Odergren et al. [6] carried out PET scans on patients with writer's cramp and demonstrated an abnormal increase in activity in the cerebellum during writing, supporting the hypothesis that there is abnormal activation of the cerebellum in dystonia. Peller et al. [7] carried out fMRI studies in writer's cramp and showed that, compared to healthy controls, patients showed a widespread bilateral increase in task-related activity in the lentiform nuclei, GI, lateral thalami, cerebellar cortex, DCN and pons. Task-related activity in the cerebellar nuclei, posterior vermis, right paramedian cerebellar hemisphere and dorsal pons was found to be inversely related to the severity of the dystonia. They hypothesized that the observed increase in activity represents an attempt to compensate for dysfunctional processing in the cortico-striato-thalamo-cortical loop. There is thus good evidence for functional reorganization in the cerebellum and DCN in dystono-dyskinetic syndromes but it is difficult to know how to interpret these findings. Is the increased activity seen in the dentate nucleus a primary or a secondary phenomenon, in other words is it the cause or the effect of the disease? It is possible that the dentate nucleus could be involved in both the pathogenesis of DDS and in the attempt to compensate for it, depending on the type of DDS. Different parts of the dentato-thalamo-cortico-ponto-cerebellar loop may be involved to different degrees in the pathogenesis of the different forms of DDS; both primary and secondary (Figure 5). There could also be a phenomenon similar to primary and secondary seizure foci in epilepsy, whereby more than one part of the loop may be abnormal. Increased metabolism in the dentate nucleus in patients with dystonia provides strong evidence for a cerebellar origin of cerebral cortex disinhibition.

**Stimulation of the dentate nucleus**

Stereotactic surgery targeting the DCN in primates was first carried out by Sir Victor Horsley and Robert Clarke at the beginning of the last century [43]. They stimulated each of the four nuclei under local anesthesia and showed that stimulation of the DCN produced movement and that different movements could be provoked by different levels of stimulation. The first surgical procedure on the dentate nucleus in man was carried out in 1935 by Delmas-Marsalet and Von Bogaert et al. [44]. They destroyed the nucleus by using a

![Diagram](image-url)
leucotome during an open operation for the treatment of Parkinson’s disease and reported a significant reduction in ipsilateral tone following surgery. Heimberger and Whitlock et al. [45] carried out stereotactic enterotomy in 12 patients with choreoathetosis and spasticity in 1965 and found a slight improvement in ipsilateral muscle tone. Zervas et al. [46] also reported reduced muscle tone following enterotomy, this time in the context of “Parkinson’s disease and dystonia” (a detailed description of the neurological signs is not provided). The results of these procedures were attributed to a reduction in cerebellar output to gamma motor neurons. Improvement in intention tremor was also reported [47]. In 1972, Knutsson and Meyerson et al. [2] stimulated the dentate nucleus under local anesthesia in 6 patients for the treatment of spasticity. They found that stimulation decreased muscle tone, predominantly ipsilateral but also contralateral, and also confirmed the previously postulated Somatotopy organization of the dentate, with the head medial and the lower limbs lateral. More recently, a number of small series have been reported on the results of dentate nucleus stimulation, including some with long term follow up [48]. Results have been variable and are often difficult to interpret due to lack of information regarding selection criteria, exact aetiology of the movement disorder and the means of assessment of function pre and post operatively, however on the whole they have been encouraging. No series has reported a higher level of complications than would be expected for any other stereotactic procedure. Recently, stimulation of dentate nuclei has been used in other movement disorders. Horisawa et al. [49] showed an interesting case report of a cerebellar deep brain stimulation including the dentate nucleus on fMRI, in a patient with a severe generalized fixed dystonia with a considerable clinical improvement. Vitale et al. [50] performed DBS of the pedunculopontine tegmental nucleus on rats to obtain an effect on motor disabilities in neurodegenerative disorders using cholinergic excitation from the pedunculopontine tegmental nucleus to the dentate nucleus. Teixeira et al. [51] used deep brain stimulation of the dentate nucleus to improve cerebellar ataxia after cerebellar stroke with interesting results. Cury et al. [52] published this good result after a long-term follow-up with a sustained benefit in tremor and ataxia. Machado et al. [53] performed a chronic electrical stimulation of the dentate nucleus region in rats after ischemic strokes with a better recovery of motor functions.

**Discussion**

There is increasing support for the theory dystono-dyskinetic syndromes are far more heterogeneous than previously thought and that different forms of DDS can result from lesions in different parts of the network connecting the cerebral cortex with the basal ganglia and cerebellum. Abnormal cerebellar output has been shown to be necessary for the expression of dystonic movements in animal models and has been demonstrated on functional imaging in humans with various different dystono-dyskinetic syndromes [54,55]. The same studies have shown that basal ganglia damage can affect the expression of the clinical syndrome, which supports the basal ganglia/cerebellum “motor network” theory. Dysfunction in one part of the network could lead to attempts to compensate for the problem in other parts of the network, which would be one explanation for the observed increased activity in both the basal ganglia and cerebellum on fMRI in some forms of DDS. Useful though they are, a degree of caution must be exercised when drawing conclusions from animal models and trying to apply that knowledge to human disease. DBS itself gives us some clues to the mechanisms underlying dystono-dyskinetic syndromes in man, and also to their heterogeneity. Pallidal stimulation could not be an effective treatment for dystonia if the trans-pallidal network were not involved in its pathophysiology but its lack of efficacy in certain types of dystonia lends support to the argument that the basal ganglia are not the whole story. The fact that dystonic movements sometimes respond to stimulation of other targets, such as the sub thalamic nucleus, the VIM or the border of the nucleus ventralis oral is anterior and the nucleus ventralis oral is posterior of the thalamus would also tend to favor a “motor network” hypothesis. It is difficult to draw conclusions about the role of the dentate nucleus in dystono-dyskinetic syndromes from previous surgical experience. The results of dentate nucleus surgery have been highly variable and selection criteria have never been strictly defined, making it impossible to be certain precisely which syndromes have responded, and to what degree. References in the literature to electrode placement for the treatment of spasticity describe the use of atlas co-ordinates rather than direct MRI targeting and there are no reports of postoperative imaging or post mortem studies to verify electrode position and correlate it with clinical effect. The continued use of atlas co-ordinates is presumably a reflection of the difficulty of seeing the dentate nucleus on conventional MR imaging but the inherent inaccuracy of the technique makes it unattractive, hence the need to find imaging techniques that will allow adequate visualization of the dentate nucleus so that a direct targeting method can be used. In view of the fMRI and electrophysiological evidence for dentate nucleus hyperactivity in some forms of DDS it would seem likely that patients with DDS refractory to both GPI stimulation and best medical therapy, and who have increased signal intensity in the dentate nucleus on fMRI, would be suitable candidates for

![Figure 5: Functional MRI in DYT1 Dystonia with stimulation ON and OFF](Image)

Functional MRI in DYT1 Dystonia with stimulation ON and OFF. Functional MRI after DBS surgery in a patient with DYT1 Dystonia with no cortical, striatal or thalamic lesions on MRI (A) and normal metabolism on FDG PET (B). The normal motor cortical activation pattern is absent when the pulse generator is OFF, even though the patient is able to perform the movement task. When the pulse generator is ON the normal pattern is recovered immediately. There is a significant difference between ON and OFF GPi stimulation conditions. Active opposition of the left thumb does not result in fMRI activation in the primary motor cortex when the contralateral pulse generator is OFF (C), but results in a clear activation when it is ON (D). No activation occurs when the ipsilateral pulse generator is ON (F).

dentate nucleus stimulation. Any future surgical studies of dentate nucleus stimulation will require strictly defined inclusion and exclusion criteria as well as postoperative stereotactic MRI to verify electrode position and correlate it with clinical response. Optimum electrode positioning is likely to depend on the clinical presentation of the patient because of the Somatotopy organization of the dentate nucleus. Ultimately, selection criteria for a new procedure have to be determined by careful analysis of outcome data from clinical trials.

**Conclusion**

The dentate nucleus is approximately half motor and half non-motor. It is part of a loop connecting the cerebellum with the thalamus, the cerebral cortex and the pontine nuclei, through which it can influence motor function. It also has direct connections with the red nucleus and with descending pathways controlling muscle tone. It is thus ideally placed as a target for deep brain stimulation for the treatment of dystono-dyskinetic movement disorders. From what is known about the functions and connections of the dentate nucleus, and from the surgical series reported in the literature to date, it would appear to be a logical target for DBS for the treatment of both hypertonia and spasticity, particularly in selected patients with mixed DDS in whom the dystonic symptoms have responded well to pallidal DBS but the hypertonic and spastic symptoms are not well controlled. It is also possible that dentate stimulation could ameliorate intention tremor and dystarthis and may therefore have applications other than DDS. Evidence would suggest that the demonstration of an abnormal increase in signal intensity in the nucleus on fMRI should be one of the selection criteria for surgery. There is certainly a need to find more effective treatments for hypertonia for the significant number of patients who cannot be treated adequately with current methods.

**References**


