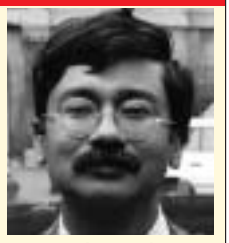
Recent advances in the surgical management of tremor in multiple sclerosis

Authors

Mr Dipankar Nandi studied medicine at the All India Institute of Medical Sciences (AIIMS), New Delhi and qualified in 1989. He then trained in the same Institute in general surgery (M.Ch. Part 1, board certification 1992) and then completed a residency programme in neurosurgery to obtain his M. Ch. Part 2, board certification in 1995. He is currently at Pembroke College, Oxford where he is working towards a D. Phil. in neurophysiology. His research involves investigation of brainstem control of akinesia and application of field potentials in functional neurosurgery.



Professor Tipu Z Aziz studied physiology at University College London graduating in 1978. During this time he developed his keen interest in the role of the basal ganglia in movement disorders. He studied medicine at King's College London (1978-1983) and obtained his surgical fellowship in 1987 following which he pursued a career in neurosurgery. He is currently a consultant neurosurgeon at the Radcliffe Infirmary, Oxford and Charing Cross Hospital London. He is an expert in functional neurosurgery and has a special interest in the surgical treatment of movement disorders.

Tremor is estimated to occur in about 50-75% of patients with multiple sclerosis (MS) (Alusi 2001) and is often severely disabling and difficult to treat. This is in part because the tremor is often one component in a more complex movement disorder that includes dysmetria and other ataxic features. Drug therapy for these types of tremor is often disappointing. Kurtzke originally made the observation that isoniazid helped the tremor of MS and occasionally this is still used, but no formal study has shown it to be effective. Nor is propanolol – so useful in essential tremor. Neurologists either declare the tremor of MS untreatable or trawl, with little expectation of success, through a list of drugs that includes clonazepam, carabamazepeine, primidone, valproate and ondansetron. Nor have physical measures, such as wrist weights, or physical restraint, ever proved popular. This has encouraged the exploration for neurosurgical options. In recent years, there has been considerable success in treating tremor in other movement disorders, particularly in Parkinson's disease (PD), by chronic high frequency deep brain stimulation (DBS) of ventrolateral thalamic nuclei - most commonly the ventralis intermedius nucleus (VIM) (Benabid 1991). Using sophisticated stereotactic functional neurosurgical techniques this approach has also been shown to benefit other tremulous conditions like benign essential tremor (BET) and post-traumatic tremor (PTT). However, when the same techniques have been applied to patients with MS tremor the results have been mixed. Those with purely distal limb tremor respond well whilst patients with the more common complex proximal and distal axial and limb tremor combined with dysmetric features do not show satisfactory improvement. Unlike in PD, there are a heterogeneous mixture of lesions which give rise to separate components of the disabling movement disorder and often respond differently to various interventions. The challenge is to effectively alleviate components of tremor, dysmetria and ataxia in the compound involuntary movements that are common in MS and to achieve reasonable functional improvement.

We, in the Oxford Movement Disorder Group at the Radcliffe Infirmary and the University Laboratory of Physiology (OMDG), have developed several refinements in the existing techniques and have re-kindled some therapeutic options tried and discarded in the past, to ensure functional benefit to a greater range of patients with MS tremor and with improved accuracy in predicting functional improvement.

1. Computer-controlled visually-guided arm tracking tasks (VGT) and EMG recording

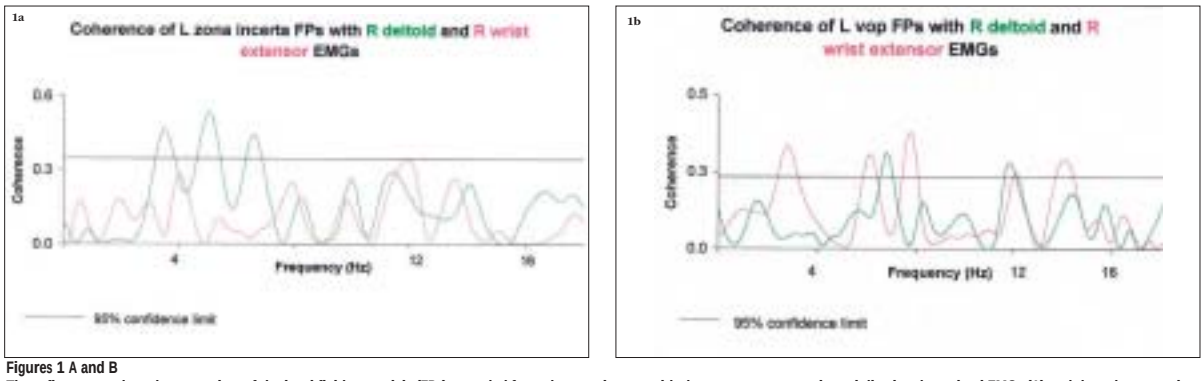
This test, which is conducted both before and after operation for tremor control, has helped us select patients who are most likely to benefit from either thalamotomy or thalamic DBS - nucleus ventro-oralis posterior (VOP) or VIM. It is easy to administer and provides detailed electrophysiological information about each patient's tremor patterns (Liu 2000).

2. Local field potential recording from deep brain nuclei (LFP)

This involves recording the synchronous electrical activity of a group of neurons lying within a few millimetres of the DBS electrode (Medtronic Inc., Minneapolis, Minnesota) used in functional neurosurgery. We have used this technique, which is still in its infancy with respect to its application in clinical neurosurgery, (in conjunction with simultaneous EMG recording) to be able to better localise the appropriate functional target for DBS (Nandi *et al* 2002). This has less risks for the patient than the more conventional electrophysiological tool of micro-electrode recording (MER) with no established loss of efficacy.

3. Zona incerta (ZI) DBS for complex proximal and distal intention tremor

We have focused on this small nucleus (Mundinger 1965), lying between the thalamus and the sub-thalamic nucleus, as a potential target for control of complex tremor, especially in MS.



Figures 1 A and B

These figures are the coherence plots of the local field potentials (FPs) recorded from the zona incerta with the concurrent contralateral distal and proximal EMGs (A) and the coherence plots of the FPs recorded from the thalamic VOP nucleus with the concurrent contralateral distal and proximal EMGs (B). Coherence plots show strength of correlation. They demonstrate that while the strength of correlation between the ZI and the proximal EMGs is significantly high in the tremor frequency range (3-6 Hz), that between the VOP FPs and the distal EMGs is significant in the same range. Thus it appears as if there is a differential oscillatory loop for proximal and distal tremor.

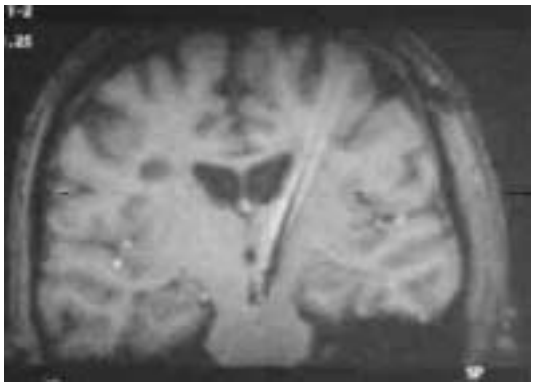


Figure 2
This figure shows the DBS lead straddling the left VOP and ZI. This placement allowed us to stimulate both structures simultaneously.

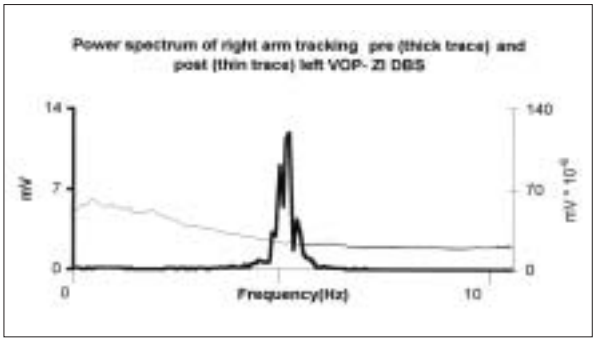


Figure 3
This figure shows the results of the VGT task performed with the right arm before and 6 months after stimulation of the VOP – ZI. There is marked reduction of the dominant 3-6 Hz tremor frequency peak, so much so that the scales needed to plot them in the same figure differ by 105.

Case report: MS with complex proximal and distal intention tremor treated successfully with ZI and VOP DBS using FP monitoring

This 29 year old woman presented with a history of MS diagnosed 5 years previously. She was referred to us with severely disabling involuntary movements affecting her right (dominant) arm. This left her unable to feed or dress herself. She had good motor power in the arm but could not use it to perform even the most basic tasks like using the TV remote control or to write. Extensive drug treatment had not helped. She was assessed clinically, radiologically and with neuropsychological testing according to the standard protocol in the OMDG. She also underwent the VGT and EMG studies. This revealed the complex combined proximal and distal nature of her tremor and based on our previous experience we offered her combined ZI and VOP DBS. She consented to this operation and using FP monitoring conducted intra-op and (following implanting of externalised DBS leads) post-op (figure 1), we successfully started DBS of both the VOP and the ZI (figure 2).

She responded immediately to the DBS and regained good functional control of her right arm. There were no untoward effects from the surgery and she was able to perform many of the routine activities of daily life like feeding herself, dressing, using the TV remote control etc. We have followed her progress for 15 months so far and the benefits are sustained. Her post-op VGT at 6 months shows marked suppression of the dominant tremor frequency peak (figure 3). There is still some residual dysmetria; however her functional status is definitely better. This is also confirmed by her neuropsychological assessment at follow-up.

We have so far successfully operated on 4 patients with complex MS limb tremor using these techniques. There seems to be a growing body of evidence in the literature which links the upper brainstem (and the region of the ZI) with proximal axial motor control. It seems that adequate treatment of complex intention tremor, especially proximal tremor, must influence the cerebellar-basal ganglia balance which is probably abnormally altered in these cases. Further investigation into the electrophysiological and pathological oscillatory circuits operating in these involuntary movement disorders is needed. We feel the way forward is for neurophysiologists to work in close co-operation with clinicians involved in movement disorders, to elicit the pathways of normal and dysfunctional motor control, which may then be influenced to achieve functional benefit for the patients suffering from these incapacitating and frustrating diseases.

Further reading

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