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## **Dentate Nucleus as Target for Deep Brain Stimulation in Dystono- Dyskinetic Syndromes**

### **L'utilisation du noyau dentelé comme cible de stimulation cérébrale profonde dans les syndromes dystono-dyskinétiques**

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## **Dentate Nucleus as 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 covered 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 from previous surgical series of dentate nucleus stimulation were promising but precise description of movement disorders being treated were lacking and outcome measures were generally not well defined.

**Conclusions.** 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 the question of dentate nucleus stimulation deserves to be revisited.

Dentate nucleus; deep brain stimulation; dystonia; spasticity; dyskinesia; hypertonia

## Résumé

**Objectif.** Discuter du potentiel de stimulation cérébrale profonde (DBS) du noyau dentelé comme traitement des syndromes dystono-dyskinétiques.

**Méthodes.** Une revue de la littérature approfondie a été réalisée, couvrant l'anatomie et la physiologie du noyau dentelé ainsi que les preuves expérimentales de son implication dans la physiopathologie de la dystonie et de la dyskinésie.

**Résultats.** Les preuves issues de modèles animaux et de l'imagerie fonctionnelle chez l'homme sont fortement en faveur de l'implication du noyau dentelé dans les syndromes dystono-dyskinétiques. Les résultats des précédentes séries chirurgicales de stimulation du noyau dentelé ont été prometteurs mais les descriptions précises des troubles du mouvement traités font défaut et les mesures des résultats n'ont généralement pas été bien définies.

**Conclusions.** À la lumière de nouvelles preuves concernant l'implication du noyau dentelé dans les syndromes dystono-dyskinétiques, nous présentons une revue de la littérature actuelle et discutons pourquoi la question de la stimulation du noyau dentelé mérite d'être réexaminée.

Noyau dentelé; stimulation cérébrale profonde; la dystonie; spasticité; dyskinésie; hypertonie

## Introduction

The idea that stimulation of the dentate nucleus could be used as a treatment for movement disorder is not new. Irving Cooper began implanting surface electrodes to stimulate the cortex of the anterior lobe of the cerebellum for cerebral palsy in the early 1970s [1], and the first reported stimulation of the dentate nucleus itself for spasticity was carried out in 1972 [2]. However, dentate nucleus lesioning and stimulation for the treatment of spasticity have fallen out of use over the last 30 years, superseded principally by baclofen and botulinum toxin.

Dystonia, defined as a neurological movement disorder in which sustained muscle contractions cause twisting and repetitive movement or abnormal posture, and dyskinesia, defined as difficulty or distortion in performing voluntary movement, often occur together, giving the clinical picture of dystono-dyskinesia, or dystono-dyskinetic syndrome (DDS). Pure dystonia (extrapyramidal hypertonia) can be present without dyskinesia, but more commonly the two symptoms co-exist. DDSs vary in severity from writer's cramp to a life-threatening dystonic storm, and have essentially two components – increased tone (the "pure dystonia" component) and involuntary movement (the dyskinetic component, which can be either akinesia or hyperkinesia, 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 useful therapeutically, because the management of each is different.

Movement disorders can be divided into four broad categories: pure dystonia (extrapyramidal tone disorder); pure dystono-dyskinetic syndrome (extrapyramidal tone and movement disorder); mixed extrapyramidal and pyramidal tone and movement disorder with either predominantly extrapyramidal symptoms or predominantly pyramidal symptoms; and pure pyramidal tone and movement disorder. The different types of movement disorder are distinguished primarily by 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. Table 1 presents a semiological classification and results of DBS.

Why, then, 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 dystonia-dyskinetic disorders. Injection of a glutamate antagonist into the cerebellar vermis in normal mice induces dystonic posture, but the same procedure in transgenic mice without Purkinje cells does not result in dystonia, implying that normal or abnormal activation of Purkinje cells is important in the pathophysiology [3]. In a mouse model of paroxysmal dyskinesia, surgical removal of the cerebellum was shown to worsen ataxia but eliminate dyskinesia, supporting the hypothesis that abnormal cerebellar output contributes to paroxysmal dyskinesia [4]. Increased metabolic activity was demonstrated in the cerebellum in humans in DYT1 disease, writer's cramp, cervical dystonia and myoclonus dystonia (DYT11) [5, 6, 7, 8, 9].

It is an attractive idea that modulation of dentate nucleus function by DBS could correct for abnormal cerebellar output and thereby control the resulting symptoms. Pallidal modulation can be a highly effective treatment for dyskinesia [10] but hypertonia, the pure dystonic 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 disorder, currently available treatments do not have significant impact. 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 can ameliorate both dyskinesia and hypertonia and could therefore be an effective treatment for mixed extrapyramidal and pyramidal movement disorder.

## Anatomy and Physiology of the Dentate Nucleus

In 1927, Demol   described the microgyric (dorsomedial) and macrogyric (rostromedial) regions of the dentate nucleus [11], corresponding to the parvocellular and magnocellular regions later described by Korneliussen [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 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 lateralis of the thalamus (known as "VIM" to neurosurgeons) and in the laterocaudal parvocellular red nucleus and 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 toward the contralateral primary motor area and premotor area and are organized somatotopically. 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 olive. The cortical projections of the non-motor dentate are principally toward the prefrontal cortex and 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 onto 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 toward 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



humans. The corticospinal 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 studies 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, cerebellar cortex, basal ganglia, hypothalamus and reticular formation. It is therefore possible that the left and right dentate nuclei can communicate via the corpus callosum, cerebellar commissure and 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" [25], with its opening facing ventromedially and rostrally. 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° at around 14-15 weeks, becoming 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 9-20 mm in width, 7-20 mm in height and 13-23 mm in length [28]. It is estimated that Purkinje cells outnumber deep cerebellar nucleus (DCN: fastigial, interposed and dentate nuclei) cells by 3-to-6:1 [29, 30], implying a degree of convergence of cerebellar cortical output. All the DCNs contain glutamatergic and GABAergic cell populations [31]. The glutamatergic cells in the DCN project mainly to the ventrolateral thalamus [32] and red [33], vestibular [34] and 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 results 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 output from the dentate 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. The 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 oralis: VO) and set up abnormal/desynchronous discharges in the pallido-thalamo-cortico-striato-subthalamic circuit (illustrated by the thick red and blue arrows in Figure 3), resulting in hypertonia and dyskinesia. VIM stimulation can be used to treat dystono-dyskinetic syndromes, either in isolation or in combination with globus pallidus internus (GPi) stimulation. The VIM is a very small irregularly-shaped target, not much larger than a DBS electrode. The size of the VIM and the proximity of the 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 activity in the pallido-thalamo-cortico-striato-subthalamic circuit. By extension, dentate nucleus stimulation should be able to modulate the pallido-thalamo-cortico-striato-subthalamic circuit indirectly. Subcortical/intrathalamic connections between the dentothalamic and pallidothalamic tracts would be consistent with the proposed "motor network" model of dystono-dyskinetic disorders [38], although experimental evidence for such connections is lacking at the present time.

## **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, but it is also rather difficult to see on conventional MRI sequences. In the past, atlas coordinates were used for electrode implantation, but this method can be susceptible to significant error [39] and we believe that direct MRI-based target selection is the technique of choice. It is therefore necessary to determine which MR sequences are the most appropriate in terms of target visualization and minimizing distortion. The standard MRI protocol used in our unit was published previously [40]. 3D T1 and T2 sequences with 1.5 mm slices are acquired under general anesthesia on a 1.5 Tesla MRI scanner with the Leksell G frame in place. 1.5 T MRI is a good compromise between image quality and field distortion. This protocol has been shown to be accurate for target definition in the basal ganglia, but does not show the dentate nucleus as well as the GPi. Dimitrova et al. [28] produced extremely clear pictures of the dentate using a 3D axial volume T1-weighted Fast Low-Angle SHot (FLASH) sequence on 1.5 Tesla MR, acquiring each sequence 5 times and then averaging the sequences to achieve a better signal-to-noise ratio. Multiple sequence acquisitions improve image quality but also lengthen scanning time significantly, and are therefore not practical in the context of pre- and post-operative stereotactic MRI under general anesthesia. Deoni and Catani [41] described using quantitative T1 and proton density sequences on 3T MRI using the rapid driven equilibrium single pulse observation of T1 (DESPOT1) mapping technique and produced very clear pictures of the dentate, showing the microgyric and macrogyric regions extremely well. The dentate nucleus has a high iron content and is therefore beautifully demonstrated on Susceptibility-Weighted MRI (SWI) (Figure 1); however, the field distortion inherent in SWI is a concern in the context of functional neurosurgery because it could lead to inaccurate electrode placement. It is possible to fuse T1 and SWI sequences, but there would still be concern that the resulting image would be distorted, and so the technique is unlikely to prove useful for targeting purposes. The best compromise for targeting is likely to be fusion of 3D T1 and T2 MR images, using the T2 image to define the target on the basis that the dentate is more clearly visible on T2 imaging.

The anatomical basis of movement control in humans remains poorly understood. The concept of a "target" in functional neurosurgery is based on the assumption that each nucleus has a specific function. While this may be true to a certain extent, each nucleus is part of a network involved in motor control, and DBS could be expected to influence the function not

just of the target but of the whole network. While MRI is able to assess the structural integrity of the target and associated structures, the spatial resolution of SPECT and functional MRI (fMRI) is not yet adequate to assess the functional integrity of the basal ganglia and DCN. Functional MRI has been used in patients with DDS treated with DBS to demonstrate the restoration of normal motor cortical activation patterns when the stimulator is on, compared to when it is off (Figure 4) [42]. Functional imaging can thus be used as an indicator of the efficacy of stimulation.

A number of papers in the literature reported abnormal activation of the dentate nucleus in various dystono-dyskinetic syndromes. Eidelberg et al. [5] studied cerebral metabolism in DYT1 dystonia on positron emission tomography (PET) in 10 affected carriers of the DYT1 mutation, 7 asymptomatic carriers and 14 controls. Asymptomatic and symptomatic carriers had increased activity in the cerebellum, supplementary motor area and lentiform nuclei at rest (which is the pattern seen in normal subjects during voluntary movement) and affected carriers had increased metabolic activity in the midbrain, cerebellum (region corresponding to the dentate nucleus) and thalamus during movement. The authors concluded that a functional imbalance in the cortico-striato-pallido-thalamo-cortical loop may mediate DYT1 dystonia. The overactivity could be reactional to an increased amount of movement. It must furthermore be kept in mind that cerebellar cortical activation could also reflect inhibition of co-contraction in a normal way. 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 found that, compared to healthy controls, patients showed widespread bilateral increase in task-related activity in the lentiform nuclei, GPi, 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 represented 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 is

involved in both the pathogenesis of DDS and 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. There could also be a phenomenon similar to primary and secondary seizure foci in epilepsy, with more than one part of the loop being abnormal. Increased metabolism in the dentate nucleus in patients with dystonia provides strong evidence for a cerebellar origin of cerebral cortex disinhibition.

## **Electrical neuromodulation 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 evoked by different levels of stimulation. The first surgical procedure on the dentate nucleus in humans was carried out in 1935 by Delmas-Marsalet and Von Bogaert [44]. They destroyed the nucleus by 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 [45] carried out stereotactic dentatotomies 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 dentatotomy, this time in the context of "Parkinson's disease and dystonia" (a detailed description of the neurological signs was 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 [2] stimulated the dentate nucleus under local anesthesia in 6 patients for the treatment of spasticity. They found that stimulation decreased muscle tone, predominantly ipsilaterally but also contralaterally, and also confirmed the previously postulated somatotopic organization of the dentate, with the head represented medially and the lower limbs laterally. More recently, a number of small series of dentate nucleus stimulation have been reported, including some with long-term follow-up [48]. Results were variable and often difficult to interpret due to lack of information regarding selection criteria, exact etiology of the movement disorder and the means of assessment of pre- and post-operative function; however, on the whole they have been encouraging. No studies 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. published an interesting case report of cerebellar deep brain stimulation including the dentate nucleus in a patient with severe generalized fixed dystonia, showing considerable clinical improvement [49]. Vitale et al. performed DBS of the pedunculopontine tegmental nucleus in rats to obtain an effect on motor disabilities in neurodegenerative disorders using cholinergic excitation from the pedunculopontine tegmental nucleus to the dentate nucleus [50].

Teixeira et al. used dentate nucleus DBS to improve cerebellar ataxia after cerebellar stroke, with interesting results [51]. Cury et al. reported good results on long-term follow-up, with sustained benefit in tremor and ataxia [52]. Machado et al. performed chronic electrical stimulation of the dentate nucleus region in rats after ischemic stroke, with better recovery of motor function [53].

We propose a target in the motor dentate nucleus (Axial Susceptibility-Weighted Imaging 1.5 Tesla MRI sequence) (Figure 5). The main results of dentate nucleus DBS are summarized in Table 2.

## Discussion

There is increasing support for the idea that 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 [54] and has been demonstrated on functional imaging in humans with various different dystono-dyskinetic syndromes. The same studies showed that basal ganglion 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 may be one explanation for the observed increase in 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 human DDS, and to their heterogeneity. It is now well

established that the GPi neuromodulation alone has no effect on isolated generalized dystonia (i.e. hypertonia). It seems that dystonia, essentially due to lack of inhibition of co-contraction, is improved in the same way as the associated dyskinesia.

It is difficult to draw conclusions from previous surgical experience about the role of the dentate nucleus in DDS. The results of dentate nucleus surgery are 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 postmortem 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, whence 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 international experience with GPi neuromodulation in DDS, it appears that it is essentially effective on the hyperkinetic component of movement disorders. A contrario, disorders presenting with a prominent hypertonic dystonia are not corrected by GPi targeting (DYT12 disease, perinatal severe anoxia with Vim-Vop lesions). In this situation, patients could be candidates for dentate nucleus neuromodulation, hypothesizing that, firstly, some desynchronization coming from denta-rubro-thalamic tract dysfunction and, secondly, possible direct action on the dentato-spinal tract, could be corrected. Demonstrating basic metabolic and/or electrophysiological dentate nucleus hyperactivity could be an important prerequisite.

In view of the fMRI and electrophysiological evidence for dentate nucleus hyperactivity in some forms of DDS, it is likely that patients with DDS refractory to both GPi modulation and best medical therapy, and who show increased signal intensity in the dentate nucleus on fMRI, are suitable candidates for 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 check 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 somatotopic organization of the dentate nucleus.

## **Conclusion**

The dentate nucleus is approximately half motor and half non-motor. It is part of a loop connecting the cerebellum with the thalamus, cerebral cortex and pontine nuclei, through which it can influence motor function. It also has direct connections with the red nucleus and 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 dyskinetic 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 dysarthria [55], and may therefore have applications other than DDS. Evidence suggests that abnormal increase in signal intensity in the nucleus on fMRI and/or metabolic hyperactivity 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.



## FIGURE LEGENDS

**Figure 1.** Axial Susceptibility-Weighted Imaging (SWI) 1.5 Tesla MRI sequence showing the dentate nucleus (source: Department of Neuroradiology, University Hospital of Montpellier)

**Figure 2.** Principal connections of the motor dentate nucleus.

CST = corticospinal tract, RST = rubrospinal tract, VST = vestibulospinal tract, DRST = dorsal reticulospinal tract, MRST = medial reticulospinal tract, INC = interstitial nucleus of Cajal, Glu = glutamate, Asp = aspartate, ACh = acetyl choline, GABA = gamma amino butyric acid, GPe = globus pallidus externus, STN = subthalamic nucleus, GPi = globus pallidus internus, VimL = *nucleus ventralis intermedialis lateralis*, VO = *nucleus ventralis oralis*, POdl = principal olive dorsal lamina. Dotted arrows indicate that the pathway has not been demonstrated in primates. Thick arrows indicate the dentato-thalamo-cortico-ponto-cerebellar loop, +ve = excitatory pathway, -ve = inhibitory pathway. (The dopaminergic pathways are not shown.)

**Figure 3.** Possible mechanisms for modulation of pallido-thalamo-cortical input by dentothalamic fibers.

VIM = nucleus ventralis intermedialis medialis, VO = nucleus ventralis oralis, GPi = Globus Pallidus internus, GPe = Globus Pallidus externus, STN = Subthalamic Nucleus, SNpr = Substantia Nigra pars reticulata, SNpc = Substantia Nigra pars compacta, Glu = glutamate, DA = dopamine

**Figure 4.** 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-E). No activation occurs when the ipsilateral pulse generator is ON (F). (Reproduced with permission from Coubes P, Zanca M (2007) Electrical pallidal

stimulation in the treatment of abnormal movements: the Montpellier experience in using functional imaging for patients' selection criteria. *Médecine Nucléaire* 31: 58–62)

**Figure 5.** Proposed Dentate Nucleus targeting for Deep Brain Stimulation.

White arrows: Proposed target in the left dentate nucleus (Axial Susceptibility-Weighted Imaging 1.5 Tesla MRI sequence)

**Table 1.** Semiological classification and results of DBS.

GPi = Internal Globus Pallidus, Vim = Thalamic Ventral Intermediate nucleus, STN = Subthalamic nucleus, DN = Dentate nucleus, Dopa+ = Dopamine sensitive, Dopa- = not sensitive to dopamine.

+: DBS effective

++: DBS very effective

+/-: Results of DBS variable

-: ineffective

?: Results of DBS unknown

**Table 2.** Main clinical results of dentate nucleus targeting for movement disorders.

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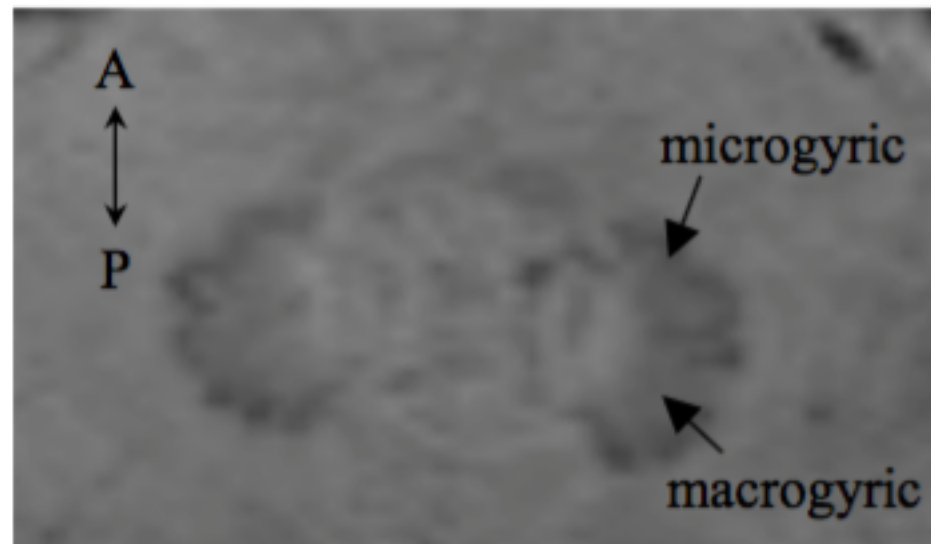
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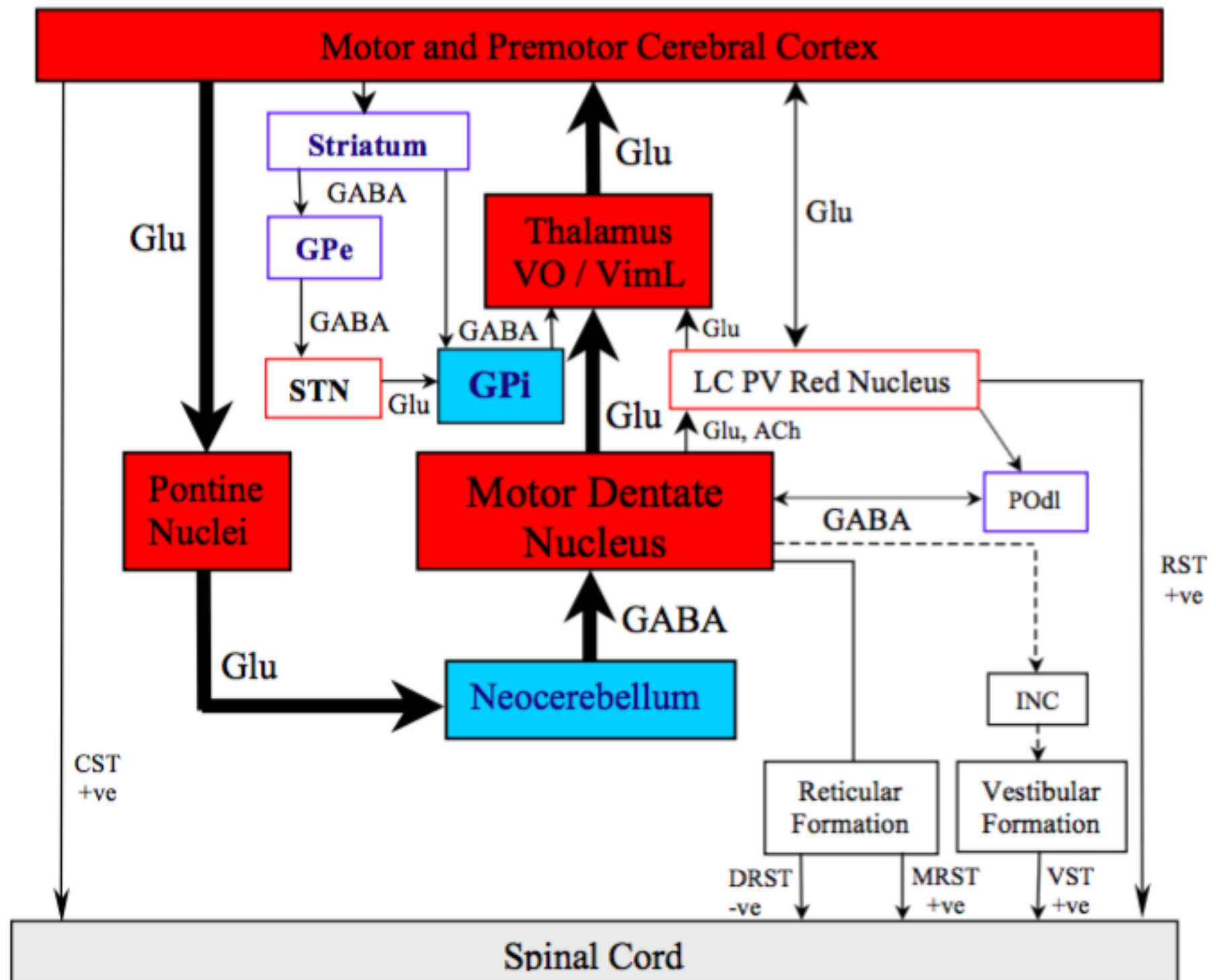
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We have no conflicts of interest

**Figure 1.** Axial Susceptibility-Weighted Imaging (SWI) 1.5 Tesla MRI sequence showing the microgyric and macrogyric regions of the dentate nucleus (source: department of neuroradiology, University Hospital of Montpellier)



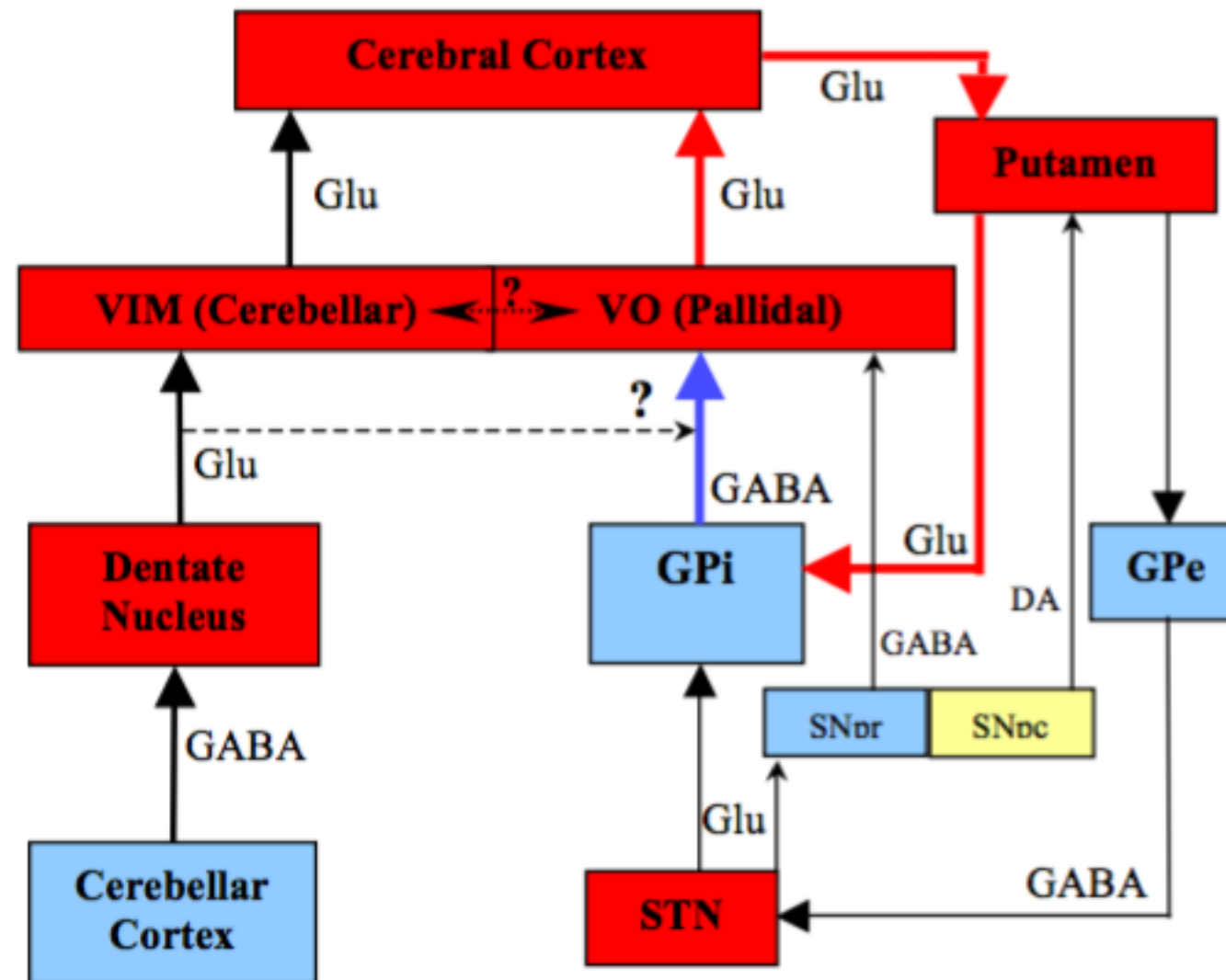
**Figure 2. Principal connections of the motor dentate nucleus**



CST = corticospinal tract, RST = rubrospinal tract, VST = vestibulospinal tract, DRST = dorsal reticulospinal tract, MRST = medial reticulospinal tract, LC PV Red Nucleus = Laterocaudal Parvocellular Red Nucleus, INC = interstitial nucleus of Cajal, Glu = glutamate, Asp = aspartate, ACh = acetyl choline, GABA = gamma amino butyric acid, GPe = globus pallidus externus, STN = subthalamic nucleus, GPI = globus pallidus internus, VimL = *nucleus ventralis intermediolateralis*, VO = *nucleus ventralis oralis*, POdl = principal olive dorsal lamina. Dotted arrows indicate that the pathway has not been demonstrated in primates. Thick arrows indicate the dentato-thalamo-cortico-ponto-cerebellar loop, +ve = excitatory pathway, -ve = inhibitory pathway. The majority of dentothalamic fibres decussate but a minority project to the ipsilateral thalamus. (The nigrostriatal pathways are not shown.)

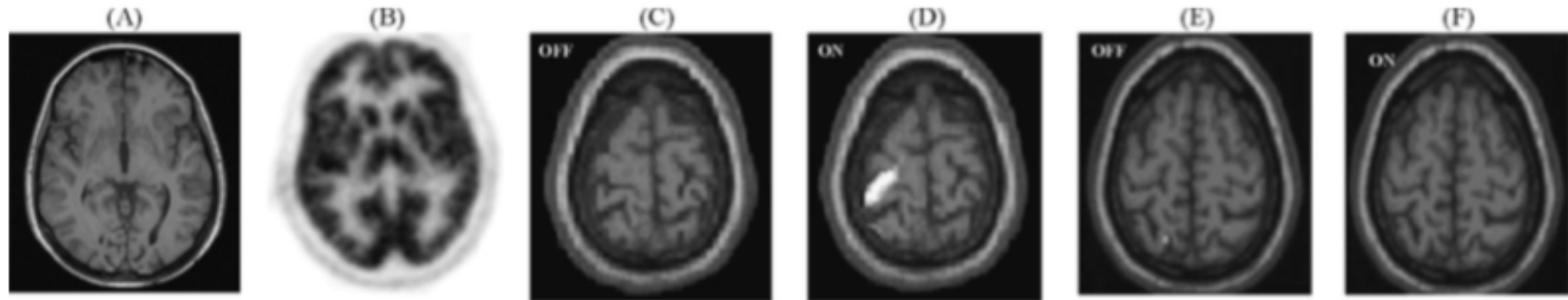


**Figure 3. Possible mechanisms for modulation of pallido-thalamo-cortical input by dentothalamic fibres**

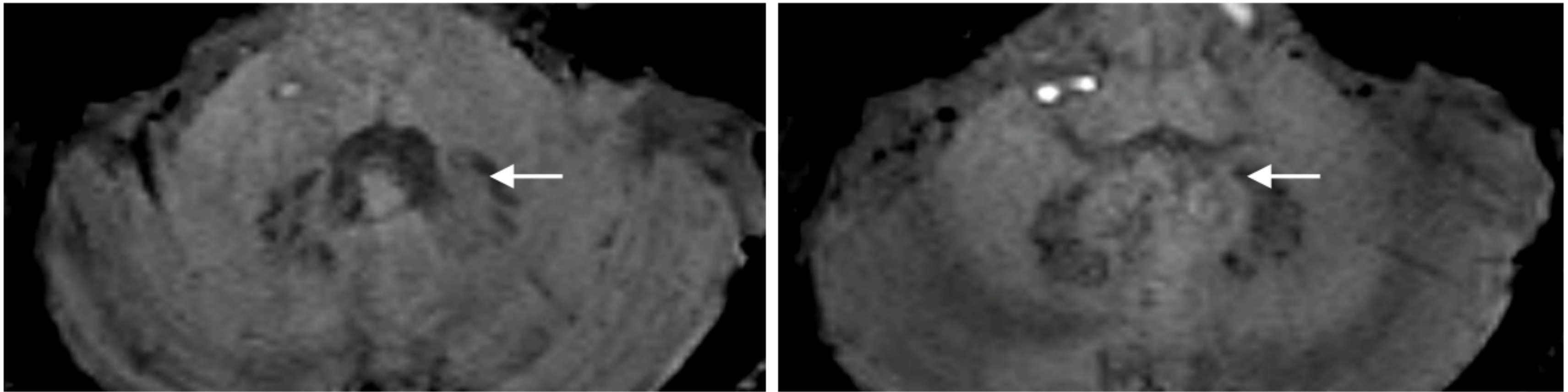


VIM = nucleus ventralis intermedius medialis, VO = nucleus ventralis oralis, GPI = Globus Pallidus internus, GPe = Globus Pallidus externus, STN = Subthalamic Nucleus, SNpr = Substantia Nigra pars reticulata, Substantia Nigra pars compacta, Glu = glutamate, DA = dopamine

**Figure 4. Functional MRI in DYT1 Dystonia with stimulation ON and OFF**



**Figure 5. Proposition of Dentate Nucleus targeting for Deep Brain Stimulation**



White arrows : Proposition of target in the left dentate nucleus (Axial Susceptibility-Weighted Imaging 1.5 Tesla MRI sequence)

**Table 1. Semiological classification and results of DBS**

	Dystonia		Dyskinesia	Oscillations	Bradykinesia
	Dopa+	Dopa-			
GPI	+	+	++	+/-	+/-
Vim	+/-	+/-	+/-	+	-
STN	+	+/-	++	+	+
DN	+?	+?	-	+?	-

GPI = Internal Globus Pallidus, Vim = Thalamic Ventral Intermediate nucleus, STN = Subthalamic nucleus, DN = Dentate nucleus, Dopa+ = Dopamine sensitive, Dopa- = not sensitive to dopamine.

+: DBS effective

++: DBS very effective

+/-: Results of DBS variable

-: ineffective

?: Results of DBS unknown

**Table 2. Main clinical results of dentate nucleus targeting for movement disorders.**

<b>Authors</b>	<b>Year</b>	<b>Indication</b>	<b>Stimulation or lesion of the dentate nucleus</b>	<b>Clinical results</b>
Knutsson E.	1972	Spasticity	Stimulation	Muscle tone decreased predominantly ipsilaterally but also contralaterally
Delmas-Marsalet P	1935	Parkinson's disease	Lesion	Reduction in ipsilateral tone
Heimbürger RF	1965	Choreoathetosis and spasticity	Lesion	Slight improvement in ipsilateral muscle tone
Zervas NT	1967	Parkinson's disease and dystonia	Lesion	Reduced muscle tone
Nashold BS	1969	Intention tremor	Stimulation and lesion	Improvement
Schvarcz JR	1987	Spasticity	Stimulation	Relieved spasticity and improved motor function
Horisawa S	2019	Generalized fixed dystonia	Stimulation	Clinical improvement
Teixeira MJ	2015	Cerebellar ataxia after cerebellar stroke	Stimulation	Clinical improvement
Cury RG	2019	Cerebellar ataxia and tremor after cerebellar stroke	Stimulation	Initial and sustained benefit in tremor and ataxia