

# Therapeutic Brain Stimulation – Both Excitation and Inhibition Required

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Over the past decade, deep brain stimulation (DBS) has revolutionized the treatment of Parkinson's disease (PD)<sup>1</sup> and other movement disorders.<sup>2</sup> In the early 1990s neurologists were just beginning to hear about Professor Benabid, the innovator who established DBS as a successful therapy for movement disorders. Since then, there has been an exponential rise in publications on DBS (Figure).

This issue of the journal includes three articles on DBS, highlighting its growing presence in Canadian neurology and neurosurgery. The article by Constantoyannis et al<sup>3</sup> discusses how to deal with DBS-induced artifacts on electrocardiograms. This is a very practical clinical issue as more and more aging patients are treated with DBS and require electrocardiography for co-existing medical problems.

Putzke et al<sup>4</sup> report one of the largest series of essential tremor patients. Most publications on thalamic DBS include patients with all tremor types and report outcomes at last available follow-up. The weakness of this approach is twofold: (i) PD tremor does better than essential tremor yet PD tremor patients vastly outnumber essential tremor patients in most series<sup>2,5</sup> and (ii) it is thought that essential tremor patients lose benefit over time,<sup>5</sup> yet the true failure rate cannot be measured without prospective data collection at fixed time intervals. Putzke tries to correct these weaknesses in his data reporting and provides recommendations for long-term outcome analysis. Using this more correct statistical method, the authors obtain similar results to other groups.<sup>6</sup> Trend analysis fails to confirm what seems clinically apparent, that one third of essential tremor DBS patients lose benefit over time.<sup>5</sup> However the authors qualify their three-year results as only 11 patients were actually followed for that time interval. When using "intent-to-treat" analysis,

"carry-forward worse" case scenarios underestimated efficacy while "carry-forward most-recent" overestimated it. With respect to side effects, Putzke confirms another clinically observed phenomenon that patients with bilateral DBS electrodes are more likely to experience dysarthria than those with unilateral electrodes. Overall this paper confirms the efficacy of thalamic DBS for essential tremor, points out how data should be analysed but, similar to other research groups in the real world, the authors had difficulty maintaining complete follow-up. It is hard to convince patients, who may be either very well or not that well, to come back into clinic for lengthy motor control assessments.

Pallidal DBS is tackled by Eltahawy et al<sup>7</sup> who report on four patients treated for cervical dystonia. Their outcomes are excellent, with a 73% reduction in combined pain, disability and severity scores. Although these results are similar to those of other small series, some groups have suggested that DBS does not improve severity of cervical dystonia as much as pain.<sup>8</sup> Other questions raised by this paper include: what is the time course over which benefit is observed in dystonia, and what are the optimal stimulation parameters. It is likely that these questions will not be answered by small case reports and larger trials will be required. Hopefully we will gain further insight with the Canadian multicentre pilot study of pallidal DBS for cervical dystonia, funded by the Canadian Institutes of Health Research Dykinesia and Torticollis Fund.<sup>9</sup>

Part of the increase in the DBS literature relates to the large number of review articles summarizing methods, results, and speculating on how it works. Therefore, original data, such as that presented in this issue of the journal, is extremely valuable. These authors performed studies on patients for accepted and reasonable indications. This leads to a note of caution: DBS is trendy and, as such, is being used for a wide variety of indications and brain sites, including anterior capsule and nucleus accumbens for obsessive-compulsive disorder<sup>10,11</sup> and hypothalamus for cluster headache<sup>12</sup> and obesity.<sup>13</sup> In contrast, the successful launch of clinical subthalamic DBS for PD followed a completely different course. It required two conditions to exist. First, DBS was known to be safe, as it had been in use since the 1970s for pain<sup>14</sup> and the motor thalamus has been clinically targeted since 1987.<sup>5</sup> Secondly, good preclinical evidence existed supporting the potential efficacy of DBS in the subthalamic nucleus. Lesioning the subthalamic nucleus abolished PD symptoms in nonhuman primate models<sup>15</sup> and high frequency electrical stimulation did the same.<sup>16</sup> Therefore, solid preclinical experiments are the key for successful clinical application of DBS.

Studies conducted in brain slices suggest that high frequency stimulation in thalamus releases neurotransmitters from axon terminals<sup>17</sup> but there is also evidence of a direct membrane effect in both thalamus and subthalamic neurons,<sup>18</sup> or the soma may not be that important at all as, theoretically, axons may be activated independently of soma.<sup>19</sup> In fact, it is likely that the mechanisms

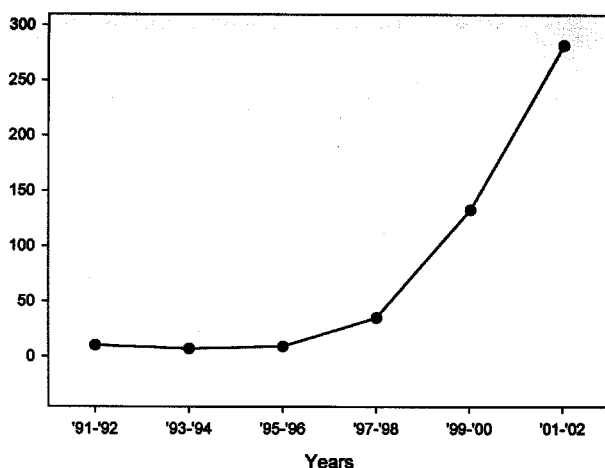


Figure: Exponential rise in publications on deep brain stimulation

of DBS are different at different brain sites. We are only now beginning to unravel the local and distant effects of high frequency stimulation in animal models.

Thus, as neurosurgeons, neurologists and psychiatrists, we should know better. We have experienced good procedures falling into disrepute by indiscriminate application. Deep brain stimulation is here to stay in the treatment of movement disorders and other select conditions. It has the potential to selectively modulate specific nuclei and pathways but it must be studied scientifically and rationally before it is used for broad clinical application.

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