

Caudal Zona Incerta as an Alternative Target for the Treatment of Tremor with Deep Brain Stimulation

Puneet Plaha, Sadaquate Khan, Shazia Javed and Steven S Gill

Institute of Neurosciences, Frenchay Hospital, Bristol

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Abstract

Stereotactic deep brain stimulation (DBS) of the thalamus and the subthalamic region has been shown to be effective in treating medically refractory tremor over the past few decades. In this article we discuss the merits and drawbacks of stimulating each of the targets in this region, in particular the caudal zona incerta nucleus (cZI). We discuss our recent work in this field and the rationale behind choosing this nucleus to implant bilateral DBS leads for all forms of tremor.

Keywords

Caudal zona incerta, tremor, deep brain stimulation

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Correspondence: Steven S Gill, Consultant Neurosurgeon, Frenchay Hospital, Bristol, BS16 1LE, UK. E: steven.gill@north-bristol.swest.nhs.uk

Tremor is defined as a rhythmic, involuntary oscillation that can affect the upper and lower extremities, head, jaw, face, tongue, voice and trunk.¹ Irrespective of the aetiology, tremor has a detrimental effect on the patient's quality of life. Surgery is offered when tremor is functionally disabling and medically refractory, or when patients develop complications from drug therapy that limit effective tremor control. A number of subcortical nuclei and white matter tracts have been defined that, when lesioned or stimulated, control different aspects of tremor. This article discusses the merits and drawbacks of stimulating each of these surgical targets for different forms of tremor and why deep brain stimulation (DBS) of the caudal or motor part of the zona incerta nucleus (cZI) is effective in alleviating all forms of tremor.

Ventrolateral Nucleus of the Thalamus

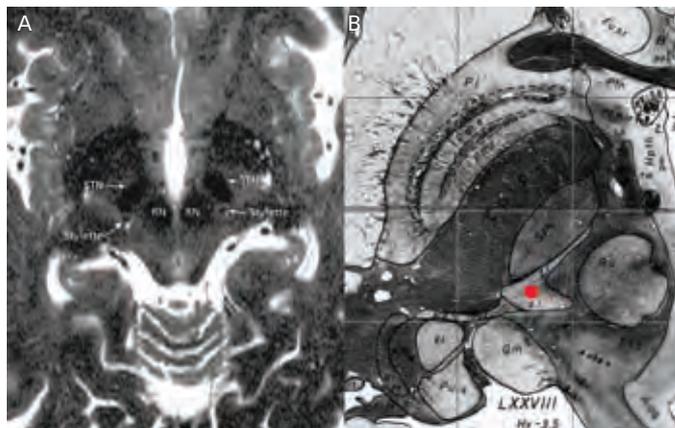
Since the 1950s, stereotactic surgery for tremor has targeted the ventrolateral (VL) nucleus of the thalamus (Hasslers ventralis intermedius) and it has been the target of choice to effectively suppress distal limb tremor having a resting or postural component, including tremor of Parkinsons disease (PD) and essential tremor (ET). Long-term studies (up to seven years) have demonstrated a 50–90% improvement in symptoms for this condition.^{2–6} However, proximal tremor and the action component of distal tremor respond poorly to DBS,⁷ with only one-third of the patients showing any significant improvement.^{8,9} Similarly, inconsistent or transient results are seen following DBS for proximal action tremor, as in multiple sclerosis (MS), with an initial 40–50% improvement in tremor but with little improvement in patient activities of daily living.^{10,11} Nguyen et al. have previously suggested that stimulating the dorsal part of the VL nucleus could suppress proximal action tremor, as single unit recordings¹² have revealed somatotopic organisation in the VL thalamus, with the head, neck and proximal part of the limb represented in the dorsal part of the nucleus and the hands in the ventral part.¹³ Improvement in head and neck and voice tremor is variable, with 15–51% improvement following unilateral DBS and

39–100% with bilateral procedures.^{3–5,14} 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.^{8,9,15–17} These side effects are generally reversible by adjusting the stimulation parameters, although this may be at the expense of satisfactory tremor control. Therefore, some centres only implant unilateral DBS leads, contralateral to the tremor dominant side. Another side effect compromising effective tremor control is that patients develop tolerance (tissue habituation) to continuous stimulation, even when the amplitude is increased.^{8,9,18} Patients are advised to turn their stimulators off at night, take stimulation holidays for weeks⁸ or use the DBS only 'on demand'¹⁹ to prevent tissue habituation. Tissue habituation also probably contributes to decline in tremor control in the long term. There are a few case reports suggesting that unilateral DBS of the VL nucleus can improve distal primary writing tremor,^{20,21} post-traumatic tremor^{22–25} and orthostatic tremor.²⁶

Subthalamic Region

Over the past few decades, stimulation of this region has been shown to be effective in alleviating both proximal and distal limb tremor in the resting, postural and kinetic state. Anatomically, this is a small volume containing the subthalamic nucleus, red nucleus and zona incerta and white fibre tracts. The subthalamic nucleus (STN) is a small biconvex nucleus surrounded on its anterior and lateral surface by myelinated fibres of the internal capsule. The pallidofugal fibres crossing the internal capsule pass over the dorsal and medial surfaces of the STN, separating it from the dorsomedially placed rostral zona incerta (rZI) and more medially the prelemniscal radiation and the red nucleus. Lying posterior to the STN is the cZI, which extends behind the prelemniscal radiation. Ventral to the ZI is the substantia nigra.^{27–29} 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 posteromedially placed medial lemniscus²⁹ (see *Figure 1*).

Figure 1: Anatomical Location of the Caudal Zona Incerta Target



A: Intraoperative axial magnetic resonance imaging scan with bilateral stylettes in the caudal zona incerta; B: Matching slice from the Schaltenbrand atlas, with the red dot defining the target location in the caudal zona incerta.

Large lesions involving the ZI and the surrounding white matter tracts, including the prelemniscal radiation, were shown to be effective in suppressing distal tremor with a resting, postural or kinetic component in patients with PD³⁰ and ET.³¹ In 1969, Bertrand and colleagues³² defined an area where the mere impact of the tip of a small probe caused abrupt and total cessation of tremor. This area was in the region of the 'prelemniscal radiation'. Bertrand and colleagues attributed their findings to lesioning the ascending fibres from the upper mesencephalic reticular substance, the pallidothalamic and pallidotegmental fibres. We now know that this area also carries the dentate- and interpositus-thalamic fibres on the way to the Vim. This white matter prelemniscal radiation has been stimulated unilaterally to alleviate resting tremor in PD^{33,34} and distal postural and kinetic tremor in ET (performed bilaterally).³⁵ Unilateral stimulation encompassing both the rZI and prelemniscal radiation has been shown to be very effective in suppressing distal PD tremor,³⁶ writing tremor³⁷ and proximal limb tremor as in ET,³⁸⁻⁴⁰ and cerebellar (CT),^{37,41} dystonic (DT)³⁷ and multiple sclerosis (MS) tremor.^{40,42} More recently, some centres have targeted the STN to improve non-parkinsonian dystonic tremor⁴³ and ET,^{43,44} although the active stimulation contact has been in the subthalamic region encompassing the rZI and the prelemniscal radiation. Most groups, as discussed above, have performed unilateral stimulation of the posterior subthalamic region encompassing the prelemniscal radiation and the rZI.^{33,36,37,39,45,46} The DBS lead has been implanted contralateral to the worst affected side. This region has a high concentration of ascending dentato-cerebello-rubro-thalamic fibres to the Vim nucleus, and when bilateral stimulation has been attempted, patients have developed disequilibrium and dysarthria as seen following bilateral Vim nucleus stimulation.⁴⁰ We noted a 40% incidence of the above complication following implantation of a bilateral DBS lead medial to the STN in patients with PD.⁴⁷

Caudal Zona Incerta Nucleus

Over the past few years we have been performing magnetic resonance imaging (MRI)-guided bilateral stimulation of the cZI nucleus using the implantable guide tube technique for both parkinsonian and non-parkinsonian tremor.⁴⁸ In our recent publication on 18 patients (five PD tremor and 13 non-PD tremor) with tremor affecting both the proximal and distal body parts (Holmes, cerebellar, ET, MS and dystonic tremor), we defined the optimal target posteromedial to the posterodorsal STN. The co-ordinates with reference to the anterior-posterior commissure were $x=14.2\pm 1.56\text{mm}$, $y=-5.7\pm 1.32\text{mm}$

and $z=-2.1\pm 1\text{mm}$.⁴⁹ This target is posterolateral to that defined by other groups who have stimulated the subthalamic region^{33,35,36,39,40,45} (see also Figure 2C in Plaha et al., 2008⁴⁹).

In five patients with tremor-dominant PD, resting tremor improved by a significant 94.8% and postural tremor by 88.2%. In six patients with distal essential tremor, the total tremor score improved by 75.9% (part A of the tremor rating scale by 85.6%, part B by 63.3% and part C by 84.5%). Four patients with proximal MS tremor showed a 57.2% improvement in the total tremor rating score (part A 83.1%, part B 55.6% and part C 36.1%). In the single patient with Holmes tremor, there was a 70.2% improvement in the total tremor score. Proximal cerebellar tremor (CT) in one patient improved by 60.4% (part A 66.7%, part B 60.6% and part C 62.5%). In the single patient with dystonic tremor there was improvement in both the dystonia and the tremor (Burke Fahn Marsden dystonia movement score 65.1% improvement; disability score 61.5% and a 70.5% improvement in the tremor score).

Bilateral cZI stimulation was very effective in completely suppressing head and neck tremor in three ET patients and one MS tremor patient along with improvement in truncal ataxia and cerebellar speech. Since the recently published data, six more patients have undergone bilateral cZI stimulation for MS and ET. Although as yet unpublished, the improvement seen in all components of tremor has been similar to the published data,⁴⁹ further cementing this nucleus as an effective target for all forms of tremor. We have seen that high-frequency stimulation (mean 140Hz) is most effective in suppressing tremor at low voltages, although a couple of patients with MS tremor have benefited from low-frequency (40Hz) stimulation at a pulse width around 210µseconds. In our published series and recently operated patients there were no peri-operative complications, especially intra-operative haemorrhage. One patient developed transient dysphagia secondary to an error in frame relocation with implantation of both DBS leads into the VL nucleus of thalamus. Transient peri-DBS-lead-related oedema in the prelemniscal radiation caused dysequilibrium in two patients. The DBS lead and generator were removed in one patient due to infection. Most importantly, all patients maintained constant bilateral stimulation to suppress their tremor and no patient developed tolerance to stimulation as is commonly seen with VL nucleus stimulation.

Tremor and Zona Incerta

The cZI nucleus as discussed above is a very effective target to suppress all forms of tremor affecting the proximal and distal body part. The mechanisms underlying the generation of tremor remain poorly understood and, despite a number of hypotheses, there remain significant gaps in our understanding of it. In none of the proposed hypotheses does the cZI nucleus play a role in either the generation or conduction of tremor oscillations and yet in recent publications we have demonstrated that high-frequency stimulation of this region has a potent antitremor effect.^{47,50} We present our current understanding of the anatomy and physiology of the cZI and then discuss its proposed role in the pathophysiology of PD and non-PD tremor. We also discuss how and why high-frequency stimulation of the cZI suppresses tremor.

Zona Incerta Nucleus and Its Function

The ZI, an embryological derivative of the ventral thalamus, is a distinct heterogenous nucleus that lies at the base of the dorsal thalamus.⁵¹ It is divided into four sectors (rostral, dorsal, ventral and caudal). The rostral component extends over the dorsal and medial surface of the STN while its caudal or motor component lies posteromedial to the STN.^{52,53} Each of

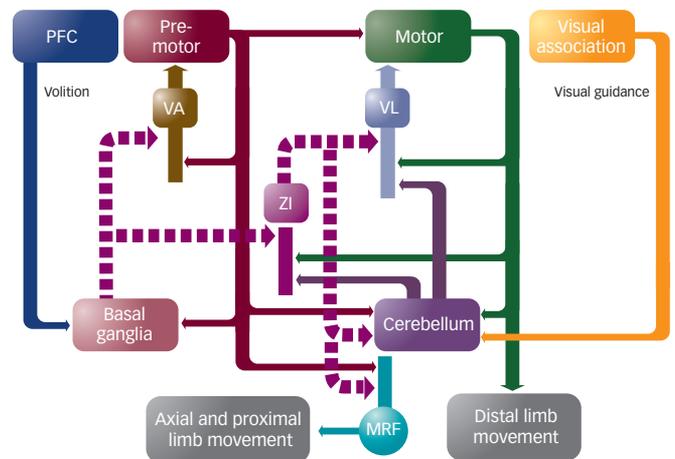
these components is divided into a dorsal and a ventral part. The ZI receives afferents from the basal ganglia output nuclei (globus pallidus internus and substantia nigra reticulata),⁵⁴⁻⁵⁷ the ascending reticular activating system⁵⁵⁻⁵⁸ and also motor, associative and limbic areas of the cortex,^{56,59} which are known to facilitate and modulate motor behaviour. The ZI sends efferents to the centromedian and parafascicular nuclei (CM/Pf) of the thalamus,^{60,61} the ventral anterior (VA) and VL nuclei of the thalamus,⁶² the midbrain extra-pyramidal area (MEA),⁵⁴ basal ganglia output nuclei⁵⁴ and the cortex.⁶³⁻⁶⁵ The interpositus nucleus of the cerebellum⁶⁶ and the inferior olive (IO) also receive ZI efferents.⁵³

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 the 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 its own intrinsic rhythm. If neurons participating in information transfer oscillate at the same or a harmonic frequency (typically in the ranges 20, 40 and 80Hz), they become hypopolarised and receptive at the same time, whereas non-co-operating neurons firing irregularly and out of phase will not be receptive.⁶⁷⁻⁷¹ The ZI provides a unique GABAergic link between the basal ganglia output nuclei and the cerebello-thalamocortical loop (see *Figure 2*). 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 medial reticular formation (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.

Caudal Zona Incerta and Kinetic Tremor

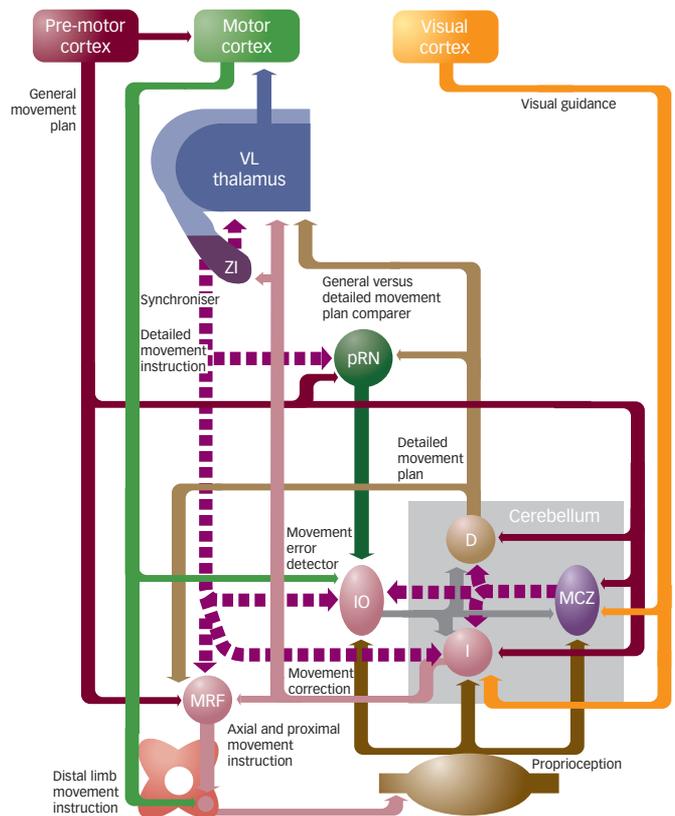
To understand this better we will look at the interaction between the cerebellum–brainstem nuclei–cZI and the cortex during limb movement and the role these dynamic loops play during limb movement (see *Figure 3*). The lateral cerebellum, including the hemispheric cortex and dentate nucleus, are responsible for generating a detailed plan of limb movement upon receiving a more general instruction from the premotor cortex.^{72,73} The cerebellar plan encompassing the spatiotemporal co-ordination and timing of limb movement⁷⁴⁻⁷⁷ is conveyed to the motor cortex via the VL nucleus of the thalamus. *En passant*, a copy of this plan is also conveyed to the IO nucleus and the parvocellular red nucleus (pRN).⁷⁸⁻⁸⁰ Once a movement instruction is sent to the spinal cord by the motor cortex, the intermediate region of the cerebellum (paravermal cortex and the anterior and posterior interpositus nuclei) are involved in implementing corrections to the

Figure 2: Synchronising Function of the Caudal Zona Incerta Nucleus



Zona incerta (ZI) provides a unique γ -aminobutyric acid (GABA)ergic 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 purple to signify its synchronising function. PFC = pre-frontal cortex; VA = ventral anterior nucleus of thalamus; VL = ventro-lateral nucleus of thalamus; MRF = medial reticular formation.

Figure 3: The Interaction Between Various Cortical, Subcortical and Brainstem Nuclei Including the Zona Incerta in the Control of Limb Movement



VL = ventro-lateral nucleus of thalamus; ZI = zona incerta; pRN = parvocellular red nucleus; IO = inferior olive; D = dentate; I = interpositus; MCZ = microcomplex zone; MRF = medial reticular formation.

ongoing proximal and distal limb movements.^{72,73,76,77} The interpositus nucleus is assisted in this by receiving visual feed back regarding the target position by afferents from the visual cortex and also proprioceptive feedback from agonist and antagonist muscles of the moving limb via afferents from the dorsal column nuclei.⁸¹⁻⁸⁴ The pRN thus acts as a comparator of the brief movement plan received from

the pre-motor cortex and the detailed plan encompassing spatiotemporal co-ordination and timing of limb movement from the dentate nucleus;^{73,85,86} on detecting a 'mismatch' between the two, fires to the IO nucleus via its major efferents to this nucleus.

The IO functions as a 'movement error detector'⁸⁷⁻⁹⁰ primarily because it receives a copy of the detailed movement plan from the dentate nucleus, final movement instruction from motor cortex, proprioceptive feedback from the moving limb muscles⁹¹⁻⁹³ and, most importantly, feedback from the pRN.⁹⁰ It continuously evaluates this data and on detecting an 'error' fires to the cerebellum via its climbing fibres to correct the output of the Purkinje cells (multizonal microcomplex functional unit^{94,95}) and subsequently the deep cerebellar nuclei. The interpositus nucleus appears to modulate proximal and distal muscles during movement correction through two different pathways. Its descending afferents⁷³ to the medial reticular formation are known to modulate proximal muscle control.⁹⁶⁻⁹⁸ Distal muscle control is modulated via its ascending efferent fibres to the motor cortex, which relay in both the VL nucleus and the magnocellular red nucleus (mRN).⁷³ As the rubrospinal tract, which originates from the mRN, is rudimentary in humans, distal muscle control is primarily via the motor cortex.⁹⁹

The Model and Proximal Tremor (Multiple Sclerosis and Cerebellar Tremor)

Tremor associated with MS and cerebellar tremor is kinetic but tends to have a greater postural element involving axial and proximal limb movements with a frequency under 5Hz. The exact mechanisms of its generation are unclear, but typically there is widespread demyelination involving the olivocerebellar circuit.¹⁰⁰ In CT a structural or functional abnormality in the interpositus nucleus is thought to cause the <5Hz intention tremor that predominantly affects proximal limb movements.¹⁰¹⁻¹⁰⁴ The model predicts that in kinetic tremors abnormal oscillations are carried in efferents from the interpositus to the VL nucleus and/or to the MRF to be expressed as distal and/or axial and proximal limb tremor, respectively. Interpositus will also transmit these oscillations to cZI, which sends GABAergic efferents to wide receptive fields in VL, MRF, IO, pRN and back to interpositus, which will help to sharpen and amplify the oscillations.

The Model and Essential Tremor

In ET, synchronised oscillations at 4–12Hz are thought to arise in the 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, imaging¹⁰⁵⁻¹⁰⁹ and electrophysiology data.¹¹⁰ These oscillations probably result from excessive electronic coupling between dendrites of the IO neurons via GABA-mediated gap junctions.¹¹¹⁻¹¹³ 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 over-correction of the now further displaced limb, etc., 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.

Summary

The model predicts that DBS of the cZI is likely to suppress distal tremor by overriding oscillations in the VL nucleus, interpositus and IO nucleus,

and proximal tremor by overriding oscillations in the interpositus, IO and MRF. By contrast, VL nucleus stimulation only affects the ascending cerebellothalamic fibres, resulting in an improvement in only distal resting, postural and sometimes action tremor. In addition, bilateral stimulation is associated with dysarthria and disequilibrium. The latter is not seen with bilateral cZI DBS, as this would only override tremor oscillations without interrupting patterns of information related to fine movements of vocal cords and proprioceptive sensation.

Caudal Zona Incerta and Parkinson's Disease Tremor

Various hypotheses have been proposed to explain the genesis of PD tremor, but it is generally accepted that tremor in PD arises from a central oscillator either in the basal ganglia–thalamocortical loop or in the cerebellothalamocortical loop.¹¹⁴ The location of the 'central oscillator' and the mechanism by which 4–6Hz tremor oscillations are generated in PD remain obscure, and there seems to be a paradox with these hypotheses.

Old Hypothesis/Models

Evidence of synchronised tremor oscillations arising in the basal ganglia–thalamocortical loop in PD comes from peri-operative electrophysiological recordings where synchronised ~10 and ~20Hz oscillations and 4–6Hz tremor frequency oscillations have been recorded in the GPi and the STN that are coherent with neuronal oscillations in the motor cortex.¹¹⁵⁻¹¹⁷ Transmission of abnormal oscillations from the pre-motor cortex to the cerebellum and thence to the thalamus and motor cortex seems possible, and MEG study data have demonstrated strong coherence between the cerebellum, diencephalon and motor cortex at tremor frequency (4–6Hz), double tremor frequency (8–12Hz) and at ~20Hz, suggesting that the propagation and maintenance of PD tremor is due to a central oscillator with oscillations entraining both the basal ganglia and cerebellothalamocortical loops.¹¹⁸ Nevertheless, although lesioning or DBS of GPi and STN can improve tremor,¹¹⁹⁻¹²³ lesioning of the VA nucleus of the thalamus (Hasslers, Voi and Lpo), which transmits the basal ganglia output to the premotor cortex,¹²⁴ does not,¹²⁵ and this implies that there must be an alternative pathway for conduction of tremor oscillations into the cerebellothalamocortical 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 a very effective surgical target for controlling distal limb tremor,⁹ including PD tremor, but because it receives predominantly cerebellar afferents and no direct basal ganglia afferents,^{126,127} the reason why it is effective in controlling PD tremor has remained a 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 antitremor effect from stimulating cZI in our PD patients.

New Model for Parkinson's Disease Tremor

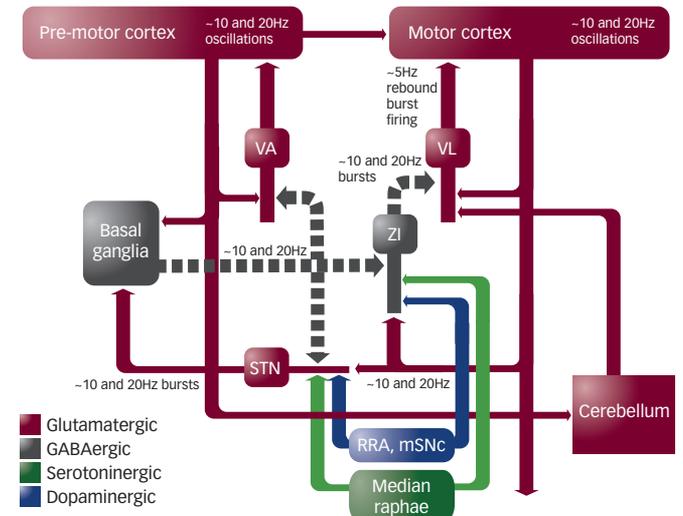
In PD, resting and postural tremor occurs when the cZI and the STN are deprived of dopamine and serotonin, causing them to become increasingly responsive to their motor cortical excitatory afferents, and they adopt a burst-like firing pattern. cZI divergent GABAergic efferents to the necks of the VL neuron dendrites will promote abnormal synchronisation of cortically driven oscillations, which, in the resting state or when maintaining posture, will be at the frequency ranges ~10–~20Hz). Alpha and frequency oscillations transmitted to a highly

responsive STN will be transmitted divergently to the globus pallidus externa (GPe), GPi and the substantia nigra reticulata (SNr), further promoting abnormally synchronised oscillations in the basal ganglia–thalamocortical pathways that will also be transmitted back to the cZI. Tremor oscillations will be generated in the VL thalamocortical neurons when they receive these potent GABAergic and frequency synchronised oscillations from their cZI afferents that will cause them to become progressively hyperpolarised and then rebound burst fire at 4–6Hz. During peripheral limb movements, discrete patterns of high frequency (~60–80Hz), oscillations will disrupt the synchronised low-frequency oscillations and tremor will be suppressed (see Figure 4).

Support for the New Model

In support of this hypothesis, Jellinger et al.,¹²⁸ in an autopsy study, have demonstrated that in tremor-predominant disease, there is loss of dopamine to the subthalamic region (including STN and ZI), in contrast to akinetic, non-tremulous PD where dopamine loss predominantly affects the striatum. This association is also supported in 1-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine (MPTP)-lesioned primate models of PD where the sensitivity of the midbrain dopaminergic nuclei to the toxin varies between species. In the rhesus monkey, MPTP causes destruction of the substantia nigra compacta (SNc), the median raphe nuclei and the locus coeruleus,^{129,130} resulting in parkinsonism but no resting tremor. Resting tremor is only expressed in the MPTP-lesioned vervet monkey where, in addition to the above neuronal loss, there is loss of retrorubral area (RRA) dopamine neurons, which contributes to the subthalamic dopamine projection.¹³¹ This projection arises from the medial part of the SNC, the RRA and the ventral tegmental area (VTA)^{132–140} and synapses pre- and post-synaptically on glutamatergic afferents from the motor cortex to both the STN^{127,141} and the ZI,⁵⁹ thereby modulating glutamate release and effect. Loss of this dopaminergic projection causes the STN to become increasingly responsive to its glutamatergic afferents and become hyperactive, adopting a burst-like firing pattern.^{116,142} The same pattern of burst firing is seen in the ZI^{143,144} and probably involves a similar mechanism. Although there is a strong association between loss of subthalamic dopamine and the presence of tremor, an isolated surgical lesion of the SNc or the midbrain dopaminergic area (RRA, VTA) does not induce a resting tremor,¹⁴⁵ but the subsequent systemic administration of p-chlorophenylalanine (serotonin synthesis inhibitor), which suppresses release of serotonin from the median raphe nuclei, does.¹⁴⁶ A surgical lesion in the ventromedial tegmentum involving the RRA and VTA dopaminergic areas and the serotonergic raphe nuclei induces a resting tremor,^{145,147,148} and this can be abolished by the administration of L-dopa or systemic 5-hydroxytryptophan (a serotonin precursor).¹⁴⁶ Other evidence in support of the role of serotonin in tremor generation comes from positron emission tomography (PET) imaging studies where loss of putamenal dopamine does not correlate with PD tremor¹⁴⁹ but the loss of midbrain serotonin does.¹⁵⁰ Additionally, selective serotonin uptake inhibitors taken for depression in PD can cause a worsening of tremor in the initial months of treatment¹⁵¹ as they result in decreased serotonin release from the terminals during the first weeks of treatment.¹⁵² Serotonin acts as a neuromodulator to improve the signal-to-noise ratio of neural transmission by hyperpolarising the post-synaptic neuron (via action on KAHP channels), thus acting as a noise filter.¹⁵³ If the ZI and STN are deprived of their serotonin afferents by degeneration of the median raphe nuclei, they will become increasingly responsive to their motor cortical drivers and this will augment their burst-like firing pattern resulting from dopamine depletion. In 1990, Paré et al.¹⁵⁴ hypothesised

Figure 4: Pathogenesis of Parkinson’s Disease Tremor



The γ -aminobutyric acid (GABA)ergic output with its synchronising function is shown as black stippled lines. ZI = zona incerta; STN = subthalamic nucleus; VA = ventral anterior nucleus of the thalamus; VL = ventrolateral nucleus of the thalamus; RRA = retrorubral area; mSnc = medial part of substantia nigra compacta.

that PD tremor is generated in VL thalamocortical neurons by converting 12–15Hz GPI GABAergic afferents from the basal ganglia to a lower 3–6Hz frequency by step-down hyperpolarisation and rebound burst firing of the thalamocortical neurons. While frequency step-down transformation has been demonstrated in thalamocortical neurons both *in vitro*¹⁵⁵ and *in vivo*,^{156,157} the major shortcoming of Pare’s hypothesis is that the VL nucleus does not receive basal ganglia afferents.¹⁵⁸ It is therefore most likely that the afferents carrying abnormally synchronised GABAergic α and β oscillations to VL are from the cZI.⁶² These are known to synapse at the necks of the VL neuron dendrites and will thus have a potent effect on their activity. Pyramidal neurons in the primary motor cortex upon receiving ~5Hz synchronised burst firing oscillations from VL will be driven to oscillate at the same frequency and manifest as PD tremor. These oscillations along with ~20Hz and ~10Hz synchronised oscillations will also be transmitted back to the basal ganglia^{115,118} and ZI,¹⁴⁴ and have been recorded in both locations.

Further Support for the New Model

To further substantiate the role of cZI in the proposed model, we recently conducted an experiment in which α - and β -frequency oscillations were imposed on the cZI using DBS leads in previously non-tremulous patients whose PD has been treated at this target. The generation of tremor and its frequency were quantified using accelerometry during stimulation of the cZI at 5, 10, 20, 40 and 80Hz, and the effects were compared with a control group of patients with akinetic parkinsonism who had DBS electrodes implanted in other subcortical targets within or associated with the known tremor circuits. These included the VL thalamic nucleus, the GPi and the STN, which are established targets for tremor control, and in addition we evaluated stimulation of the centromedian parafascicular nuclei (CM/Pf) and the pedunculopontine nucleus (PPN).¹⁵⁹ We observed, with maximal tolerated stimulation of the cZI, the STN and the VL nucleus within the frequency range of 5–40Hz, that a 4–6Hz resting hand tremor was induced in non-tremulous, akinetic parkinsonian patients. However, the STN group required high stimulation voltages compared with the cZI and the VL nucleus groups and did not manifest tremor with <5 volts stimulation. Tremor could not be induced with maximal stimulation of

the GPI, CM/Pf or the PPN. No tremor was seen following 80Hz stimulation of any of the target sites. This study supported our hypothesis that PD tremor is generated when VL thalamocortical neurons receive abnormally synchronised α and β oscillations in GABAergic afferents from the cZI, causing them to become hyperpolarised and rebound burst fire in the 4–6Hz range. However, further studies are required to further substantiate our hypothesis/model for PD tremor. We suggest that the next step would be to stimulate the motor cortex in a normal non-human primate at 10 and 20Hz so that these oscillations are then transmitted to ZI, and we predict that no tremor will be induced. The second part of the experiment would be to infuse a dopamine and serotonin antagonist into the ZI, and we

would anticipate the generation of a 4–6Hz tremor in the contralateral limb. PET studies to quantify loss of nigrosubthalamic dopamine in tremor-dominant PD patients compared with akinesia-dominant patients would further help in our understanding of the pathogenesis of PD tremor.

Conclusion

The cZI is the optimal site for DBS to alleviate both proximal and distal limb tremor in all three states (rest, postural and action). Bilateral stimulation can be safely performed and patients do not develop tolerance to stimulation. The ZI plays a key role in the genesis of PD and kinetic tremors. ■

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Saffron House
6-10 Kirby Street
London
EC1N 8TS

EDITORIAL
Tel: +44 (0) 20 7452 5232
Fax: +44 (0) 20 7452 5050

SALES
Tel: +44 (0) 20 7452 5361
Fax: +44 (0) 20 7452 5606

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