La neuromodulazione nel trattamento delle alterazioni funzionali del sistema nervoso centrale

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NEUROMODULATION

- What are we talking about?
- Neuromodulation and “neuroelectrogenesis”
- Development and clinical applications
- Future perspectives
NEUROMODULATION

• What are we talking about?
  • Neuromodulation and neuroelectrogeneration
  • Development and clinical applications
  • Future perspectives
NEUROMODULATION

- Procedure able to alter quality and/or intensity of neurologic functions: *reversible*
Surgical procedures aiming at treating neurological symptoms and restoring function, independently from the underlying pathology.
NEUROMODULATION

• Procedure able to alter quality and/or intensity of neurologic functions

• Means: electricity
Electricity is generated by cell membranes, which are at the same time electrically excitable.

Electricity represents the signaling for neuron communication.
The part played by electric fish in the early history of bioelectricity and electrotherapy

**Bull Hist Med 20:112-37, 1946**

Electric torpedo ray (*Torpedo nobiliana*) used by Dioscorides for the treatment of seizures in 76 AD (“On medical matter”)

Beneficial effects of electrical discharges on rheumatic pain by mediterranean *Torpedo* in Roman Age (from mosaic of Pompeii)

**1804**: early experimental human trials of brain stimulation using Volta batteries (Albe-Fessard, 1961-1963)
NEUROMODULATION

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EEG

- Berger H.: Über das Electrenkephalogram des Menschen
  - Arch Psychiatr Nervenkr. 1929; 87: 527-570.
ECoG

- Foerster O., Altenburger H.: Elektrobiologische Vorgänge an der menschlichen Hirnrinde
Electrocorticography
Epilepsy and the Functional Anatomy of the Human Brain

by

WILDER PENFIELD, O.M., C.M.G.
M.D. (Johns Hopkins)
F.R.C.S. (Canada), Hon. F.R.C.S. (England), F.R.S. (London)

and

HERBERT JASPER
M.D., C.M. (McGill), B.A. (Reed), M.A. (Oregon)
Ph.D. (Iowa), D. ès Sci. (Paris)

Chapter XIV by Francis McNaughton
B.A. and M.D., C.M. (McGill)

8 color plates and
314 black and white illustrations

Little, Brown and Company . Boston
Fig. III-11. Rolandic motor cortex. Each dot represents a point which gave a motor response in a complete summary of 163 cases of cortical stimulation (Penfield and Boldrey, 1937).
HUMAN

Fig. III-1
Fig. III-1. Chart of cytoarchitectonic subdivisions of the human cerebral cortex (Campbell, 1905).

Fig. III-2
Fig. III-2. Chart of architectonic subdivisions of the human cerebral cortex (Brodmann, 1909).
Functional Anatomy of Subcortical Structures
F. Mundinger, G. Yasargil and R. Hassler
Hassler R: Anatomie des Thalamus, Arch Psychiatr 184:249-256, 1950
Hassler R: Anatomy of the Thalamus, Thieme, 230-290, 1959
STN nucleus microrecording
Intra-operative stimulation for target confirmation

Chronic therapeutic HF stimulation
NEUROMODULATION

• What are we talking about?
• Neuromodulation and neuroelectrogenesis
• Development and clinical applications
• Future perspectives
La DBS nei disturbi del movimento

Mundinger, 1977  VL, ZI  distonia, tremore
Mundinger, 1978  PL  distonia, spasticità
Brloe, 1980  VL  tremore (SM)
Siegfried, 1982  VL  tremore
Andy, 1983  VL  tremore
Benabid, 1987  VIM  tremore
Siegfried, 1992  GPI  m. Parkinson
Benabid, 1993  GPI, STN  m. Parkinson
The Model 3387 DBS™ lead has four electrodes (0,1,2,3) spaced 1.5 mm apart.

The Model 3389 DBS™ lead has four electrodes (0,1,2,3) spaced 0.5 mm apart.
HFS for Parkinson’s Disease

Subthalamic Nucleus

- Larger connections with BG
- Direct influence on GPI and SNr
Bilateral deep brain stimulation in Parkinson’s disease: a multicentre study with 4 years follow-up


Deep brain stimulation (DBS) is associated with significant improvement of motor complications in patients with severe Parkinson’s disease after some 6–12 months of treatment. Long-term results in a large number of patients have been reported only from a single study centre. We report 69 Parkinson’s disease patients treated with bilateral DBS of the subthalamic nucleus (STN, n = 49) or globus pallidus internus (GPI, n = 20) included in a multicentre study. Patients were assessed preoperatively and at 1 year and 3–4 years after surgery. The primary outcome measure was the change in the ‘off’ medication score of the Unified Parkinson’s Disease Rating Scale motor part (UPDRS-III) at 3–4 years. Stimulation of the STN or GPI induced a significant improvement (50 and 39%; P < 0.0001) of the ‘off’ medication UPDRS-III score at 3–4 years with respect to baseline. Stimulation improved cardinal features and activities of daily living (ADL) (P < 0.0001 and P < 0.02 for STN and GPI, respectively) and prolonged the ‘on’ time spent with good mobility without dyskinesias (P < 0.00001). Daily dosage of levodopa was significantly reduced (35%) in the STN-treated group only (P < 0.001). Comparison of the improvement induced by stimulation at 1 year with 3–4 years showed a significant worsening in the ‘on’ medication motor states of the UPDRS-III, ADL and gait in both STN and GPI groups, and speech and postural stability in the STN-treated group. Adverse events (AEs) included cognitive decline, speech difficulty, instability, gait disorders and depression. These were more common in patients treated with DBS of the STN. No patient abandoned treatment as a result of these side effects. This experience, which represents the first multicentre study assessing the long-term efficacy of either STN or GPI stimulation, shows a significant and substantial clinically important therapeutic benefit for at least 3–4 years in a large cohort of patients with severe Parkinson’s disease.
Bilateral deep brain stimulation in Parkinson’s disease: a multicentre study with 4 years follow-up

Brain (2005) Page 1 of 10

• # 69 (STN #49; GPI #20)
• Significant and substantial clinically important therapeutic benefit for at least 3-4 years
• UPDRS III (STN 50%; GPI 39%; p< .0001)
• LEDD (35% STN: p< .00001)
• 1yr vs. 4 yrs: relative loss of improvement for gait, speech, postural stability
• Aes: cognitive decline, speech difficulty, instability, gait disorders and depression
• No pt abandoned treatment as results of Aes
Multicenter study on deep brain stimulation in Parkinson's disease: an independent assessment of reported adverse events at 4 years.

Hariz MI, Rehncrona S, Quinn NP, Speelman JD, Wensing C; Multicentre Advanced Parkinson's Disease Deep Brain Stimulation Group.

*Mov Disord. 2008 Feb 15;23(3):416-21*

Long-term effects of pallidal or subthalamic deep brain stimulation on quality of life in Parkinson's disease.


Most of the AEs were not deemed severe. The majority of the AEs affected patients' cognitive, psychiatric and behavioral status, as well as speech, gait, and balance. Most of these AEs occurred in STN DBS patients. At 3 years, sustained improvements were observed in all the QOL scores. Despite sustained motor improvements many of these initial benefits were lost after 3 years. This may reflect either progression of the disease or adaptive changes in the subjective perception of health-related wellbeing over time.

Alternative surgical procedures to help drug-resistant epilepsy - a review

Polkey CE

Stereotactic lesioning, popular in the 1950's has been largely abandoned but stereotactic radiosurgery emerges as a useful technique, especially in the treatment of mesial temporal sclerosis. Disconnection by callosotomy has fewer applications than previously and multiple subpial transection (MST) has limited applications. Stimulation is a technique with increasing usefulness. Vagus nerve stimulation (VNS) is an accepted method of treatment with low morbidity and mortality, which improves seizure control in at least 30% of patients, together with concomitant improvements in QOL and economic advantages. Stimulation of deep brain targets in the thalamus, subthalamus and mesial temporal structures is practical. There are indications that this improves seizure control in groups of patients previously unhelped by surgery, and this methodology has enormous potential.
EPILEPSY SURGERY
PALLIATIVE PROCEDURES

• The focus is not usually the target of the treatment

• The final aim is not seizure suppression, but the decrease of seizure frequency and/or intensity.
SANTE’: Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (2006)

Purpose:

• To assess the SAFETY AND EFFICACY of bilateral neurostimulation of the ANTERIOR NUCLEUS OF THE TALAMUS (ANT) as ADJUNCTIVE THERAPY in adults diagnosed with epilepsy characterized by PARTIAL-ONSET SEIZURE, with or without secondary generalization

• 110 pts enrolled and monitored for a minimum of 13 months

SANTE STUDY Results (2008)

• 38% seizure frequency decrease in the treatment group vs 14.5% in the control group

• Long term results seems even better in terms of seizures frequency decrease for the majority of the patients
PSYCHOSURGERY

Implications

- **Epistemic**: relationships between anatomical structure and psychological function
- **Ethical**: alteration of personality

*guidelines and interdisciplinary committees*
DBS Stimulation for Obsessive Compulsive Disorders

*Nuttin BJ et al, Neurosurgery 2003*

- Anterior limb of internal capsule
- #6 patients with OCD
- Significant and long standing reduction of the severity score
- Decreased frontal metabolism (PET) during stimulation
- No adverse or side effects

The evolution of deep brain stimulation for neuropsychiatric disorders.

Psychiatric neurosurgery 2009: review and perspective.
Read CN, Greenberg BD. Semin Neurol. 2009 Jul;29(3):256-65
Gate Control Theory of Pain
Melzack R and Wall PD, 1965

Closed Gate: $\alpha\beta$ fibres close the gate through inhibitory interneurons

Open Gate: $C$ fibres block inhibitory interneurons and open the gate to nociceptive impulses
Gate Control Theory of Pain
Melzack R and Wall PD, 1965

Substantia gelatinosa cells (Aβ fibers) as exerting presynaptic inhibitory action onto cutaneous afferents in dorsal horn, acting as a gate that control the traffic of afferent inputs.

Descending influences from periaqueductal gray, median raphe and dorsolateral funiculus may inhibit nociception.
Neurostimulation Therapy for Chronic Neuropathic and Non-Cancerous Pain

- Spinal Cord Stimulation (SCS)
- Deep Brain Stimulation (DBS)
- Epidural Motor Cortex Stimulation (MCS)
Spinal Cord Stimulation

A direct clinical application of the gate control theory

The effect is mediated by large-myelinated Aβ afferents, whose collaterals ascend in the dorsal columns

Trial stimulation via externalized leads is widely employed

European Journal of Neurology, 2007

EFNS guidelines on neurostimulation therapy for neuropathic pain

We found level B evidence for the effectiveness of SCS in FBSS and CRPS I. The available evidence is also positive for CRPS II, peripheral nerve injury, diabetic neuropathy, PHN, brachial plexus lesion, amputation (stump and phantom pains) and partial spinal cord injury, but still requires confirmation before the use of SCS can be unreservedly recommended in these conditions.

Failed Back Surgery Syndrome

Complex regional pain syndrome I
Spinal Cord Stimulation (SCS)

European Journal of Neurology, 2007

EFNS guidelines on neurostimulation therapy for neuropathic pain

class II RCTs have showed that SCS...

...is more effective than reoperation
...its addition is more effective than conventional medical care alone

In these trials the responders (pain relief >50%) to SCS were 47-48% vs. 9-12% with comparator, at 6-24 months. [North 2005; Kumar 2005,2007]

In the pooled data from case series in 3307 FBSS patients, responders were 62%.

in a class II RCT SCS reduced the VAS score by a mean 2,6 cm more than conventional care alone at 6 months and by 1,7 cm at 5 years

In the pooled data from case series (n=561) in CRPS I and II, the proportion of responders was 67%.
Spinal Cord Stimulation for Patients with Failed Back Surgery Syndrome: A Systematic Review

Cost-Effectiveness:

Cost-effectiveness was evaluated in 2 systematic reviews (5,43) and 3 studies (96-98) yielding positive results.

Thus, SCS is most cost-effective when patients forego repeat operation and finally, if SCS should fail, reoperation is unlikely to succeed.
Spinal Cord Stimulation (SCS) is not a risk-free endeavor. Taylor et al (3) reported that 43% of patients with chronic back and leg pain/FBSS experienced one or more complications with SCS, with the majority of these due to electrode or lead problems (27%). Infections (6%), generator problems (6%), extension cable problems (10%), and other issues, such as cerebrospinal fluid leaks (7%), accounted for most of the remainder. On the positive side, no neurologic-related complications were reported in this systematic review. Recently, a case report was published describing a patient who experienced acute renal failure during a trial of SCS (123).
Deep Brain Stimulation (DBS)

European Journal of Neurology, 2007

EFNS guidelines on neurostimulation therapy for neuropathic pain

DBS is more effective for nociceptive pain than for neuropathic pain (63% vs. 47% long-term success)

weak positive evidence in peripheral neuropathic pain including pain after amputation and facial pain.

DBS

- Thalamus (VPL/VPM)
  - Antinociceptive Opioid system
  - Activation of medial thalamic nuclei

- PAG/Brain Stem
  - Paresthesia producing stimulation
  - Direct modulation of specific somatosensory relay
  - ACC

Plow, 2012

**Neural network involved in the origin of cluster headache pain and vegetative phenomena**

**DBS of the pHyp:**

- 22 pts affected by *chronic cluster headache* (CCH);
- 1 pt by short-lasting unilateral neuralgiform headache attacks with conjuntival injection and tearing (*SUNCT*);
- 5 pts by *refractory recurrent trigeminal neuralgia* (TN) involving the 1st trigeminal branch and associated with multiple sclerosis (MS);
- 4 pts by *atypical facial pain*.

**CCH**

- 71% of postoperative days were pain free, and intensity and duration of pain bouts was significatively reduced
- Medications have been reduced to less than 20% of the preoperative level
- At long-term FU (8 years), 63% of CCH pts were classified as DBS responders
DBS for refractory headaches


DBS of the pHyp:

• 22 pts affected by chronic cluster headache (CCH);

• 1 pt by short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT);

• 5 pts by refractory recurrent trigeminal neuralgia (TN) involving the 1st trigeminal branch and associated with multiple sclerosis (MS);

• 4 pts by atypical facial pain.

SUNCT

• DBS along with the adjunct treatment of lamotrigine (100 mg/die) led to the complete and definitive remission of symptoms, which was confirmed at the last clinical examination at the 5-year FU

**DBS of the pHyp:**

- 22 pts affected by chronic cluster headache (CCH);
- 1 pt by short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT);
- 5 pts by refractory recurrent trigeminal neuralgia (TN) involving the 1st trigeminal branch and associated with multiple sclerosis (MS);
- 4 pts by atypical facial pain.

All the 5 pts described a reduction of paroxysmal pain attacks.

However, **DBS efficacy seemed to be limited to the trigeminal ophthalmic branch**
**DBS for refractory headaches**


**DBS of the pHyp:**

- 22 pts affected by chronic cluster headache (CCH);
- 1 pt by short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT);
- 5 pts by refractory recurrent trigeminal neuralgia (TN) involving the 1st trigeminal branch and associated with multiple sclerosis (MS);
- 4 pts by atypical facial pain.

**Atypical facial pain**

- No beneficial effect after pHyp-DBS
Epidural Motor Cortex Stimulation (MCS)

European Journal of Neurology, 2007

EFNS guidelines on neurostimulation therapy for neuropathic pain

There is a level C evidence that MCS is useful in 50-60% of patients with central post-stroke pain (CPSP) and central or peripheral facial neuropathic pain, with small risk of medical complications. The evidence about any other condition remains insufficient.

MCS

Plow, 2012

Cortico-thalamic:

• Modulation of thalamocortical circuits
• Via ACC, striatum, prefrontal cortices, PAG

Post-operative pain

• Via M1
NEUROMODULATION

• What are we talking about?
• Neuromodulation and neuroelectrogenesis
• Development and clinical applications
• Future perspectives
What about ............

......the FUTURE?
....repairing STRUCTURE

To restore

....FUNCTION!
Gene therapy is the delivery of a gene to modify the phenotypic characteristics of the target cell of interest.

Gene therapy is an exciting new discipline in which neurosurgery and neurosurgeons can have a direct impact on both patient care and emerging scientific developments.

Although brain neoplasms have been the most commonly studied application of genetic therapeutics in neurological surgery, there are many other potential applications of this technology to neurosurgical disorders, including spinal instability, neurodegenerative disease, neurogenetic diseases, central nervous system (CNS) injury, aneurysms, trauma, stroke, and epilepsy.
Gene Therapy may be divided into two broad categories of interest: cytotoxic and restorative.

In **cytotoxic** gene therapy, the goal is to introduce a gene that can destroy a target cell such as a glioma cell within a glioblastoma multiforme.

In **restorative** gene therapy, the goal is to introduce a gene that provides a new or missing function to the cell.
The cell replacement strategy in PD has been based on the idea that neural graft-induced restoration of dopamine neurotransmission in the striatum, even if the disease is chronic and also affects other neuronal systems and brain regions, could lead to substantial and long-lasting functional recovery.

Stem cells could be useful as an unlimited source of dopamine neurons, but it is still unclear if they function as normal dopamine neurons.
Stabilizing the membrane potentials of neurons at a seizure focus clearly is an exciting application of gene therapy, but certainly requires additional laboratory work before it is ready for clinical application.


Growth factor gene therapy for Alzheimer disease

Departments of Neurosciences and Surgery, Division of Neurosurgery, University of California at San Diego, La Jolla; Veterans Administration Medical Center, San Diego, California; and Department of Surgery, Division of Neurosurgery, Rush-Presbyterian Medical Center, Chicago, Illinois
The role of cell therapy for stroke
D. Kondziolka, L. Wechsler, E. Tyler-Kabara, C. Achim.
Departments of Neurological Surgery, Neurology, and Pathology (Neuropathology), and the Neurotransplantation Research Program, University of Pittsburgh, Pennsylvania

Cellular therapy has been evaluated in small animals, subhuman primates, and now humans for the potential repair of brain injury due to stroke.

The treatment of ischemic strokes with nucleic acid therapeutics has been successfully achieved, but may be difficult to apply clinically secondary to delays between gene transfer, transcription, and translation.


A nanometer is a billionth of a meter \((10^{-9} \text{ m})\) and spans approximately 10 atomic diameters.

Nanotechnology is the technology for designing, fabricating, and applying “nanosystems” - nanometer-scale-systems (a synthesis of EE, biotech, chemistry and physis).

**Molecular Nanotechnology**

Three dimensional positional control of atomic and molecular structure to create materials and devices with molecular precision.
Associate the progress in molecular biology to microsurgical techniques
From
FUNCTIONAL ANATOMY

To
FUNCTIONAL BIOLOGY?
Thank you
The relations of brain (*anatomy*) and behaviour (*function*) have been known for centuries.

*Edgar M. Housepian, M.D.*
*Professor Emeritus of Clinical Neurological Surgery*
*Columbia University, New York, USA*
*1998*
Serious cerebral surgery cannot be carried out without knowledge of the **physiology of the brain**, which in turn had to be learned by experiment.....in spite of iniquitous opposition to scientific experiment and foolish ignorance
Adulteration of Beer in Paris—There is evidently a strong and creditable dealer on the part of the authorities in Paris to put a stop to the adulteration of beer. This belief, already been attended with good results, and several foreign brewers are said to have given up the use. Dr. Otvos, the Committee of the Municipal Laboratory do not, however, mean to rest satisfied with half measures. They have had a recent interview with the Minister of Justice, in which they asked that the beer should be thrown away as soon as it reached the frontier, or, if that were not possible, immediately after it enters the Paris railway stations.

Syrup Gardiner; but since it has again found a suitable home, its importance and value have increased year by year, and now, I think, should be considered as almost unrivalled. We are indebted for the progress, largely to the enlightened liberality of the treasurer and governors, and directly to the admirable labours of two successive curators: Professor Charles Stewart, who was with us for many years, and who was a year or two ago, much to our loss, elevated to the chairmanship of the museum of the College of Surgeons; and Samuel Shattock, who now occupies the post, and has signalised his brief tenure of office by the most splendid work, and of whom I may mention especially that during the last few months, with the aid of Dr. Stone and Mr. Pownall, he has re-arranged, renovated, and enlarged the museum of materia medicus, which, now that it is properly the finest, most perfect, and most serviceable museum of the kind in existence.

Year by year, gentlemen, during the fifteen years we have occupied our present site, our school, which has been so often and so seriously checked in its career, has increased in usefulness and prosperity, and once more it occupies a leading position among the metropolitan schools of medicine. Nor can I see any cloud on the horizon—any reason why our success should not be maintained in the future. But, while the school grows and prospers, those who contribute to its progress drop out one by one, and on the new comers fall the tasks thus vacated. Fifteen years is a short time—at any rate seems short to those whose journey of life approaches completion, and for whom the abyss into which all must finally plunge is already within easy distance. Yet many changes have occurred even in this short time; and not only have we lost amongst those who were with us from the beginning, but some of those who joined us later have disappeared from our midst. Some have died; some have left us from age or from ill health; some have transferred themselves to other spheres of usefulness. Our late treasurer, Sir Francis Hicks, under whose reign the present hospital was built, and to whose sagacity we are indebted for the securing of many of the improvements which I have discussed, died, after a short illness, nine years ago. Mr. Withfield passed away a year earlier. Poor old Raimond, whose labours and useful career among us had extended over so many years, worked with us for a time at this hospital; but he was falling into ill health, and probably from that cause only knew him here could form any conception of what kind of man he had been. He retired on a pension some years ago, and died but recently. Peacock and Murchison are both dead; and within the last four months that poor Frank Mason, whose genial temper and kindness of heart, for him the warmest all his colleagues, and of everyone who knew him, whose musical accomplishments were our admiration and delight, and whose eminence as a surgeon was universally recognized, was, to our infiuency, a grief, snatched away by death, in the prime of life, in the fullness of his powers, and where there seemed for him the promise and the assurance of a long and prosperous career. But great though our sorrow is when those we love are removed from among us, Time, the healer, brings its compensations, and the hallowed memories then, when the sting of loss is no longer acutely felt. And irreparable though our loss may seem when eminent colleagues and great teachers depart, they are yet not wholly lost to us, for their names, their examples, and their works survive, and add acumulating lustre to the school which they adorned.

I have now completed, however inadequately, the task which I had set myself; and it only remains for me to give, on behalf of myself and colleagues, a word of welcome to you, who come and the first two days of the meeting, to see you, and to exult in the worthy heirs of those proud traditions which are the common heritage of all who join our ancient hospital and ancient school; and lastly, to thank you, Miss Treasurer, and you, Madam, for the kind patience with which you have listened to my address.

BRITISH MEDICAL ASSOCIATION.

FIFTY-FOURTH ANNUAL MEETING.

PROCEEDINGS OF SECTIONS.

BRAIN-SURGERY.

Read in the Section of Surgery at the Annual Meeting of the British Medical Association in Brighton.

BY VICTOR HORSLEY, B.S., F.R.S.,
Sergeon to the National Hospital for the Paralysed and Epileptic, Queen's Square; Assistant-Surgeon to University College Hospital, etc.

The following paper is necessarily, owing to the brevity of the time at the disposal of these readers at the meeting, a simple description of that method of operating on the brain which I have employed as one which successfully meets the various difficulties and dangers of the task.

Since in many very essential points my method differs from what are considered by some of the eminent surgeons, I think the subject may best be handled by my describing, in detail, the treatment of an imaginary case, illustrating the same by these photographs and specimens removed from the patient you see before you, and from the lower animals the subjects of experiments.

Preparation of the Patient.—The day before the operation, the patient's head is shaved, and washed with soft soap and then ether; next the position of the lesion is ascertained by measurement and marked on the scalp. The head is then covered with lint, soaked in 1 in 20 solution of carbolic acid, oil-silk and cotton-wool, being thus thoroughly carbolicised for at least twelve hours before operation. Finally, the patient has the usual purgative administered the evening before, followed by a enema on the morning of the operation.

Anaesthetic—The method of carrying out the patient is most important, and consists of the administration, by hypodermic injection, of a quarter of a grain of quinine after which the patient is chloroformed. The object of giving the morphia is two-fold. In the first place, as is well known, it allows of the performance of a prolonged operation without the necessity of giving a large amount of chloroform. In fact, the amount actually used in an operation lasting two hours, I have found to be very small. The second reason for employing morphia is that it is more effective than chloroform, for instance, in the case of operation on the central nervous system; and that, consequently, an incision into the brain is accompanied by very little coring if the patient be chloroformed as its influence. I have not employed ether either in operations on man, fearing that it would tend to cause cerebral excitement; chloroform, on the contrary, well marked depression. I have not wholly, if there existed any degree of reaction, the above considerations of the principle, consideration was disregarded in favour of the safer narcotic.

In the case of the second patient I show you today, from whom I removed this tumour, the heart is displaced outwards, and the lower lobes of the left lung rendered practically of very little use by repeated attacks of pleurisy; but I did not consider this condition was sufficient to negative the use of chloroform. In a case where considerable heart-mixture exists, no doubt an anaesthetic of the kind commonly used should be done under the influence of morphia. But this attempted, care must be taken to employ a very strong solution when the dura is exposed, since that membrane is extremely sensitive (being supplied by branches of the fifth cranial nerve), a fact which appears to be unknown to clinicians, although it is obviously of immense importance in considering the cause of intracranial pain, cranial tenderness, etc.

Although solutions of cocaine can, it is said, be perfectly safe, further confirmation of this assertion must be produced before it is used as I have just suggested, since it can hardly be repeated too strongly, that mesospia is the one cardinal point on which brain-surgery rests.
V. Horsley: “Brain Surgery”
1886: The British Medical Journal

• Present state
  – “...The left thumb was frequently in a state of rigidity, alternating with clonic spasm...”

• Diagnosis
  – “...In a paper referred to in the foregoing case (No. 1), Dr. Beevor and myself have shown that the movement of opposition of the thumb and finger can be elicited by minimal stimulation of the ascending frontal and parietal convolutions at the line of junction of their lower and middle thirds...”

- At 5 years, the UPDRS motor score had improved by 54.2% and levodopa equivalent dose was reduced by 61.9%, compared with preimplant.
- Rest tremor, rigidity, gait, lower and upper limb akinesia, and total axial score were improved in decreasing order. Postural stability and speech improved transiently, whereas on-period freezing of gait, motor fluctuations and dyskinesias recovered durably.
- Chronic STN stimulation allows to replace for dopaminergic medications in the long-term at the expense of an increase of the total energy delivered.

Bilateral deep-brain stimulation of the globus pallidus in primary generalized dystonia


- prospective, controlled, multicenter study assessing the efficacy and safety of bilateral pallidal stimulation in 22 patients with primary generalized dystonia
- **dystonia movement score improved** from a mean (+/-SD) of 46.3+/−21.3 before surgery to 21.0+/−14.1 at 12 months (P<0.001)
- **disability score improved** from 11.6+/−5.5 before surgery to 6.5+/−4.9 at 12 months (P<0.001)
- five adverse events (in three patients); all resolved without permanent sequelae
- these findings support the efficacy and safety of the use of bilateral stimulation of the internal globus pallidus in selected patients with **primary generalized dystonia**
To alter neuronal systems, whose function is impaired by pathological events


Paris, Masson (1965)
Fig. 3. — *Epilepsie bravais-jacksonienne gauche.*

Obs. Simone Le... : SEEG. Crise provoquée.

1, 2, 3, 4, 5, 6 : cortex central; 7, 8, 9, 10, 11 : capsule interne; 12 : EEG.
M. Antonietta, 16.06.1995, DBS/STN for Parkinson Disease
Responsive Neurostimulation Trial

This study is currently recruiting participant (2005-2010)

Patients with at least 4 seizures per month, > 18 yrs old

The RNS System Pivotal Clinical Investigation is a randomized, double-blind, sham stimulation controlled investigation. The double-blinded portion of the trial begins 28 days after the RNS is implanted and lasts about four months.

Half of the participants will be randomly assigned (by chance) to have responsive stimulation turned ON and half will have responsive stimulation turned OFF (sham-stimulation).
De novo and rescue DBS leads for refractory Tourette syndrome patients with severe comorbid OCD: a multiple case report.
Servello D, Sassi M, Brambilla A, Porta M, Haq I, Foote KD, Okun MS.

Deep brain stimulation in 18 patients with severe Gilles de la Tourette syndrome refractory to treatment: the surgery and stimulation.
Servello D, Porta M, Sassi M, Brambilla A, Robertson MM.
J Neurol Neurosurg Psychiatry. 2008 Feb;79(2):136-42

Thalamic deep brain stimulation for treatment-refractory Tourette syndrome: two-year outcome.
Porta M, Brambilla A, Cavanna AE, Servello D, Sassi M, Rickards H, Robertson MM.
Surgery of Epilepsy

The first team

- John Hughlings Jackson
  Neurologist

- David Ferrier
  Neurophysiologist

- Victor Horsley
  Neurosurgeon

25th May 1886
• Stimulation delivered to epileptogenic zone when the onset of ictal activity is detected
• Acute seizure interruption (on demand) rather than chronic alteration of cortical excitability

Problems: where in the brain the stimulus should be delivered and what type of stimulation would be most effective
Preparing the **ethical future** of deep brain stimulation.


- Important ethical and social challenges exist in the current and extending practice of DBS, notably in patient selection, informed consent, resource allocation, and in public understanding.
- These challenges are likely to be amplified if emerging uses of DBS in psychiatry are approved.
- A combination of approaches previously used in neuroethics, such as expert consensus workshops to establish ethical guidelines and public engagement to improve public understanding, may be fruitful to explore.
Closed Gate: $\alpha\beta$ fibres close the gate through inhibitory interneurons

Open Gate: C fibres block inhibitory interneurons and open the gate to nociceptive impulses
Elettrodo DBS nel lemnisco mediale (sindrome talamica)
(A. Paul, Freiburg, 21 Lug 78. Op.: F. Mundinger, M. Scerrati)