

Institution: University of Oxford
Unit of Assessment: UOA5
Title of case study: <p style="text-align: center;">A new form of deep brain stimulation alleviates severe ‘freezing’ and loss of balance in advanced Parkinson’s disease</p>
<p>1. Summary of the impact</p> <p>Research by Professors John Stein and Tipu Aziz at the University of Oxford has had a significant impact on advanced Parkinson's disease patients affected by freezing of gait and loss of balance. Since 2008 deep brain stimulation of the pedunculopontine nucleus has resulted in major improvements in both gait and posture in Parkinson's disease patients who have been treated with dopaminergic drugs for several years, but who had suffered the return of severely disabling movement problems. Around two hundred patients have been successfully treated worldwide through this pioneering surgery, with associated improvements in quality of life.</p>
<p>2. Underpinning research</p> <p>Millions of people worldwide suffer from Parkinson's disease (PD) and the numbers are set to rise dramatically over the next decades, owing to an increase in life-expectancy. PD has been treated with dopaminergic drugs since the discovery of levodopa in the 1960s, but this treatment, while effective, has serious long-term consequences, since many patients experience a return of severe and disabling movement problems after several years' treatment. Deep brain stimulation of the subthalamic nucleus was developed by Professor Tipu Aziz, now Consultant Neurosurgeon at the John Radcliffe Hospital in Oxford, as a means of alleviating severe dyskinesia (uncontrollable movement) in advanced PD patients; the method has proven extremely effective. However around 10% of PD patients suffer most from the opposite problem, akinesia (loss of ability to create muscular movements), one of the most intractable and distressing symptoms of advanced PD. Therefore, in conjunction with Professor Aziz (then at the Department of Neurology at the University of Oxford), Professor John Stein of the Department of Physiology, Anatomy and Genetics at the University of Oxford, who had the only laboratory studying motor control in monkeys, set out to investigate whether other forms of deep brain stimulation could help patients with gait freezing and related problems.</p> <p>The pedunculopontine nucleus (PPN), an area in the brainstem adjacent to the subthalamic nucleus, was already known to play an important part in motor control; for example, stimulation of the PPN region in rats and cats induces stepping movements. In experiments beginning in 1995 Stein and Aziz demonstrated that normal macaque monkeys developed akinesia following radio-frequency lesioning in the region of the PPN, and that selectively destroying only neurones in the PPN area also resulted in severe locomotor akinesia and postural instability in normal monkeys¹. Following on from this Stein, Aziz and Nandi (also of Oxford University's Department of Physiology and John Radcliffe Hospital) began experiments on normal monkeys to test responses to deep brain stimulation of the PPN. They found that high frequency stimulation induced severe akinesia, but that at lower frequencies some positive motor effects resulted². This study also established that electrodes implanted in the PPN had no adverse effects on the monkey, which was an important consideration for further primate studies and possible future clinical application.</p> <p>Using a monkey with Parkinson symptoms induced by the drug MPTP, Stein, Aziz and Nandi then showed that microinjections of bicuculline into the PPN reversed akinesia and also improved balance because it combatted the inhibition of the PPN that occurs in PD³. A further study into the effects of low-frequency PPN stimulation in a monkey with induced Parkinson symptoms showed that this led to significant increases in activity, thus providing encouraging evidence that this kind of treatment could be effective in patients with PD⁴. An extension of this study demonstrated that,</p>

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when PPN stimulation and levodopa treatment were combined, the activity of the monkey was significantly greater than either treatment given alone. This suggested that PPN stimulation worked via a non-dopaminergic pathway⁵. Work was then done to establish the connections between the PPN, subthalamic nucleus and other areas of the brain stem in humans. This study enabled Stein and Aziz to begin to infer the optimal locations in the PPN for deep brain stimulation, and also added to the understanding of the role of these nuclei in PD⁶.

This work was swiftly taken up clinically by other researchers and applied to human subjects with the result that PPN stimulation as a treatment for severe akinesia in PD (either in isolation, or in combination with other forms of DBS or drug therapy) is now becoming more widely available. The rate of publications on deep brain stimulation of the PPN has been accelerating since Stein and Aziz published their findings; over 150 related papers have appeared since the start of 2008, indicating the level of active research taking place into the PPN.

3. References to the research

1. Munro-Davies LE, Winter J, Aziz TZ, Stein JF. (1999) The role of the pedunculo pontine region in basal-ganglia mechanisms of akinesia. *Experimental Brain Research* 129: 511-517 doi: 10.1007/s002210050921 **Paper reporting that selective destruction of neurones in the PPN results in akinesia.**
2. Nandi D, Liu X, Winter JL, Aziz TZ, Stein JF. (2002) Deep brain stimulation of the pedunculo pontine region in the normal non-human primate. *Journal of Clinical Neuroscience* 9: 170-174. doi: 10.1054/jocn.2001.0943 **Paper reporting that low-frequency stimulation of the PPN in a normal monkey shows positive motor results.**
3. Nandi D, Aziz TZ, Giladi N, Winter J, Stein JF. (2002) Reversal of akinesia in experimental parkinsonism by GABA antagonist microinjections in the pedunculo pontine nucleus. *Brain* 125: 2418-2430. doi:10.1093/brain/awf259 **Paper reporting that injections of a levodopa-type drug into the PPN improves movement.**
4. Jenkinson N, Nandi D, Miall RC, Stein JF, Aziz TZ. (2004) Pedunculo pontine nucleus stimulation improves akinesia in a Parkinsonian monkey. *NeuroReport* 15: 2621-2624. doi: 10.1097/00001756-200412030-00012 **Paper reporting that low-frequency stimulation of the PPN in a monkey with simulated PD significantly improves movement.**
5. Jenkinson N, Nandi D, Oram R, Stein JF, Aziz TZ. (2006) Pedunculo pontine nucleus electric stimulation alleviates akinesia independently of dopaminergic mechanisms. *NeuroReport* 17: 639-641. doi: 10.1097/00001756-200604240-00016 **Paper reporting that PPN stimulation is additive to the effects of dopaminergic drugs alone.**
6. Aravamuthan BR, Muthusamy KA, Stein JF, Aziz TZ, Johansen-Berg H. (2007) Topography of cortical and subcortical connections of the human pedunculo pontine and subthalamic nuclei. *NeuroImage* 37: 694-705. doi:10.1016/j.neuroimage.2007.05.050 **Paper outlining the connections between the PPN and other brain stem areas, indicating the optimal areas for deep brain stimulation.**

Funding for research: Since 1993 grants in excess of £2.5M have been received for this research from the Wellcome Trust, the Remedi Trust, the MRC, the Wolfson Trust and the Norman Collison Trust.

4. Details of the impact

Since 2008, the research conducted by Professors Stein and Aziz has had a major impact on some long-term PD patients for whom treatment with dopaminergic drugs no longer works. The new form of deep brain stimulation which Stein and Aziz have pioneered has led to very significant improvements in symptoms and quality of life for this group of patients.

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Parkinson's disease principally affects older people, although early-onset Parkinson's also affects a significant number (15% of sufferers will develop the disease before age 50). As people in the developing world live longer, many more are expected to develop PD in the coming years. The organisation Parkinson's UK reports that there are currently 127,000 people with PD in the UK and that this figure is expected to rise by 28% by 2020. Symptoms of PD are both physical (tremor, rigidity, freezing of movement, falls, speech problems, bladder and bowel problems) and mental (depression, anxiety, hallucinations, insomnia). Although patients with PD often initially respond well to treatment with dopaminergic drugs such as levodopa, long-term drug treatment can exacerbate the original problems and leave patients with severe drug-resistant symptoms. Of these, the symptoms affecting movement are probably the most distressing; dyskinesia can cause patients to writhe uncontrollably, while akinesia means they can suddenly 'freeze' and be unable to move at all, rendering them prone to loss of balance and falling. The desperation caused by advanced PD is evidenced by the fact that prior to the development of effective drug treatments, patients were prepared to undergo radical experimental brain surgery in an attempt to curb the symptoms.

Around 60,000 patients with advanced PD who have drug-resistant dyskinesia have had their lives transformed by deep brain stimulation of the subthalamic nucleus, but this treatment does not work for the 10% of patients who are severely disabled by drug-resistant gait freezing and postural imbalance. The work of Stein, Aziz and Nandi in establishing the role of the PPN in controlling movement led very quickly to their collaboration on a series of studies in humans. These confirmed that the effects demonstrated in macaque monkeys also occurred clinically, and that PPN stimulation in human subjects led to significant improvements in gait freezing, balance problems and falling^{7,8,9}. A multi-centre clinical trial is in the process of being organised by the Movement Disorders Society, convened by Dr Elena Moro of Grenoble, to investigate the procedure further and to establish which targets in the PPN are most effective for stimulation.

Since 2008, around 200 PD patients have been successfully treated using PPN DBS, experiencing great improvements in their symptoms and quality of life. 'Before and after' videos of patients show radical changes in gait and balance. Before surgery, people are shown unable to get up from a chair unaided; walking with a slow, shuffling, stiff gait (often needing help with balance to avoid falling); freezing completely when attempting to turn a corner or go through a doorway; and losing balance when turning round. After surgery, patients are transformed, able to get up from a chair, walk and turn with virtually normal movements¹⁰. In addition to surgery carried out by Professor Aziz, PPN DBS has been successfully performed by a number of other neurosurgeons worldwide, for example in France¹¹. The numbers undergoing PPN DBS are expected to grow rapidly in line with those for other forms of DBS already established, eventually extending the treatment to thousands of suitable advanced PD patients. The success of this technique in PD has led to PPN DBS also being investigated as a treatment for progressive supranuclear palsy, another difficult-to-treat condition in which patients suffer severe dyskinesia¹².

As well as alleviating severe gait problems, there is mounting evidence that PPN stimulation also improves sleep in PD patients. Chronic sleep disturbance is a major cause of distress in PD; insomnia, excessive daytime sleepiness, nightmares, sleep attacks (sudden involuntary episodes of sleep) and REM sleep behaviour disorder are all common. A 2011 review confirmed that PPN DBS led to significant improvements in REM sleep amongst PD patients¹³, and a 2012 study that investigated patients before surgery, immediately after surgery and one year later found that stimulation of the PPN produced a remarkable long-term improvement of night-time sleep as well as a significant amelioration of daytime sleepiness¹⁴.

The effectiveness of PPN stimulation has been described in neuroscience and neurosurgical journals, at international meetings, through the Parkinson's Disease Society and through the PPN task force, a group set up by the Movement Disorders Society, upon which both Aziz and Stein serve.

5. Sources to corroborate the impact

7. Stefani A, Lozano AM, Peppe A, Stanzione P, et al. (2007) Bilateral deep brain stimulation of the pedunculopontine nucleus and subthalamic nuclei in severe Parkinson's disease. *Brain* 130: 1596-1607. doi:10.1093/brain/awl346 **Study confirming the effectiveness of PPN stimulation in tackling problems of akinesia in Parkinson's sufferers.**
8. Moro E, Hamani C, Poon YY, Al-Khairallah T, et al. (2010) Unilateral pedunculopontine stimulation improves falls in Parkinson's disease. *Brain* 133: 215-224. doi: 10.1093/brain/awp261 **Study confirming the effectiveness of PPN stimulation in tackling problems of akinesia in Parkinson's sufferers.**
9. Thevathasan W, Coyne TJ, Hyam JA, Kerr G, et al. (2011) Pedunculopontine nucleus stimulation improves gait freezing in Parkinson disease. *Neurosurgery* 69: 1248-1254. doi: 10.1227/NEU.0b013e31822b6f71 **Study confirming the effectiveness of PPN stimulation in tackling problems of akinesia in Parkinson's sufferers.**
10. 'Before and after' videos demonstrating the benefits of surgery for advanced PD patients are held by Professor Stein at the Department of Physiology, Anatomy and Genetics.
11. Email correspondence (held on file), corroborating the successful use of PPN DBS surgery by a French neurosurgeon. In addition Professor Stein has contacts with neurosurgeons who have successfully used PPN DBS.
12. Hazrati L-N, Wong JC, Hamani C, Lozano AM, et al. (2012) Clinicopathological study in progressive supranuclear palsy with pedunculopontine stimulation. *Movement Disorders* 27: 1304-1307. doi: 10.1002/mds.25123 **Paper reporting some positive results of PPN stimulation in patients with progressive supranuclear palsy.**
13. Amara AW, Watts RL, Walker HC (2011). The effects of deep brain stimulation on sleep in Parkinson's disease. *Therapeutic Advances in Neurological Disorders* 4: 15-24. doi: 10.1177/1756285610392446 **Review confirming that pedunculopontine nucleus DBS increases REM sleep in PD patients.**
14. Peppe A, Pierantozzi M, Baiamonte V, Moschella V, et al. (2012). Deep brain stimulation of pedunculopontine tegmental nucleus: role in sleep modulation in advanced Parkinson disease patients – one-year follow-up. *Sleep* 35: 1637-1642. doi: 10.5665/sleep.2234 **Paper reporting that PPN stimulation leads to long-term amelioration of sleep problems in PD patients.**