Subthalamic deep brain stimulation for advanced Parkinson’s disease: all that glitters is not gold

I read with interest the article “Behavioural disorders, Parkinson’s disease and subthalamic stimulation” by Houeto et al and the accompanying editorial published last year in your journal.1,2 One of the main conclusions of that study was that sometimes the reality cannot be completely reflected in a paper because many studies conducted to assess the efficacy of therapeutic interventions in Parkinson’s disease focus on the motor aspects of the disease, while other aspects—cognitive or emotional, for example—are forgotten or insufficiently assessed by current rating scales such as the UPDRS. This is the case with most of the published studies related to deep brain stimulation (DBS). For this reason, I would like to add our experience with 18 patients operated on in our centre and included in the largest multicentre study conducted up to now.3 In this study neither cognitive functioning nor quality of life were properly evaluated. Four of the 18 patients were prematurely withdrawn because of the occurrence of one or more adverse events (two intracranial haemorrhages, one possible cortical venous thrombosis resulting in infarction, and one severe infection necessitating the removal of the DBS systems). In another patient with an impressive clinical result, one electrode was removed because of an infection, leading to a loss of efficacy in the contralateral hemisphere. Three patients showed an improvement in motor function but also cognitive deterioration which was clinically relevant in one of them. Motor symptoms were significantly ameliorated in another patient; however, he developed postural instability with falls and mild cognitive deterioration with confusional episodes requiring institutionalisation. Another patient with Parkinson’s disease and an associated gait disorder poorly responsive to levodopa, and with multiple lacunae on MRI, experienced a mixed result: whereas rest tremor and rigidity were markedly improved, the gait remained unchanged. Moreover, she started to have urinary incontinence and remained in a wheelchair. In two further patients, though DBS markedly improved all the cardinal symptoms of Parkinson’s disease and levodopa induced dyskinesias, they both developed profound depression with apathy and social isolation.

In summary, with respect to the global clinical impression and quality of life, we can conclude that six months after the intervention DBS was highly beneficial in six patients. However, the remaining 12 patients suffered from a series of adverse effects that precluded a good clinical outcome, although an improvement in motor function was observed in many of them. Thus one can obtain an unrealistic impression of the impact of DBS in real life in this particular group of patients if only the motor aspects of the disease are analysed and summarised in a table.

Furthermore, as has been repeatedly noted in several congresses, around 25–30% of patients included in the multicentre study improved by less than 25% in the motor subscale of the UPDRS in double blind assessment, a result that can be considered unsatisfactory. For this reason, in this and other studies it would be important to indicate the percentage of patients improving more or less than a given level (for example, 25% in UPDRS III). It should be emphasised that this was our initial experience and, in fact, it is quite similar to the one reported by Kumar et al with their initial nine patients.4 Seven of them completed evaluations and four of them (elderly patients with advanced disease) developed operative complications. In spite of this, the reduction in off-period parkinsonism and the increase in daily “on” time were impressive. These investigators concluded that the motor benefits outweighed the adverse effects. This was also the case in some (but not all) of our patients.

Finally, a recently published retrospective study of 211 patients conducted by Spanish teams showed that 19% of the operated patients failed to achieve the expected result.5 Analysis of the possible reasons for these unsatisfactory results showed that the correct selection of surgical candidates (72% were elderly patients with cognitive deficits, lacunae on MRI, or levodopa resistant symptoms) and definition of the target, along with surgical experience, were of crucial importance in obtaining the best results. The use of stricter selection criteria, a careful preoperative evaluation of psychiatric and cognitive function seems to be mandatory after the report by Houeto et al, and a larger surgical experience to evaluate these results. Therefore, I am convinced that at present the results are improving and will be even better in the future. I hope that the experiences of Houeto et al, along with those reported in this letter, will be useful for teams who are ready to start DBS procedures.

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References

Authors’ reply
We thank Dr Linazasoro for his comments following the publication of our article.6 The marked differences between our results and those of Dr Linazasoro are not related to the behavioural disorders we observed in some parkinsonian patients following bilateral subthalamic nucleus (STN) stimulation. Indeed, the response of parkinsonian motor disability to levodopa treatment was poor; and there were axial motor signs poorly responsive to levodopa (gait disorder, postural instability, falls), cognitive impairment, and abnormal MRI (lacunae). It is therefore not surprising that the postoperative clinical outcome was poor, including severe adverse events. We agree with Dr Linazasoro that strict criteria need to be used to select appropriate candidates for neurosurgery. In our own experience, excellent results can be obtained provided that strict inclusion criteria are fully respected: the response of the patients to levodopa treatment must be excellent, which means that axial motor symptoms (that is, freezing, postural instability, hypophonia), known to poorly respond to levodopa, must be absent or moderate; cognitive and psychic impairment must also be absent, and the MRI must be normal.

Needless to say, the effect of the neurosurgery also depends upon the optimal placement of the electrodes within the STN, together with careful postoperative fine tuning of the electrical parameters.

In brief, the success of this neurosurgical approach to levodopa responsive forms of Parkinson’s disease requires the expertise of a multidisciplinary team including neurosurgeons, neuroradiologists, neurophysiologists, and neurologists.

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References

Head injury outcome prediction in the emergency department: a role for protein S-100B?

I read with great interest the recent article by Townsend et al in which the authors studied the predictive value of protein S-100B in patients with head injury upon performance in the extended Glasgow outcome scale (GOSE). One important criticism is that the study was performed in patients with head injury defined as “any blow to the head causing a clinical diagnosis of head injury to be made, even if insufficient to cause definite loss of consciousness” and not only in patients with traumatic brain injury, which is defined...
at least through loss of consciousness or amnesia, or postconcussion syndrome. Consequently, relevant abnormality of the brain even in minor traumatic brain injury was only detected in a few patients.

In addition, cerebral computed tomography (CT) was performed in 15 of 148 patients. The extent of possible traumatic brain injury in the patients in the study by Townsend et al. cannot be estimated. Patients with frontal contusion lesions in CCT and/or diffuse axonal injury were not separately identified in this study. Those patients are at high risk of having neuropsychological deficits and also frequently suffer from loss of insight. This might falsify the outcome measured by the extended Glasgow coma scale that was obtained by telephone interview only. Assessment by phone has limitations and cannot substitute a detailed neurological and neuropsychological examination that would reveal the above mentioned deficits.

In literature, CT controlled studies by Romner et al. (RIA), Ingebrigtsen et al. (RIA) and Biberthaler et al. (LIA-mat) calculated that an undetectable protein S-100B level below 0.1 ng/ml in serum or protein S-100B below a cut off point at 0.1 ng/ml predicts normal intracranial findings in CT. Herrmann et al. (LIA-mat) showed that an initial S-100B value above 0.14 ng/ml has a high sensitivity for short-term and long-term neuropsychological deficits in traumatic brain injury. A prospective study has not been performed yet.

In the study by Townsend et al. measurements of protein S-100B were performed retrospectively without CT control or short-term or long-term clinical monitoring, the study is of no clinical value.

The demonstration of a much needed neurobiochemical marker of brain damage in traumatic brain injury, there is a need for a prospective study of protein S-100B as a neurobiochemical marker of brain damage. This would include hospital monitoring of the patients with an initial cranial CT and MRI control as well as a short-term and long-term neuropsychological follow up.

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References

Authors’ reply
We thank Wunderlich for his thoughtful provoking letter. The chief reservations expressed regarding the potential applicability of our findings seem to be that the entry criteria were too broad, that the measurements of protein S-100B were made retrospectively, and that no CT control was performed, and that follow up might be biased. We will consider these points later.

The entry criteria were kept as broad as possible to enable the full cross section of patients with head injury to be evaluated. We are aware that traumatic brain injury is delineated more precisely due to the presence of a period of altered consciousness, particularly for research purposes. However, we were unable to find evidence in published literature that disability after head injury is managed more precisely than the rate would be expected to be higher than in those without such an alteration of conscious level. Also, there are no published data that we are aware of that demonstrate S-100B levels in those without altered consciousness after head trauma. We thought this would be of interest as clearly if there was a large proportion of this group with raised S-100B level and a usual clinical outcome, then its use as a prognostic marker would be limited by this false positive rate. For these reasons we consider our entry criteria apposite. By keeping patient selection as simple as possible, we anticipate that the least experienced practitioner would be competent to identify a patient in their practice that would be represented by our data. Our study, therefore, passes the test of appeal.

Wunderlich states that our S-100B measurements were made retroactively. Our cohort was recruited prospectively. The blood samples taken for S-100B level estimation at initial presentation were analysed once outcome had been assessed. Blinding the outcome assessor to the S-100B level in this way was intended to reduce the risk of bias. If the results were subsequently to be published, the assessor would be competent to identify a patient in their practice that would be represented by our data. Our study, therefore, passes the test of appeal.

Wunderlich may have agreed to undertake.

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Screening for variant Creutzfeldt-Jakob disease
The letter by Joiner et al. describes the lack of detectable prion protein (PrP) in three of four necropsy appendix samples from vCJD cases using a combination of immunocytochemistry and western blotting, thereby questioning the sensitivity of large scale screening of appendix tissue samples as an estimate of people who may be incubating vCJD. In our original description of PrP accumulation in the appendix before the onset of symptoms, we noted that PrP accumulation was focal and therefore we have used extensive sampling of the appendix for our study, resulting in a median of more than 24 secondary lymphoid follicles examined in each appendix case included. In addition we have used two different monoclonal antibodies to PrP and a very sensitive detection system, to reduce the risk of false negatives. Using this approach we were able to detect lympohiocytoclastic PrP accumulation in 19 of 22 vCJD necropsy appendix samples tested (two of the three negative samples had inadequate amounts of lymphoid tissue for assessment and would not have met inclusion criteria for our study). In the addition, of the three appendix samples removed before the onset of symptoms, the two removed in the 1990s were positive, and the third, removed in 1987 was negative. All samples included in our study were removed between 1995 and 1999. The discrepancy between our findings and those of Joiner et al. may therefore result from our use of a more sensitive immunocytochemical approach and extensive tissue sampling.

While we accept that the sensitivity and specificity of screening tissue samples for lymphocytoclastic accumulation of PrP as a marker for vCJD is unknown, it seems to be a reliable approach in our opinion to address the lack of an alternative test and considerable uncertainty about future numbers of vCJD cases, we feel that such a study is justified. Our study has necessarily concentrated on appendix samples (as comparatively few tonsillar samples are archived), however we have recommended large scale screening of fresh tonsil tissue on a prospective basis, which the Department of Health has now agreed to undertake.
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References

BOOK REVIEWS
The Nobel prize in medicine and the Karolinska Institute

The considerable enjoyment to be had from this unusual book is not altogether to be anticipated from the title. It derives from the diversity of material it contains, which ranges from the history of medicine in Sweden and the rivalry between the upstart Karolinska Institute (founded in 1810) and the old universities of Uppsala (1477) and Lund (1668), to the opening lines of a poem written at the age of 19 by Alfred Nobel after his first meeting with a Mlle Rivière in Paris. The book is built around the life and contributions of Axel Key, whom neurologists remember for his definitive demonstration with Retzius of the nature of the circulation of the cerebrospinal fluid. His achievements were, however, much wider. Under his influence first as Professor of Pathological Anatomy (from 1862) and later as Rector (1886–1897) and a Member of Parliament (1881–1890), the Karolinska Institute expanded and gained in international prestige until by 1895 it was the natural choice of Alfred Nobel for the responsibility of selecting the laureates for his prize in physiology or medicine. More generally, Key raised the profile of Scandinavian medicine by founding, in 1862, a journal for the Institute, which in 1869 became the Nordic Medical Archives, the forerunner of the Acta Medica et Acta Citrigica Scandinavica. Key’s other great achievement was a huge study of school hygiene that led directly to the establishment of the school medicine system in Sweden and was widely influential elsewhere in Europe.

The style of the present book is discursive. For example, there is a chapter devoted to the life, loves, and intellectual achievements of the extraordinary Russian Professor of Mathematics in Stockholm, Sonya Kovalevskaya, the first woman professor in any subject in Europe; this because Kay had performed a postmortem on her in 1891. There are lengthy extracts from Key’s letters to his wife written on two great journeys to European university centres in 1872 and in 1893. During the former Key met again Rudolf Virchow, with whom he had studied in 1861, and some of his fellow students from that period, including Billroth and von Recklinghausen. On the later journey he spent an evening, by chance, with Alfred Nobel—their only meeting. Nobel had already made a generous gift to the Karolinska and told Key it would not be the last. The letters tell of Key’s impressions of the people he met and give a flavour of the (often very grand) style in which senior figures in the university world lived in those days. The scientific contributions of many of his hosts are summarised in an extensive appendix.

There is much less about Nobel, although his originality, his breadth (he was interested in experimental physiology as well as explosives), and his naive faith that “my dynamite factories can put an end to war quicker than... peace congresses” comes clearly across.

The book is extensively illustrated, mostly by portraits, and is lavishly produced.

W I MacDonald
The parahippocampal region: organization and role in cognitive function

The parahippocampal region is a curious place: it genuinely has the potential to be of interest to a variety of neuroscientists and clinical disciplines. This book is certainly worth taking a look at if you are interested in learning and memory or high level visual processing in healthy individuals; or if your predilection is for disease states of such diversity as dementia, temporal lobe epilepsy, and schizophrenia.

Many of the chapters cover the basic neuroscience of the parahippocampal region—its anatomical parcellation, connectivity, neurophysiology, and the effects of lesions in animal models. There is a plethora of terminology here and I did wonder whether the reader could not have been helped greatly by the use of more line drawings, particularly when it comes to the anatomy. My working memory was certainly pushed to its capacity limits on occasions by the nomenclature! Despite this shortcoming, these chapters really do provide a wealth of useful information and direct access to the primary animal literature.

When it comes to humans, several chapters make a useful contribution. I found the chapter by Van Hoesen on the anatomy of the human parahippocampal region and its involvement in dementia to be particularly helpful and clear. The discussion on imaging cognitive functions of the parahippocampal region by Fernandez and Tendolkar was also interesting but surprisingly short given the explosion of interest in this region. My overall impression is that this book is a useful resource, but it is unlikely that anyone will find more than a handful of chapters here that are directly useful and relevant to their interests. Nevertheless, this is a useful reference book that most medical libraries would find well worth obtaining.

M Husain
Cancer neurology in clinical practice

This is another welcome addition to the expanding number of neuro-oncology textbooks that have exploded onto the market in the past few years. It has been edited by two alumni of Memorial Sloan-Kettering Cancer Center and 24 of the 50 authors received their neurological training at Sloan-Kettering, so they are well placed to address the problems of neurological complications of systemic cancer.

This book is a reference text and is aimed at providing clinicians from various backgrounds with a core text to help them diagnose and manage neurological complications of cancer. There are 31 chapters written on 650 pages and the editors have subdivided the book into seven parts, starting with an overview of the prevalence and impact of neurological disease in cancer. The subsequent chapters cover neurological symptoms, particularly headache, confusion and cancer pain, direct and indirect complications of cancer, complications of cancer therapy, diagnostic studies (really a single chapter on imaging), and then complications of specific malignancies. This last part considers all the different cancers, including paediatric cancers but not primary brain tumours. Because of the general adage that “anything can happen in cancer”, there is considerable repetition but this does not really detract from this book. The editors have certainly done well to produce this book. The discussion on imaging cognitive function of the parahippocampal region by Fernandez and Tendolkar was also interesting but surprisingly short given the explosion of interest in this region. My overall impression is that this book is a useful resource, but it is unlikely that anyone will find more than a handful of chapters here that are directly useful and relevant to their interests. Nevertheless, this is a useful reference book that most medical libraries would find well worth obtaining.

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Head injury outcome prediction in the emergency department: a role for protein S-100B?

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