Bilateral stimulation of the caudal zona incerta nucleus for tremor control

P Plaha, S Khan, S S Gill

ABSTRACT

Introduction: The ventrolateral (VL) nucleus of the thalamus is the commonly chosen target for deep brain stimulation (DBS) to alleviate tremor. However, it has a poor efficacy in alleviating proximal tremor and patients may develop tolerance to the action component of tremor. We performed bilateral stimulation of the caudal or motor part of the zona incerta nucleus (cZI) to determine its safety and efficacy in alleviating tremor.

Methods: 5 patients with parkinsonian tremor and 13 with a range of tremors (Holmes (HT), cerebellar (CT), essential (ET), multiple sclerosis (MS) and dystonic tremor (DT)) affecting both the proximal and distal body parts underwent MRI guided, bilateral cZI DBS. Tremor was assessed by the Fahn–Tolosa–Marin (FTM) tremor scale at baseline and at a mean follow-up of 12 months.

Results: Resting PD tremor improved by 94.8% and postural tremor by 88.2%. The total tremor score improved by 75.9% in 6 patients with ET, HT improved by 70.2%, proximal CT by 60.4% and proximal MS tremor by 57.2% in the total tremor rating score. In the single patient with DT, there was improvement in both the dystonia and the tremor. Patients required low voltages of high-frequency stimulation and did not develop tolerance to it. Stimulation-related side effects were transient.

Conclusion: This prospective study shows that the cZI may be an alternative target for the treatment of tremor with DBS. In contrast to bilateral DBS of the VL nucleus, it improves all components of tremor affecting both the distal and proximal limbs as well as the axial musculature.

Tremor is defined as a rhythmic, involuntary oscillation of a body part. It is classified according to the body part that it affects (eg, the axis, proximal or distal limbs), and the circumstances under which it occurs (eg, at rest (tremor at rest) or during active muscle contraction (kinetic tremor)). Kinetic tremor is subclassified into tremor that occurs when maintaining limb position or posture (postural tremor), during active limb movement (action tremor) or when a limb is approaching a target (intention tremor). Parkinsonian tremor is classically described as a resting and postural tremor. Essential tremor (ET) and tremor associated with multiple sclerosis (MS) are usually postural but can manifest an action component. Cerebellar tremor (CT) classically manifests as an intention tremor, dystonic tremor (DT) is either a postural or task-specific tremor, and Holmes tremor (HT) is both a resting and kinetic tremor.

The aetiology of tremor is multifactorial and drug therapy is usually the first line of management. Functional neurosurgery is offered when tremor is functionally disabling and medically refractory. A number of subcortical nuclei and white matter tracts have been defined, which, when lesioned or stimulated, control different aspects of tremor.

Typically, the ventrolateral (VL) nucleus of the thalamus (Hasslers ventralis intermedius) is the target of choice to effectively suppress distal limb tremor having a resting or postural component. However, proximal tremor and the action component of distal tremor respond poorly to DBS,1 with only a third of the patients showing any significant improvement.2 3 4 Nguyen et al have, however, reported that stimulating the dorsal part of the VL nucleus could suppress proximal action tremor.5 Perhaps the key limiting factor in effectively suppressing tremor by DBS of this nucleus is the high incidence (30–50%) of bilateral stimulation-related dysarthria and disequilibrium.6 7 8 Therefore, in order to avoid the above complications, most centres lesion or implant the DBS lead only unilaterally, contralateral to the tremor-dominant side.

The other subcortical area that has been explored to suppress tremor is the subthalamic region, which includes the subthalamic nucleus (STN), the zona incerta nucleus (ZI) and the white matter fibre tracts surrounding them.9 The STN is an effective target to suppress resting tremor with DBS in patients with Parkinson’s disease (PD).9 In addition, stimulation of this nucleus improves rigidity and bradykinesia.10 11 Large lesions involving the ZI and the surrounding white matter tracts, including the prelemniscal radiation, have been shown to be effective in suppressing distal tremor in patients with PD,12 13 Between tremor-predominant PD, ET.14 This area has also been unilaterally stimulated to suppress resting tremor in PD,14 proximal action tremor in ET13 15 16 and MS tremor.17 The white matter prelemniscal radiation has also been exclusively stimulated unilaterally to alleviate resting tremor in PD15 and distal tremor in ET.13 14

In this prospective study, we present our results of bilateral stimulation of the caudal or motor component of the zona incerta (cZI) nucleus in 18 patients with a range of tremor types.

MATERIALS AND METHODS

Demographics

Included in this consecutive study were 5 patients with tremor-predominant PD, 6 with ET, 4 with MS tremor, 1 with CT, 1 with HT and 1 with DT (table 1).

All patients underwent bilateral implantation of DBS leads, having given fully informed consent. The Frenchay Hospital local ethical committee...
Clinical evaluation
PD tremor was evaluated by applying the tremor subscores of the motor component (Part-III) of the Unified Parkinson’s Disease Rating Scale (UPDRS). All patents with non-parkinsonian tremor were assessed using the FTM Tremor Rating scale. The severity of dystonia in the patient with dystonic tremor and the functional disability caused by it was evaluated by applying the Burke–Fahn–Marsden Dystonia (BFMD) rating scale.

Preoperative assessments were performed with patients who were off all anti-tremor or anti-parkinsonian medications for 12 hours overnight. Post-operatively, they were assessed 12 hours after stopping anti-parkinsonian and anti-tremor medications and switching off the stimulation (off medication/off stimulation); and then after switching on the DBS (off medication/on stimulation). Patients who were not on any anti-tremor medications (4 MS and 1 CT patient) were assessed after switching off the DBS for 12 hours. A Specialist Movement disorder nurse performed all evaluations preoperatively and at follow-up. All pre- and post-operative tremor scores were evaluated independently from videos, which were scored independently by a blinded neurosurgeon.

Outcome measures
The primary outcome measure in patients with PD tremor was the percentage change in tremor subscores of the motor UPDRS from baseline (off medication) to follow-up at 12 months (off medication/on stimulation). The secondary outcome measure was the percentage improvement in the subscores of rigidity and bradykinesia between baseline and follow-up.

In all patients with non-parkinsonian tremor, our primary outcome measure was the percentage change of each of the subscores of the tremor rating scale (parts A–C) between baseline and follow-up (off medication versus off medication/on stimulation score). In the single patient with dystonic tremor, the secondary outcome measure was the percentage change in the BFMD movement and disability score from baseline to follow-up. We also recorded complications related to the surgical procedure, stimulation-related complications and the stimulation parameters required for optimal symptom control.

Surgery
Surgery was performed under general anaesthesia using high-resolution long-acquisition MRI scans acquired under stereotactic conditions to identify the cZI target that is located posterior-medial to the posterior-dorsal STN (fig 1). A transfrontal trajectory to the target, 45° to the AC–PC plane was planned and the anatomical position of each contact on the DBS lead was defined such that the second contact from its distal end (contacts 1 or 5) was placed at the target site. A frontal burr hole was made and a rigid probe inserted into the target and over which a plastic guide tube (Electrode Introducer Kit; Renishaw, UK) was advanced so that its distal end was short of the target by 12 mm. A hub on the proximal end of the guide tube was bonded in the Burr hole with acrylic cement. The probe was then withdrawn and replaced with a plastic stylette to the planned position in the cZI. An intraoperative MRI was performed to verify the position of the plastic stylette in relation to the planned target. On confirmation of satisfactory placement, the stylette was removed and replaced with a DBS lead (model 3389; Medtronic, Minneapolis, MN, USA). The procedure was performed bilaterally and the leads connected to a DBS pulse generator (Kineta), which was implanted in the infra-clavicular location.

Postoperative management
The Kineta generator was switched on immediately following surgery. The movement disorder nurse programmed the patients. Anti-parkinsonian and anti-tremor medications were reduced as appropriate by the neurologist.

Anatomical location of active contacts
To compare the mean location of the active contacts in our patient cohort with those defined by other groups, we plotted the location of each individual’s active contacts at their known position from the tip of the plastic stylette visualised on their perieoperaive scans (fig 2). The spatial location of each active contact with respect to the boundary of the STN, defined by MRI, was then transposed to a standardised STN, as defined on the Schaltenbrand and Warren atlas.

Table 1  Patient demographics and clinical history

<table>
<thead>
<tr>
<th>No</th>
<th>Age, years (SD; range)</th>
<th>Sex</th>
<th>Mean duration</th>
<th>Clinical history</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD tremor</td>
<td>5</td>
<td>62.3 (6.56; 54–65)</td>
<td>4 M/1 F</td>
<td>4.8 years</td>
</tr>
<tr>
<td>Essential tremor</td>
<td>6</td>
<td>68.8 (7.9; 58–80)</td>
<td>4 M/2 F</td>
<td>24.83 years</td>
</tr>
<tr>
<td>MS tremor</td>
<td>4</td>
<td>40.3 (5.7; 35–48)</td>
<td>1 M/3 F</td>
<td>5 years</td>
</tr>
<tr>
<td>Holmes tremor</td>
<td>1</td>
<td>84</td>
<td>1 M</td>
<td>6 years</td>
</tr>
<tr>
<td>Cerebellar tremor</td>
<td>1</td>
<td>41</td>
<td>1 M</td>
<td>20 years</td>
</tr>
<tr>
<td>Dystonic tremor</td>
<td>1</td>
<td>53</td>
<td>1 M</td>
<td>8 years</td>
</tr>
</tbody>
</table>

DT, dystonic tremor; ET, essential tremor; F, female; M, male; MS, multiple sclerosis; PD, Parkinson’s disease.
Figure 1  (A) An intraoperative axial MRI scan with bilateral stylettes in the caudal zona incerta. (B) A matching slice from the Schaltenbrand atlas with the red dot defining the target location in the caudal zona incerta. (C) An intraoperative sagittal MRI scan with the stylette passing dorsal and posterior to the subthalamic nucleus (STN) via a transfrontal trajectory. The tip of the stylette is in the caudal zona incerta. (D) A matching sagittal slice from the Schaltenbrand atlas. RN, red nucleus.

Figure 2  Anatomical location of active contacts. (A) Shows the spatial location of the active contacts as transposed onto the Schaltenbrand atlas. The subthalamic nucleus (STN) and zona incerta from axial slice H.v –1.5 (drawn in red) are superimposed onto axial slice H.v –3.5 (shown in black) and the STN on H.v –2.5 is drawn out in between the two (dotted green). Active contacts (shown as crosses) positioned at/or within 1 mm dorsal to a defined axial plane are shown in the same colour. (B) Shows the active contacts in the STN in the sagittal plane between slice S.l 12.0 (black colour) and the STN from slice S.I 13 (grey colour). (C) Shows the mean location of our active contact in the caudal ZI in comparison with that of other groups that have targeted the subthalamic region for tremor.
Statistical analysis
The primary efficacy was analysed using the paired Wilcoxon signed-rank and sign test. The test of significance was applied to the subscores of the motor UPDRS and the tremor rating score. The test of significance was not applied to the four patients with MS tremor, single patients with HT, DT or CT.

RESULTS
Parkinsonian tremor
In the 5 patients with tremor-dominant PD, the resting tremor score improved by 94.8% (preoperative mean score of 11.6 ± 4.72 to 0.6 ± 0.55 post-surgery, p = 0.006); and postural tremor by 88.2% (preoperative mean score of 3.4 ± 1.67 to 0.4 ± 0.54 post-surgery, p = 0.028) (fig 3). Other cardinal signs of PD, such as bradykinesia and rigidity, also improved by 62.1% (preoperative mean score of 14.8 ± 7.91 to 5.6 ± 4.21 post-surgery, p = 0.008) and 77.4% (preoperative mean score of 10.6 ± 5.36 to 2.4 ± 1.4 post-surgery, p = 0.014), respectively.

ET, CT and MS tremor
Clinical improvement is detailed in table 2. Following surgery, there was complete suppression of a grade 4 head and neck tremor in two ET patients, whereas one patient had a residual grade 1 tremor.

Dystonic tremor
The BFM Dystonia movement score improved by 65% from a preoperative score of 63 to 22 at 12 months. The Fahn–Marsden disability score improved by 61.5% (preoperative score 13 and follow-up score of 5). There was a 70.5% improvement in the FTM Tremor Rating scale (baseline score 68 to 20 and at the 12-month follow-up).

Complications
There was one surgery-related complication. The single patient with HT developed dysphagia for a period of about 3 months post-surgery. This was secondary to an error in frame relocation, which resulted in both guide tube stylettes being implanted into the Vim nucleus. Both the stylettes were subsequently relocated to the cZI. Two patients developed transient stimulation-related disequilibrium, with one lasting for 8 weeks and the other for 8–10 weeks post-surgery. In both cases, oedema was seen in the target region, extending into the prelemniscal radiation on the intraoperative MRI scan. One patient with MS complained of prolonged lethargy and reduced mobility following the procedure. Examination of this patient by the neurologist responsible for his care found no new neurological deficit and excluded a relapse of MS. The patient’s mobility returned to baseline within 3 months.

DISCUSSION
This study shows that stimulation of the cZI is effective in suppressing both resting and kinetic tremor, whether affecting the proximal, distal or the axial musculature.

Localisation of active contacts
The location of the active contacts in our patients transposed onto the Schaltenbrand Warren atlas shows that they lie within the cZI postero-medial to the postero-dorsal STN (fig 2). Velasco et al have implanted unilateral DBS electrodes into the posterior subthalamic region in the prelemniscal radiation, which is more medial and deeper than our cZI target.18 The prelemniscal radiation lies between the medial border of the STN and the lateral border of the red nucleus, with its posterior extent limited by the cZI and the postero-medially placed medial lemniscus.8 Kitagawa et al define an effective target for treating ET and tremulous PD that lies in the region of ZI and the prelemniscal radiation14–16—that is, between our target and the target defined by Velasco et al18 (see fig 2). Nandi et al have
Table 2  Improvement in essential tremor, multiple sclerosis tremor, Holmes tremor and cerebellar tremor

<table>
<thead>
<tr>
<th>Tremor type</th>
<th>% Improvement total tremor rating scale</th>
<th>% Improvement in part A of the tremor scale</th>
<th>% Improvement in part B of the tremor scale</th>
<th>% Improvement in part C of the tremor scale</th>
</tr>
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<tbody>
<tr>
<td>ET</td>
<td>75.9% (59.5 ± 16.7 to 14.3 ± 5.1)</td>
<td>85.6% (17.3 ± 5.4 to 2.5 ± 1.6)</td>
<td>63.3% (25.0 ± 7.56 to 9.2 ± 3.7)</td>
<td>84.5% (17.2 ± 4.9 to 2.7 ± 1.9)</td>
</tr>
<tr>
<td>MS tremor</td>
<td>57.2% (59 ± 15.6 to 26.3 ± 11.4)</td>
<td>83.1% (16.3 ± 10.1 to 2.8 ± 1.3)</td>
<td>55.6% (24.8 ± 4.4 to 11.0 ± 5.8)</td>
<td>36.1% (18.0 ± 2.9 to 11.5 ± 4.7)</td>
</tr>
<tr>
<td>HT</td>
<td>70.2% (71 to 20)</td>
<td>79.2% (24 to 5)</td>
<td>68.2% (28 to 8)</td>
<td>66.6% (21 to 7)</td>
</tr>
<tr>
<td>CT</td>
<td>60.4% (58 to 21)</td>
<td>66.7% (9 to 3)</td>
<td>60.6% (33 to 14)</td>
<td>62.5% (16 to 4)</td>
</tr>
</tbody>
</table>

The values represent the percentage improvement between the baseline mean scores and the postoperative mean scores (scores are shown in parentheses). CT: cerebellar tremor; ET: essential tremor; HT: Holmes tremor; MS: multiple sclerosis tremor.

Stimulated the rostral ZI ventral to the Ventral oralis posterior (Vop) nucleus of the thalamus, to treat MS tremor.17

Patient outcomes
The conventional targets for the surgical treatment of PD tremor are the VL nucleus of the thalamus and the STN. Although the number of patients in our series with PD tremor is small, we have seen an 94.8% improvement in resting tremor and an 88.2% improvement in postural and action tremor. This is consistent with our previous results in a larger cohort of patients with PD in which we saw a 95% improvement in tremor scores contralateral to 27 electrodes implanted into the cZI.23 Stimulation of the VL nucleus and the STN typically achieve an improvement in tremor scores in the region of 80%.2

In our small series of MS tremor patients, the postural component improved by 87% and the intention component by 75%. Nandi and Aziz performed bilateral stimulation of the cZI and proffer an explanation of the findings in our study.24 25

In our single case of HT, there was no anatomical abnormality identified on the MRI scan but the patient expressed all three components of tremor—that is, resting, postural and intention—which improved with cZI DBS. This condition has been previously treated by stereotactic lesions26 27 or DBS of the Vim nucleus of the thalamus with variable outcome. Romanelli et al30 have performed unilateral stimulation of both the Vim nucleus and the STN in a single patient with HT with a 55% reduction in tremor. Foote and Okun28 implanted unilateral twin VL/VA thalamic DBS leads to suppress tremor in this condition, overriding the abnormality in both the pallidothalamic and cerebellothalamic circuit.

In the single patient with dystonic tremor, there was an improvement in both components of this syndrome—that is, dystonia by 65% on the dystonia movement scale and tremor by 70.5% on the tremor rating scale. Both dystonia and tremor components can be suppressed by stimulating separate subcortical nuclei, such as the Gpi for dystonia and the Vim nucleus for tremor.31 32

Stimulation parameters and tolerance
Although there was no statistical difference between the stimulation parameters in patients with parkinsonian tremor in contrast to non-parkinsonian tremor, the non-parkinsonian group required a higher pulse width to suppress the tremor. The mean stimulation parameters are comparable to those in other series of DBS of the STN for PD11 46 and stimulation of the other areas in the subthalamic region for non-parkinsonian tremor (ET, CT and MS tremor).33 35 36 Interestingly, in one patient with MS tremor, improvement was seen at 40 Hz frequency in contrast to higher frequencies of 130 Hz and above. In the second patient with MS tremor, there was moderate improvement in tremor at 40 Hz, but stimulation at 130 Hz was found to be optimal. Tolerance to Vim stimulation has been reported, especially to the action component of tremor, in up to 18% of cases by 3–6 months.36 37 Some patients therefore switch off the stimulator at night for a variable period to postpone the appearance of tolerance. In our series, tolerance was not seen despite the fact that constant stimulation was maintained.

Interpretation of our findings
In this study, we have demonstrated that high-frequency DBS of the cZI is effective in suppressing all forms of tremor. Although a number of hypotheses have been put forward to explain the mechanisms underlying the generation of tremor and the pathways involved, none of these incorporate the cZI. Here, we describe the anatomy and putative physiological role of the cZI and proffer an explanation of the findings in our clinical study.

Table 3  Stimulation parameters (mean (SD)) for all the patients

<table>
<thead>
<tr>
<th></th>
<th>Voltage (V)</th>
<th>Pulse width (PW)</th>
<th>Frequency (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinsonian tremor</td>
<td>2.74 (0.42)</td>
<td>93.3 (18.3)</td>
<td>145.1 (21.76)</td>
</tr>
<tr>
<td>Non-Parkinsonian tremor</td>
<td>2.48 (1.04)</td>
<td>120 (42.42)</td>
<td>147.14 (21.7)</td>
</tr>
<tr>
<td>Multiple sclerosis tremor</td>
<td>1.5</td>
<td>210</td>
<td>40</td>
</tr>
</tbody>
</table>

One patient with multiple sclerosis tremor responded to 40 Hz stimulation and has been shown separately.
ZI nucleus and its function
The ZI, an embryological derivative of the ventral thalamus, is a distinct heterogeneous nucleus that lies at the base of the dorsal thalamus and is an extension of the reticular thalamic nucleus (MRF). The ZI receives afferents from the globus pallidus internus (GPi) and the substantia nigra reticulate (SNr); the ascending reticular activating system; the interpositus nucleus of the cerebellum; and also motor, associative and limbic areas of the cerebral cortex, which are known to facilitate and modulate motor behaviour.

ZI neurons are predominantly γ-aminobutyric acid (GABA)ergic and, as with other GABAergic systems such as the reticular thalamic nucleus, the basal ganglia neurons (striatum, GPi and SNr) and the universally distributed local circuit neurons, they probably play a role in synchronising firing between neuronal assemblies. Typically, GABAergic neurons synapse on the necks of dendrites of large assemblies of neurons, which are usually driven by glutamatergic afferents. The inhibitory GABAergic neurons control both the frequency and magnitude of the signal transmitted by the group. Synchronisation of neuronal firing between assemblies of neurons is the means by which the brain facilitates and directs...
information processing in its otherwise noisy and complex network of 100 billion interconnected neurons, each with their own intrinsic rhythm. If neurons participating in information transfer oscillate at the same or a harmonic frequency (typically in the ranges 20, 40 and 80 Hz), they become hypopolarised and receptive at the same time, whereas non-co-operating neurons firing irregularly and out of phase will not be receptive.\(^5\)–\(^6\)

The ZI provides a unique GABAergic link between the basal ganglia output nuclei and the cerebello-thalamo cortical loop (fig 5). This places it in a key position to transmit synchronised oscillations into this loop; these oscillations are generated in the basal ganglia during the preparation and execution of volitional movement plans. The loop carries detailed spatiotemporal movement instructions to the motor cortex and is powerfully influenced by visual guidance. ZI efferents to the VL neurons in the cerebello-thalamocortical loop synapse on the necks of their dendrites. Consequently, the volitionally led basal ganglia oscillations transmitted via ZI will dominate and facilitate coherent and integrated information processing during the planning and execution of the movement. Similarly, the efferents of ZI to the brainstem motor effectors, the MRF and MEA, which are involved in controlling axial and proximal limb muscles, will presumably help to synchronise their firing frequency with neurons in those areas of the motor cortex, controlling distal limb movements.

**ZI and tremor**

Current hypotheses regarding the mechanisms of tremor generation point to abnormal synchronisation of neuronal firing in the basal ganglia-thalamocortical loop (in PD and DT) or the cerebello-thalamocortical loop (in ET, CT and MS tremor) or involving both loops (HT).

We believe that the cZI is an effective target for the surgical control of all forms of tremor because of its unique GABAergic connections with both the basal ganglia and cerebello-thalamocortical loops, in addition to the brain stem motor effectors through which tremor oscillation may be transmitted.

**PD tremor**

Evidence of synchronised tremor oscillations arising in the basal ganglia-thalamocortical loop in PD come from peri-operative electrophysiological recordings in which synchronised \(\sim 10\) and \(\sim 20\) Hz oscillations and \(4–6\) Hz tremor frequency oscillations have been recorded in the GPI and the STN, which are coherent with neuronal oscillations in the motor cortex.\(^6\)–\(^8\) Transmission of abnormal oscillations from the premotor cortex to the cerebellum and thence to thalamus and motor cortex seems possible, and MEG study data has demonstrated strong coherence between the cerebellum, diencephalon and motor cortex at tremor frequency (4–6 Hz), double tremor frequency (8–12 Hz) and at \(\sim 20\) Hz, suggesting that the propagation and maintenance of PD tremor is due to a central oscillator with oscillations entraining both the basal ganglia and cerebello-thalamocortical-loops.\(^6\)–\(^9\) Nevertheless, although lesioning or DBS of GPI and STN can improve tremor,\(^1\)–\(^4\) lesioning of the VA nucleus of the thalamus (Hasslers Voi and Lpo), which transmits the basal ganglia output to the premotor cortex,\(^7\) does not.\(^7\) This implies that there must be an alternative pathway for conduction of tremor oscillations into the cerebello-thalamocortical loop. We propose that the key pathway involved is via the cZI, which receives direct afferents from the GPI and SNr and sends efferents to the VL thalamus, the cerebellar interpositus nucleus and the IO.

The VL thalamus has long been established as an effective surgical target for controlling distal limb tremor,\(^4\) including PD tremor. However, because it receives predominantly cerebellar afferents and no direct basal ganglia afferents,\(^7\) the reason why it is effective in controlling PD tremor has remained a

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**Figure 5** Shows how the ZI provides a unique GABAergic link between the basal ganglia output nuclei, the cerebello-thalamocortical loop and the brainstem nuclei, and synchronises the oscillatory firing of these subcortical nuclei. The GABAergic ZI output is shown as stippled blue to signify its synchronising function. MRF, medial reticular formation; PFC, prefrontal cortex; VA, ventralis anterior nucleus of thalamus; VL, ventro-lateral nucleus of thalamus; ZI, zona incerta.
paradox. The conduction of abnormal oscillations generated in the basal ganglia in PD to the VL nucleus via cZI would therefore explain this paradox and also explain why we observed such a potent anti-tremor effect from stimulating cZI in our patients with PD.

Essential tremor
In ET, synchronised oscillations at 4–12 Hz are thought to arise in the IO (IO) nucleus and are transmitted to the cerebellar cortex and then distributed along the ascending cerebellothalamic pathway and the descending brainstem medial reticular formation to manifest as tremor. The transmission of oscillations along both pathways is supported by clinical, imaging\(^{14,37}\) and electrophysiology data.\(^{79}\) These oscillations probably result from excessive electrotonic coupling between dendrites of the IO neurons via GABA-mediated gap junctions.\(^{50,52}\)

Physiologically, the IO is thought to act as a “movement error detector”\(^{50–52}\) (Fig 4) in that it receives information regarding the movement plan via the cerebellum and parvocellular red nucleus (pRN),\(^{53}\) as well as the movement instruction from the motor cortex and can compare this with the proprioceptive feedback that it receives during movement.\(^{53–56}\) On detecting a movement error, it modulates a correction via its efferent climbing fibres that synapse directly on purkinje cells in the cerebellar cortex and on the deep cerebellar nuclei (dentate and interpositus).\(^{52,55}\)

The interpositus effects the ongoing movement correction assisted by visual and proprioceptive feedback.\(^{25,26,94–96}\) Ascending efferents from interpositus pass to the VL nucleus and descending fibres to the MRF carrying information related to both distal limb movement correction and axial and proximal limb movement correction, respectively. En passant interpositus sends efferents to cZI.\(^{17}\)

It is presumed that the consequence of the abnormal electronic coupling in the IO in ET will be excessive movement correction in response to limb displacement detection and then overcorrection of the new further displaced limb that is creating oscillations. This will be seen as postural tremor while trying to hold a limb in space; action tremor during limb movement and intention tremor as the limb approaches a target and proprioceptive feedback is maximal.

Other kinetic tremors
Tremor associated with MS and ET is kinetic but tends to have a greater postural element involving axial and proximal limb movements. The exact mechanisms of its generation are unclear but, typically, there is widespread demyelination involving the olivocerebellar circuit.\(^{91}\) In CT, a structural or functional movement plan via the cerebellum and parvocellular red nucleus,\(^{98}\) but, typically, there is widespread demyelination involving the olivocerebellar circuit.\(^{98}\) In CT, a structural or functional movement plan via the cerebellum and parvocellular red nucleus,\(^{98}\) but, typically, there is widespread demyelination involving the olivocerebellar circuit.\(^{98}\) In ET, synchronised oscillations at 4–12 Hz are thought to arise in the IO (IO) nucleus and are transmitted to the cerebellar cortex and then distributed along the ascending cerebellothalamic pathway and the descending brainstem medial reticular formation to manifest as tremor. The transmission of oscillations along both pathways is supported by clinical, imaging\(^{14,37}\) and electrophysiology data.\(^{79}\) These oscillations probably result from excessive electrotonic coupling between dendrites of the IO neurons via GABA-mediated gap junctions.\(^{50,52}\)

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REFERENCES


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- At least one of the applicants must be a member of COPE.
- Calls for applications will be made twice a year with closing dates of 1 December and 1 June. An electronic version of the application form must be sent to the Administrator no later than 12 pm (noon GMT) on the closing date for consideration by COPE Council.
- The application must contain a lay summary of the project, a definition of the question to be posed, sufficient methodological detail to allow assessment of the viability of the project, a clear timeline and a definition of the likely deliverables. A full justification for the sum requested must accompany the application.
- A report on the progress of the research should be presented within one year of the award and at the end of the project. The grant must be used within two years from the date of award, and balance sheets must be forwarded annually. These should be sent to the Administrator. Any remaining funds after two years must be returned.

Applications are reviewed by a COPE sub-committee. Applicants will be advised of a decision as soon as practicable after the deadline date.

An application form can be obtained by contacting Linda Gough, COPE administrator, at LGough@bmj.com or 020 7383 6602. For more information on COPE, see http://www.publicationethics.org.uk/

The closing date for receipt of applications is 1 December 2007 or 1 June 2008.
Bilateral stimulation of the caudal zona incerta nucleus for tremor control

P Plaha, S Khan and S S Gill

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