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# Preface

This supplement of Acta Neurochirurgica is the fourth in the series of proceedings covering the official biennial conferences of the Neurorehabilitation Committee of the World Federation of Neurosurgical Societies (WFNS) in connection with the 1st congress of the International Society of Reconstructive Neurosurgery (ISRN) which was held in Seoul in September 1–3, 2005. This supplement deals with various forms of neuromodulation and neurorehabilitation therapies in the field of stereotactic and functional neurosurgery. Recent advances in stereotactic and functional neurosurgery have opened up an important new area in which neurosurgeons can collaborate with basic neuroscientists, engineers, and other specialists from diverse fields such as rehabilitation, ENT, eye, orthopaedic surgery etc. I have no doubt that the authors assembled to address these topics have presented a balanced and up-to date analysis of the knowledge and approaches in this new era. Furthermore, I am confident that this supplement has been conceived to provide timely and pertinent reviews of clinically and neuroscientifically relevant topics for the practicing neurosurgeons in this field.

I would also like to express my sincere and cordial thanks to Professor Katayama and Professor Yamamoto for their heartfelt cooperation and guidance in the accomplishment of this supplement and for the successful meeting. I would also like to thank all the authors for submitting their original papers for inclusion into this 4th supplement. Finally, I wish to say a special word of thanks to Professor Steiger, the editor of Acta Neurochirurgica, for his support and aid in achieving this supplement.

*Jin Woo Chang*
Congress President
4th Scientific Meeting of the WFNS
Neurorehabilitation Committees
1st Congress of ISRN

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# Early rehabilitation of higher cortical brain functioning in neurosurgery, humanizing the restoration of human skills after acute brain lesions

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## Summary

*Objective.* Increasingly more patients after brain damage survive, however, suffering from severe impairments of higher cerebral functioning.

*Methods.* Patients after acute brain damage, mainly secondary to TBI, are referred for early neurosurgical rehabilitation. Our concept follows the German Guidelines. It is based on a multidisciplinary team approach. Next-of kin are included in the treatment and caring.

*Results.* The essential aspect of early neurosurgical rehabilitation is the integration of disciplines and consistent goal setting to regard individual patients' needs. Good structural organization of the team, notice of basic communication rules, conflict management and a definite decision making increase productive interdisciplinary working. The film (shown at the symposium) shows how to humanize human skills after brain damage.

*Discussion.* Obviously the impairment of mental-cognitive and neurobehavioral functioning and not the loss of physical skills cause the patients' loss of life transactions and final outcome after brain damage. Our concept supports and fosters the individuals' neural plasticity and final social reintegration.

*Conclusion.* Functional rehabilitation is a process whereby patients regain their former abilities or, if full recovery is not possible, achieve their optimum physical, mental, social and vocational capacity. Neurosurgeons will have to work in close collaboration with the neuropsychologist and all other members of the interdisciplinary team day by day.

*Keywords:* Concept of early rehabilitation in neurosurgery; traumatic and nontraumatic brain damage; restoration of neurological and mental-cognitive, neurobehavioral functioning; team work.

## Introduction

"Brain damage has become synonymous with loss of skills, while rehabilitation of brain damaged individuals has become known as method to restructure lives within a social context" as Anne-Lise Christensen (3 p XV) quotes.

Severe acute brain damage is a major ethical and social burden in the industrialized and in the emerging countries with regard to life-long disability, unnatural death, and the enormous social-economic costs. Most patients suffer from cranio cerebral injury (CCI) (mainly after accident and violence) and nontraumatic brain lesions secondary to stroke, intracranial subarachnoid and/or intracerebral hemorrhages, and tumours and increasingly secondary to cerebral hypoxemia and toxic insults [1, 2, 5–7, 9, 10, 15, 22, 25, 29, 30]. A head injury is often complicated by primary extracranial multiple organ lesions and early secondary complications requiring an interdisciplinary neurosurgical acute management and early rehabilitation. Advanced life support, intensive care treatment and emergency cranial computerized tomography (CCT) has enabled increasingly more patients to survive, in many cases, however, suffering from severe impairments of higher cerebral function [5, 10, 11, 14–16, 18, 23, 25, 28–30]. Mental neurobehavioral disability calls for a different degree of adjustment than does the need to cope with most physical disabilities [2, 3, 7, 9, 12, 15, 18, 25, 29]. This is why nowadays neurosurgeons have become more and more responsible to start off patient's holistic rehabilitation [2, 18], as it can be seen in the spectrum of neurorehabilitation (Fig. 1) [16, 29]. The author's concept with a specially designed department (Fig. 2) that is based on The German Task Force for Early Neurological Neurosurgical Rehabilitation (ENNR) and its Guidelines has been accepted and meanwhile followed in central Europe [16, 28]. ENNR is addressed: 1) to refer the patient as early as possible from the intensive-care unit (ICU) for ENNR in the same building and 2) to start the individually designed rehabilitative intervention very early on, 3) to promote functional recovery, brain plasticity, and compensation strategies [21], and 4) to prevent and treat frequent secondary and tertiary complications that keep the patient on the ward.

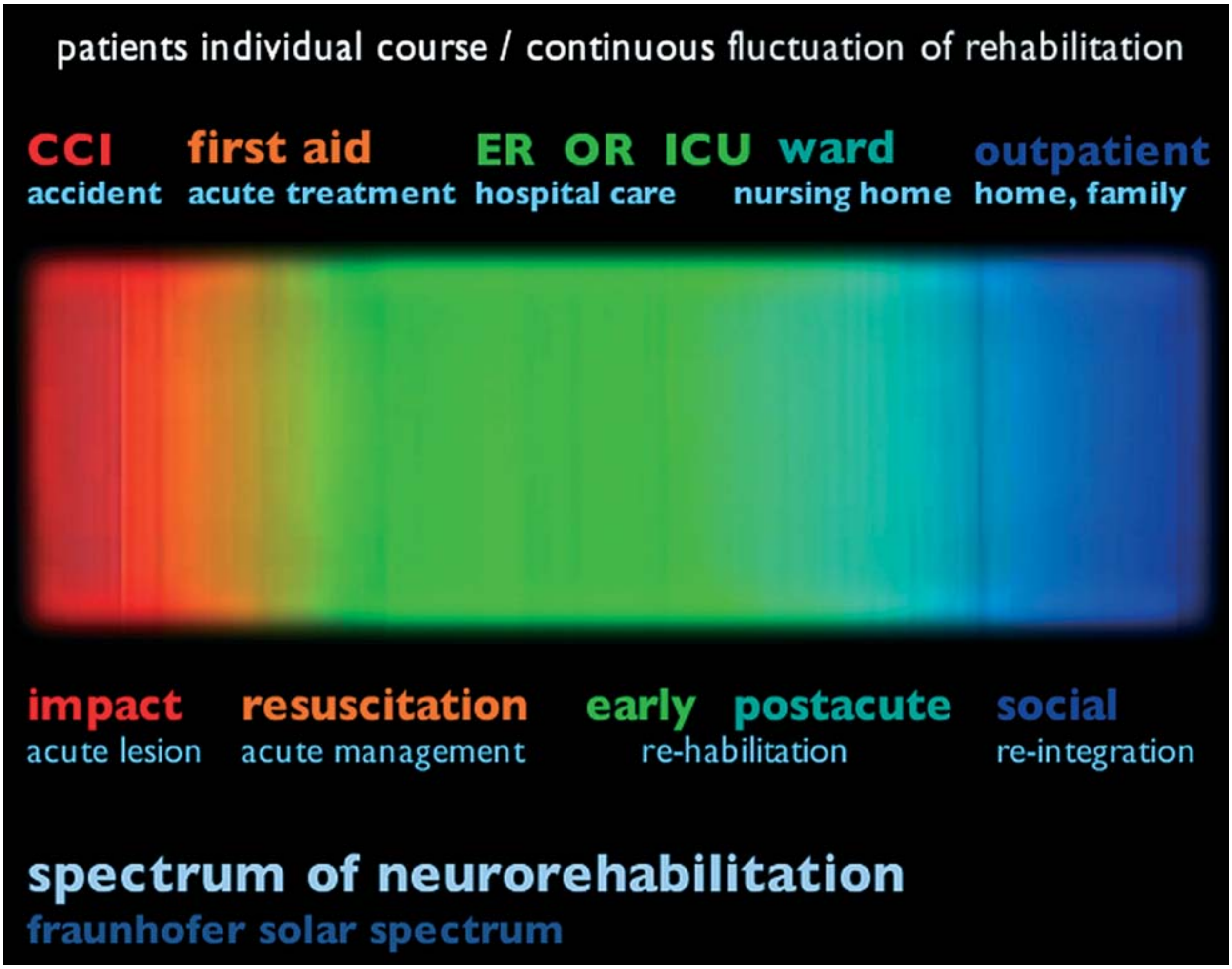


Fig. 1. Spectrum of neurorehabilitation. The patient's process of functional recovery can be seen in analogy to the solar spectrum with its colours and characteristic Fraunhofer lines. CCI patients show also typical landmarks of different phases of recovery over time. Spectrum of neurorehabilitation reflects the interventions for the complex process of holistic functional rehabilitation over time. Rehabilitation starts after the impact to the brain together with first aid and resuscitation at the site of the brain damage. Emergency management and critical care aims at brain protection via restoration and stabilization of ventilation and circulation to prevent secondary hypoxic episodes. Emergency surgery for thoracic, vascular or abdominal lesions go first if of vital importance before operable intracranial haematoma must be evacuated immediately. Intensive-care treatment aims at neuroprotection. This is why early rehabilitation starts at the ICU with assessment of functional impairments for further rehabilitation interventions. The victim is referred as soon as possible for ENNR (phase "B"), followed by subacute ("B, C") and long-lasting rehabilitation ("D") including vocational therapy targeted to reintegrate the victim into family, social life where he or she can enjoy social contacts, job, play, recreation and leisure time, mobility and fun

## Patients and methods

The concept of ENNR has been described in detail elsewhere [16, 28, 29]. ENNR interventions require more staff than any other form of rehabilitation [12]. Staffing requirements for 20 patients are calculated as follows: 1 (head) neurosurgeon, 1 (rehabilitation) doctor, and 2 ward assistants if not covered by the central neurosurgical services; 20 (intensive care) nurses, 1½ neuropsychologists, 2 speech and language, 2 physio- and 2 (massage) physical, 4 occupational, and 2 music therapists, 1 social worker, 1 secretary, 1 technical assistant (EEG, EVPs, TCMS, EMG, Doppler, Near-infrared diagnostics) [14, 16, 27, 29]. The classic triad of physical therapy, physiotherapy, and occupational therapy constitute the undisputed basis for motor rehabilitation [8]. Neuropsychological, mental-cognitive, language-speech, and music therapy are becoming ever more critical factors for the patient's final outcome [3, 12]. Social services have the task of psychosocial counselling in economic problems. Electrophysiological diagnostics help to assess impairments (cerebral coma, prolonged unawareness, and minimal consciousness, silent epileptic fits, and recovery of cortical functioning including pharmacological studies [6, 16, 17, 27, 28].

## Results

Patients referred for early neurosurgical rehabilitation are those with complex impairments of sensorimotor functioning and/or mental-cognitive, neurobehavioural impairments. Their level of awareness might vary between a certain "cloudiness" to severe states of unconsciousness, Apallic Syndrome (AS/VS) (full stage or early remission stage), and coma [9, 22, 26, 27, 29].

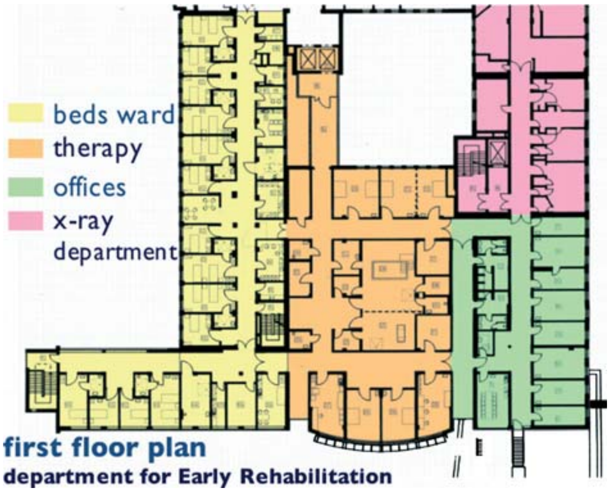


Fig. 2. The authors' specially designed department for ENNR at Clemenshospital. L-shaped ground plan of the ENNR department as part of the neurosurgical clinic where all rooms are located on the first floor (1200 sqm) and connected by short access. Offices to the north, next to the X-ray department, and bed-rooms (single and twin beds, cardiology intensive care style) to the south-east. All necessary therapeutic and diagnostic facilities in the middle next to patients' rooms and two elevators and two staircases

The basic work is done by intensive-care nursing staff [16, 29]. Activating nursing is the fundamental form of therapy in neurosurgical early rehabilitation. Independently from the stage of consciousness and awareness caring procedures and all therapy stages are explained to the patient. With the help of basal stimulation by touching and posturing, the patient's perception of his body and motions in connection with personal hygiene and when being dressed is enhanced in the sense of active daily-living (ADL) training [13, 20, 24, 26]. These measures include the changing of wound dressings, and the laying of gastric tubes, suprapubic urinal catheters, and tracheostoma. Reposturing helps reduce spasticity and enhance the patient's self awareness and sense of his own body, at the same time promoting local blood circulation. Pressure sores and pathological ossifications of the major joints can definitely be prevented by these measures. The rehabilitation management of posturing includes multiple modalities, such as positioning techniques and bringing the patient in an upright and/or a standing position influence arousal reactions and are a highly intensive central acting stimulus. All activities and observations are dutifully documented.

*Physical therapy*

Body massage is part of classical physical therapy, focussed on relaxing and softening tense muscles of the body and limbs and at the same time stimulating sensorial perception. Locally it increases the blood supply to the cutaneous tissue and prevents pressure sores. The risk of local thrombosis is diminished because of supporting the venous blood backflow. Physical therapy aims at finding strategies to overcome sensory motor impairments.

Tremor, clonus, myoclonic and dystonic crises are clinical signs of specific functional lesions of the cortex and subcortical structures of the brain stem and cerebellum. Brain damage is frequently associated with an increased muscle tone and resultant spasticity and rigidity [8]. Because of his consciousness impairments, the anxious patient might be agitated. Daily warm baths will help the patient to relax and to decrease spastic movement disorders. Without any additional medication spasticity decreases, and the patient will become relaxed, aroused, and positively motivated for the rest of the day. Therapies in the swimming pool are an enormous help in stabilizing the patients' body control and in enabling him to stand and to walk again using the water lift. One will notice here the enjoyment the individual patient derives from personal attention of the physiotherapist.

*Physiotherapy*

The assessment of impairments of the musculoskeletal system by the doctors and physiotherapists examines the aspects: Is the muscle spastic to passive extension? Does the muscle show increased stiffness when stretched? Does the muscle have fixed shortening? Careful treatment depends on clinical patterns of motor dysfunction in order to identify the best method of treating functional problems as there are: the flexed hip, scissoring thighs, stiff knees, equinovarus foot, bent elbow, pronated forearm, bent wrist, clenched fist, thumb-in-palm deformity. In addition, pharmacological reduction of spasticity can be achieved by local injections of phenol for peripheral nerve blocks and today by the local application of Botulinum toxin, which inhibits the release of actetylcholine causing flaccid paralysis. Both techniques are helpful adjuncts for standard use of casting [15, 16]. Sometimes long-bone and pelvic fractures that are stabilized with the aid of a fixateur externe after polytrauma might hinder nursing, activities of daily living (ADL) [24, 26], physical- and physiotherapeutic interventions [8].

*Occupational therapy [16, 19, 24, 29]*

Person-to-person devotion is of utmost importance. The daily exercise of practical day-to-day life habits and activities (ADL) helps the patient to regain a sense of self and to cope with his environment. Functional problems after brain damage are typically caused by spastic phenomena embedded within the impaired selective motor control. Patients in coma or with a minimal responsiveness status manifest rigidity as decerebrate or decorticate posturing. Motor control may be affected at many different functional levels, so that patients present with spasticity and abnormal extension or flexion positioning of the limbs. The purpose of posturing patients in an upright sitting position when emerging from coma or apallic syndrome is to enhance vigilance and cognition by stimulating the ascending system of the reticular formation. The unconscious patient is first treated and mobilized with the aid of a tilting bed for standing. Continuous monitoring of vital signs – for instance systemic blood pressure, heart rate, and cerebral blood perfusion – with the aid of transcutaneous near infrared spectroscopy are helpful [29]. Sitting in an upright position is a strong central stimulus that helps to establish new proprioceptive inputs and to reorganize the vestibular and the central blood-pressure control systems. ADL is performed by occupational therapists in cooperation with nurses, physiotherapists and speech therapists, depending on the nature and severity of the functional impairments involved. The physiological posturing of the patient also plays an important role here. Putting the patient into a standing apparatus for 10–15 minutes helps him to reorganize and to actively train the subcortical autonomous centres for blood pressure, respiration, and heart rate. The benefit of upright positioning is the stimulation of arousal and cognition, and hence the coordination of central motor cortical functions and frontal brain activities. Therefore we check sitting and standing of the patient for assessment of behaviour and cognition with the aid of our CRS [22, 28].

Occupational Snoezel therapy is new and stands for a combined multisensorial stimulation therapy within a special environment [29]. Snoezel helps to arouse and to calm down agitated patients, with the patient himself positioned on a water bed and held tight in the arms of the therapist to feel and to enjoy the physical nearness and warmth. Snoezel aims at the stimulation and treatment of perception disorders: the stimuli applied are tactile, proprioceptive, vestibulary, visual-acoustic, gustatory, and olfactory [12, 13].

### *Music therapy*

Music therapy is based on a neuroscience model of music perception and production and the influence of music on functional changes of emotions and perception in the brain with influence on behaviour functions to neurological disease of the human nervous system [29].

The music therapist aims at reaching the awareness of the patient that cannot be accessed through verbal communication. The music therapist improvises vocally to the breathing of the patient reflecting changes in intensity, tempo, and dynamics. This offers the patient a unique possibility to express his individual self in an expressive musical form. Music therapy on a two-patient basis and in small groups enhances personal and social integration following individuals' isolation and social withdrawal. Recovery of awareness and cognition over time can exemplarily be shown in comatose and apallic patients during recovery.

### *Neuropsychological therapy*

Neuropsychological therapy has become key therapy in ENNR as mental disabilities are both more persistent and constitute a greater handicap than focal neurological signs [2, 3, 12, 16, 18, 29]. Practically all patients after brain damage suffer from impairments of higher integrated cerebral functions. Most of the patients have impairments in alertness and vigilance, problems with memory and learning, and difficulties with abstract reasoning and flexible problem solving. Their capacity to perceive the meaning of ongoing interactions objectively is diminished. In following the treatment concepts of Christensen and Uzzell [3] and Prigatano [18] neuropsychological therapy during early rehabilitation is mainly based on a phenomenological approach [12]. The significance of symptoms and signs can be understood only in the context of the functional system. There is no specific treatment of neglect syndrome, for example secondary to intracranial haemorrhage with left-sided hemiparesis, but general psychological motivation and ease of mind improve over time. The functional system in the brain consists of a number of parts, each being very specific, particularly the cortical one. A preliminary conversation provides information regarding the history, general state, and particular aspects of the patient's mental activity. So we try to provide feedback and to gauge progress and development and, as demonstrated during the treatment of an aphasic patient after ICB, by lending support and modifying the ambient conditions it is possible to encourage the patient when we try to guide his attempts and compensation. Functional training with the aid of personal-computer programmes may be indicated at a certain stage of progress in the restoration of cognition. Self-assessment and feedback is part of the emotional interaction during psychological treatment. Computer training has become an additional adjunct [12].

*Social services*

Our social worker turned out to be the main connecting link between the patient's family and hospital affairs complementary to the neuropsychologist, trying to achieve a good quality of life for the patient and the relatives after discharge from hospital.

Brain damage is a family affair [3]. Relatives, therefore, are touched emotionally and socially. They cannot come to terms with the catastrophic situation and are worried about the future. They insist on knowing more about the chance of survival and the functional prognosis. The senior physician informs the family about the functional impairments, risks, and complications, and goes on to explain the design of our therapeutic concept on the basis of careful clinical and psychological assessment. The near and dear become partners of the multidisciplinary team approach for functional recovery and they are included in the daily rehabilitative measures, thus learning how to approach and how to cope with the new situation. The next-of-kin know best the personal structure of the patient from the time before the event, a feature that is prerequisite for individual treatment, and they usually make more detailed observations than do the clinic staff so that they often are the first to register when the comatose patient regains conscious reactions. The next-of-kin are trusted by the patient and especially in the early stage they can help to calm the disoriented and confused patient, thus helping to avoid or reduce vegetative disregulation and while accompanying frightened patients to their therapy sessions they can assist in the stimulation process by taking care of various everyday life activities. The team respects the patient's cultural, religious, and social-economic background. The neuropsychologist and social worker assist here, too, since they are aware of the patient's functional impairment and social background. "In the beginning, 6 weeks after the traffic accident, the doctors told me that it could be that my daughter Heike, who was in a full stage of apallic syndrome, might be discharged home functionally unchanged if she survived at all, despite all intensive rehabilitation measures that would be taken over the following twelve months. However, they all gave me hope and I was kept informed about her situation at all times!" patient Heike's father quotes.

*Daily visits*

The object of the daily visits is to check the state of the patient's health, documenting the functional impairments as well as any improvements in his condition [12, 16, 17, 29]. Even the slightest clinical changes in awareness and motor functions can indicate the progressive recovery of the patient or else an imminent secondary complication, generally involving the respiratory system or of an intestinal, urological, or neurosurgical nature. Intracranial mass lesions and hydrocephalus cause typical neurological and mental-cognitive impairments.

*Complications*

Respiratory complications and bronchopneumonia are frequent due to swallowing disorders and silent aspiration [6]. The incidence of dysphagia after severe brain damage secondary to TBI and stroke is in the region of 30% [19]. The majority suffer from delayed or totally absent of swallowing responses, with approximately one half showing reduced tongue control and about one-third having reduced pharyngeal transit times and the rest a reduced laryngeal closure, elevation, or spasms. Treatment efforts focus on compensation mechanisms. Video fluoroscopy has become the gold standard for evaluating patients for dysphagia. This method enables the operator to observe the anatomy and physiology of the swallowing mechanism after the bolus administration of barium-impregnated liquid on its way to the oesophagus. The vast majority of patients improve spontaneously [19].

The hospital's X-ray department is next to the ENNR unit (Fig. 2) which is necessary because of frequently required plain films and special radiological diagnostics. Computerized cranial tomography (CCT) has become the gold standard as an imaging diagnostic procedure. Thin-section tomography, vascular imaging, and spinal CT with bone fenestration reveal potential pathological symptoms in the brain, vascular system, ventricular system, and bone structures, also in the region of the base of the cranium. Magnetic resonance tomography (MRT) follow-up studies of the damaged brain allow prognostic prediction [27, 29].

Exclusion criteria for ENNR: All patients with acute brain lesions and suffering from neurological and/or mental cognitive impairments of higher cerebral functioning are eligible for referral to an ENNR department provided they are no longer on the ventilator, sufficiently stable in terms of circulation and breathing, without increased intracranial pressure, and not suffering from severe infection or progressive malignancy nor from progressive cerebral diseases such as M. Alzheimer or Chorea Huntington. All team members meet in weekly rounds to discuss and assess the patients' individual status. Diagnostic findings are presented with comments on the charts. The performance of sensory motor and cognitive-psychological recovery of functioning is assessed by all team members who are in charge of the patient over weeks and months.

### *Cut-off points*

The functional impairment and fluctuation is best mirrored with the aid of the coma remission scale score. A score of 24 points on the 24 points CRS [16, 28, 29] in conjunction with ERBI $> +40$ points [20] constitute the cut-off criterion.

No patient with less than 20 points on day 40 reached a functional outcome of the Glasgow outcome scale score 4 or 5, no patient with fewer than 10 points emerged from apallic syndrome within one year.

Time interval (see Table 1) between head injury and the start of neurorehabilitation was less than one month for 175 TBI (= 67.2%) and one to three months for 60 patients while average time of stay for ENNR "B" was 58 days (1–366 days) and for postacute "C" 41 days (2–300 days) respectively according to the prospectively controlled study on TBI management in Germany [29].

Functional outcome [7, 29] and quality of life [25] (Fig. 1) after some years of two of our patients which is in accordance with the results obtained in the prospective study of 6800 acute TBI [29] confirm our concept for ENNR exemplarily. Case 1: Three years ago a young lady, a student of chemistry, experienced a severe CCI of the GCS 3 category followed by an apallic syndrome lasting over nine months. Now she lives on her own in a specially equipped environment for handicapped people.

Table 1. *Time interval and frequency of TBI patients admittance for ENNR (N = 100)*

| Interval/ days | MS | MS and other hospitals | H | Other hospitals | *N* | (%) |
|---|---|---|---|---|---|---|
| 1–7 | 16 | 2 | 0 | 1 | 19 | 19.0 |
| 8–14 | 9 | 4 | 2 | 2 | 17 | 17.0 |
| 15–21 | 15 | 3 | 5 | 2 | 25 | 25.0 |
| 22–30 | 7 | 3 | 4 | 7 | 21 | 21.0 |
| 30–90 | 5 | 0 | 5 | 7 | 17 | 17.0 |
| 91–180 | 0 | 0 | 0 | 1 | 1 | 1.0 |
| Patients (%) | 52 | 12 | 16 | 20 | 100 | 100.0 |

Time interval between acute brain damage in respect to the primary hospital that referred the TBI patient for ENNR. MS = same (author's) hospital as neurosurgical rehab unit, MS and other hospitals include second neurosurgical department Münster without unit for ENNR and other hospitals in the Münster area; *H* admission from two neurosurgical departments of Hannover area, other hospitals = rest of hospitals of the Hannover region. Data from the prospective study on quality management of TBI in Hannover and Münster regions 2000/2.

Her beloved best friend is her horse from earlier times, when she went for competitions. Three times a week she goes for horseback riding. Her teacher said that she has constantly improved her sensorimotor, vestibular, and cognitive behavioural functioning. Case 2: Two years ago, one gentleman was twice virtually dead because of severe brainstem haemorrhage. He was in coma and mechanically ventilated for two weeks, gradually making a slow recovery during early rehabilitation two years before. Now back at his normal environment again, he enjoys his family, home, horses, leisure time, and the beautiful landscape. He enjoys his social reintegration and visits his factory twice a week. A young male nurse takes care of his active daily living and has become his chauffeur for the new Daimler. Although partly disabled, this man and his family are entirely happy with the functional result and his mobility.

## Discussion

In Germany roughly 6000 people die as a consequence of traffic accidents each year, 2500 as a direct result of traumatic brain injury. Year by year, 260,000 patients are admitted to German hospitals for the treatment of traumatic brain injury (TBI). Of this total, about 5% suffer from the severest forms, 10–15% from a more moderate form, and most patients from so-called mild TBI. Stroke shows exactly the same incidence of 320 per 100,000 population. In respect to the consequences of the severest form of brain damage the prevalence of an Apallic Syndrome (AS)/VS secondary to traumatic and nontraumatic brain lesions, as reported in the international literature, ranges widely, for Europe 0.5 to 2.0/100,000 population. Recently Stepan *et al.* reported objective figures of 1.7 per 100,000 population for Vienna, the capital of Austria, with 1,620,170 population at the time of analysis (Nov. 2003) which are based on their personal examination of patients with AS and expertise in AS diagnostics and treatment [22]. Recovery from AS is defined as the ability to establish visual or verbal contact with the outside world. The AS recovery rate is reported to be mainly dependent on age when children do better (about 70%) than adults (45–50%) and on the primary impact to the brain when patients with cerebral hypoxemia secondary to cardiac arrest, strangle, and near-drowning or hypoglycaemic intoxication after resuscitation do worst. Most patients who regained consciousness did so in the first 3 months. After one year only some few of the AS patients may achieve some minimal responsiveness and early stage of functional recovery or they remain in AS full stage. Techniques of FES (functional electrical stimulation) are not yet routinely applied in our department, although there is clear evidence of safety and effectiveness as reported by Kanno for his dorsal column spinal cord stimulation (DCS) [10, 11, 14], by Tsubokawa *et al.* for deep-brain stimulation [23, 30], and for Edwin B Cooper's right median nerve electrical stimulation [4] to hasten awaking from coma and AS/VS.

Functioning in the sense of WHO-ICF is an umbrella term encompassing all body functions, activities and participation taking into account all the physical, neurological and mental-cognitive impairments. Quality of life (QoL) [1] is accordingly mirrored by the impairments that refer to loss of structures and functions, while disabilities refer to limitations or participating restrictions (Fig. 1) [25]. Our data on the epidemiology and quality management of ENNR [29] met the criteria set in 1993 [12, 16, 28]. Management of frequent multiple organ lesions and complications (= 57%) without referring the patient to another hospital [5, 6, 29] and early functional outcome [7, 25, 29] confirm the authors' concept of neurosurgical early rehabilitation.

## Aknowledgement

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## Addendum

### Coma Remission Scale (CRS)

*GERMAN TASK FORCE ON*

Neurological-Neurosurgical
Early Rehabilitation 1993 [28]

**Patient name:**

| | |
|---|---|
| **Date:** | |
| **Investigator** (initials): | |

**1. Arousability/attention** (to any stimulus)

| | | |
|---|---|---|
| Attention span for 1 minute or longer | 5 | |
| Attention remains on stimulus (longer than 5 sec) | 4 | |
| Turning towards a stimulus | 3 | |
| Spontaneous eye opening | 2 | |
| Eye opening in response to pain | 1 | |
| None | 0 | |

**2. Motoric response** (minus 6 points from max. attainable sum if tetraplegic)

| | | |
|---|---|---|
| Spontaneous grasping (also from prone position) | 6 | |
| Localized movement in response to pain | 5 | |
| Body posture recognizable | 4 | |
| Unspecific movement in response to pain (vegetative or spastic pattern) | 3 | |
| Flexion in response to pain | 2 | |
| Extension in response to pain | 1 | |
| None | 0 | |

**3. Response to acoustic stimuli (e.g. clicker)** (minus 3 points from max. attainable sum if deaf)

| | | |
|---|---|---|
| Recognizes a well-acquainted voice, music, etc. | 3 | |
| Eye opening, turning of head, perhaps smiling | 2 | |
| Vegetative reaction (startle) | 1 | |
| None | 0 | |

**4. Response to visual stimuli** (minus 4 points from max. attainable sum if blind)

| | | |
|---|---|---|
| Recognizes pictures, persons, objects | 4 | |
| Follows pictures, persons, objects | 3 | |
| Fixates on pictures, persons, objects | 2 | |
| Occasional, random eye movements | 1 | |
| None | 0 | |

**5. Response to tactile stimuli**

| | | |
|---|---|---|
| **Recognizes by touching/feeling** | 3 | |
| Spontaneous, targeted grasping (if blind), albeit without comprehension of sense | 2 | |
| Only vegetative response to passive touching | 1 | |
| None | 0 | |

**6. Speech motor (logomotor) response** (tracheostoma = 3 if lips can be heard to utter guttural sounds/seen to mime "letters")

| | | |
|---|---|---|
| At least one understandably articulated word | 3 | |
| Unintelligible (unarticulated) sounds | 2 | |
| Groaning, screaming, coughing (emotional, vegetatively tinged) | 1 | |
| No phonetics/articulation audible/recognizable | 0 | |

| | | |
|---|---|---|
| **Sum score:** | | |
| Max. Attainable score (of 24) for this patient | | |

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# Involuntary movement disorders

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# Deep brain stimulation as a functional scalpel

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## Summary

Since 1995, at the Istituto Nazionale Neurologico "Carlo Besta" in Milan (INNCB,) 401 deep brain electrodes were implanted to treat several drug-resistant neurological syndromes (Fig. 1). More than 200 patients are still available for follow-up and therapeutical considerations. In this paper our experience is reviewed and pioneered fields are highlighted.

The reported series of patients extends the use of deep brain stimulation beyond the field of Parkinson's disease to new fields such as cluster headache, disruptive behaviour, SUNCt, epilepsy and tardive dystonia.

The low complication rate, the reversibility of the procedure and the available image guided surgery tools will further increase the therapeutic applications of DBS. New therapeutical applications are expected for this functional scalpel.

*Keywords:* Deep brain stimulation; movement disorder; chronic pain; dystonia; Parkinson's disease.

## Introduction

At the beginning of the century stereotactic neurosurgery was used on animals for experimental purpose with the aim of mapping the brain's electrical activity and functional responses. The mapping process was followed by the development of surgery that was capable of changing function of brain, through small lesions in a "key" area. In the nineties, deep brain stimulation (DBS), after its optimization by Benabid [2–5], for the control of parkinsonian tremor gained worldwide the role of a promising therapeutical tool. The administration of high frequency and low amplitude electric stimulation, allows the modulation of neuronal activity in a reversible way: the parameter of stimulation can be adapted according to the clinical response. Nevertheless the way DBS works is still unclear. More experimental data are required to understand whether the interaction with the neurological functions is obtained through the inhibition or the activation of cellular activity which modulates the output of specific neural networks. There is interest, moreover, to investigate new targets in order to find new therapeutical applications to approach otherwise untreatable diseases. The development of computer-based workstations allows the use of multimodality image sets for the surgical planning, while neuroimaging provides a functional scalpel and a powerful research tool in the hand of the neurosurgeon. Since 1995 at Istituto Nazionale Neurologico "Carlo Besta" in Milan (INNCB), 401 deep brain electrodes were implanted to treat several drug-resistant neurological syndromes (Fig. 1). More than 200 patients are still available for follow-up and therapeutical considerations. In this paper our experience is reviewed and pioneered fields are highlighted.

## Patients and methods

### *Movement disorders*

Parkinson's disease: The long term results of 85 parkinsonian patients submitted to bilateral stereotactically guided implant of electrodes into the subthalamic nucleus (STN) are available. Mean age $55.7 \pm 7.7$ yrs, duration of the disease $11.9 \pm 4.2$ yrs, follow-up $25.4 \pm 16.7$ yrs. UPDRS motor score were of $55.1 \pm 14.8$ in off-drug and $19.0 \pm 11.0$ in on-drug.

The present series extends to the long-term observation (FU$>$12 months) of our previous follow-up [6, 7]. Eight more patients affected by dopa-related diskinesias underwent Gpi neurostimulation.

Tremor: twelve patients underwent Voa-Vop-Zi high frequency stimulation (HFS). Four patients were affected by multiple sclerosis (MS), three patients by posttraumatic tremor, and five patients Parkinsonian tremor. Four patients affected by essential familial tremor, underwent Vim (HFS).

Dystonia: twenty-eight dystonic patients underwent Gpi HFS. This series include patients affected by primary dystonia DYT 1−, DYT 1+ (only one patient) and symptomatic dystonia (including three cases of drug induced tardive dystonia). Onset of symptoms ranged between

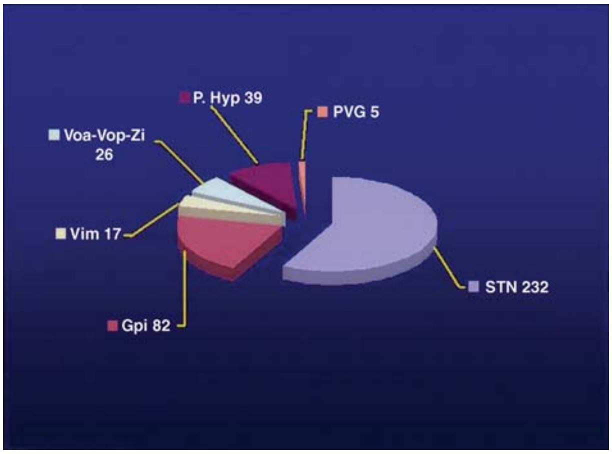


Fig. 1. Graphic representation of the whole series of deep brain electrodes implanted since 1995 at the neurological institute "C. Besta", Milan (*stn* subthalamic nucleus, *GPi* globus pallio pars interna, *Vim* ventralis intermediate nucleus, *Voa-Vop-Zi* ventral oralis ventral posterior and zona incerta, *P. Hyp* posterior hypothalamus, *PVG* periventricular grey)

2 and 50 years of age. Duration of the disease at the time of surgery ranged between 4 and 30 years. Preoperative and postoperative evaluation included video recording and assessment of dystonia with Burke-Fahn-Marsden Dystonia Rating Scales (BMFDRS).

*Chronic pain*

Posterior medial hypothalamic stimulation has been performed in 16 patients with chronic Cluster Headache (CH), one patient with short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), and three patients with neurogenic facial pain.

*Disruptive behaviour*

Posterior medial hypothalamic stimulation has been performed in two patients with major psychorganic diseases and disruptive behaviors, all patients were institutionalized and required continuous sedation.

*Epilepsy*

Chronic stimulation of the posteromedial portion of the substantia nigra has been performed in one young female (age 26) suffering from disabling posttraumatic drug resistant partial motor seizures (more than 100 seizures per month).

## Surgical technique

Today different imaging modalities are available to calculate the target position coordinates by direct visualization of anatomical structures and by indirect calculations based on the commissural reference system. Even if the approach to planned target is more accurate than several years ago, many factors may lead to an error in the final position of the electrode (e.g. MRI distortion and individual variability). So microrecording of neuronal activity and micro-macrostimulation is still helpful. The introduction of this peroperative neurophysiological investigation has improved the safety and accuracy of functional neurosurgical procedures.

The day before surgery we perform accurate planning by imaging. MRI (T1 and fast spin echo inversion recovery sequences with double dose of contrast-agent) is used to obtain high definition anatomical images of the intercommissural plane, allowing the calculation of the midcommissural point coordinates. MR images are merged with computed tomography (CT) images obtained stereotactically (CRW or Leksell frame) through a dedicated workstation (Stealth Station Treon SofamorDanek, Medtronic Inc. Minneapolis/US). The stereotactic coordinates of the chosen target are obtained within the virtually built 3D space enriched by vessels enhancement. The planning of the target is refined comparing the results obtained by the workstation with a dedicated software developed at our Institute (Virtualventriculography, Solaris), which is a self learning atlas based on the statistical analysis of previous implants. In this way the targeting procedures may take advantages from a probabilistic functional stereotactic atlas (Fig. 3).

a

| **GPi** | x | ±19 |
|---|---|---|
| | y | 2 |
| | z | -6 |

b

| **STN** | x | ±12 |
|---|---|---|
| | y | -4 |
| | z | -4 |

c

| **Zi** | x | ±15 |
|---|---|---|
| | y | -7 |
| | z | -4 |

d

| **SN** | x | ±10 |
|---|---|---|
| | y | -7 |
| | z | -6 |

e

| **Hypothalamus** | x | 2 |
|---|---|---|
| | y | -3 |
| | z | -5 |

Fig. 2. Target coordinates registered to the AC-PC midpoint: (a) Dystonia; (b) Parkinson's disease; (c) tremor; (d) epilepsy; (e) cluster headache and aggressive behaviour

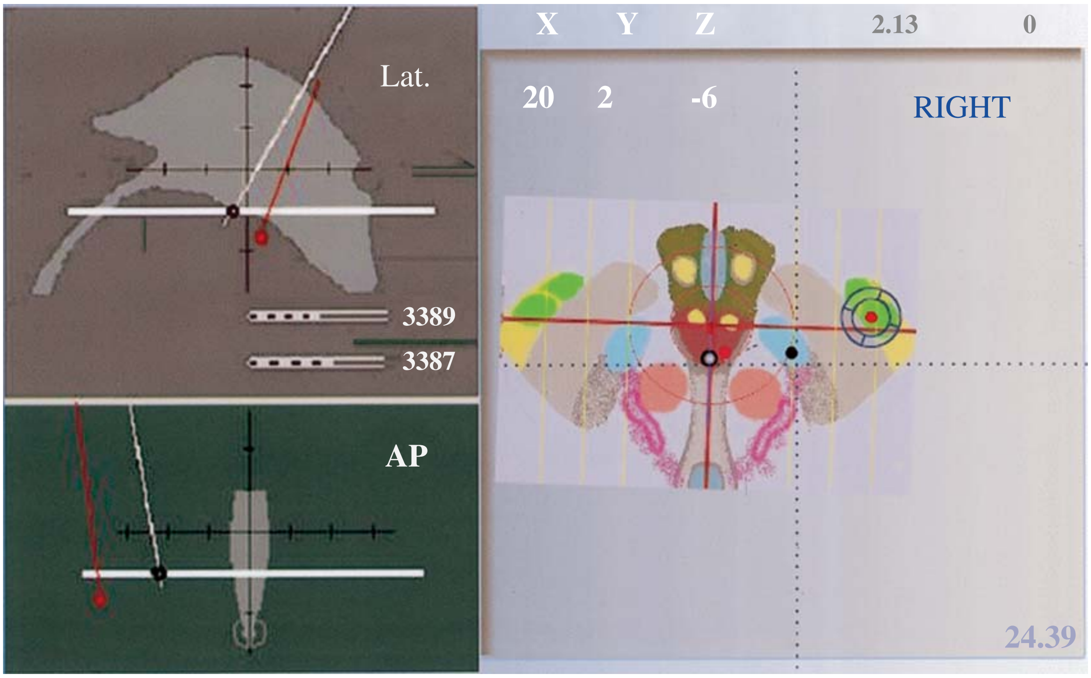


Fig. 3. Snapshot of the virtual ventriculography program (Wandor software, Dolgo, PC, Italy) showing the plate 6 mm below the commissural plane. The trajectories to the GPi (red) and STN (black) nuclei are represented on the ventricles AP and lateral profile. Targets are represented on the corresponding axial section (green: GPi, yellow: optic tract, cyan: STN, dark dotted grey: substantia nigra, pale grey: internal capsula, pink red nucleus, dotted violet: sensory lemniscal fibres)

Most of the procedures have been performed through a 7 mm precoronaric paramedian burr hole. Microrecording is used for the neurophysiological confirmation of the target in Parkinson's disease. Micro and/or macrostimulation has been performed in all procedures to rule out the adverse effects induced by electrical current delivered at therapeutical levels.

All the procedures were conducted in local anaesthesia except for generalized dystonia where general anaesthesia without curarization was preferred. Patients in general anaesthesia underwent only macrostimulation to establish the motor threshold avoiding implants too close to the internal capsule.

The individual variability of the target along the anteroposterior axis due to the high individual variability of the midbrain angle is considered and corrected in all the procedures below the commissural plane. In these cases a third point 8 mm below the commissural plane is considered to correct the AC-PC registered system. To verify the position of the electrode, CT was always performed after stereotactic surgery but before the pulse

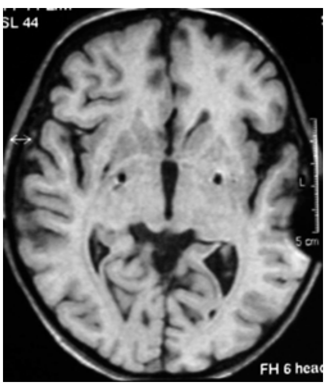


Fig. 4. Postoperative MRI merged with the preoperative MRI planning showing electrode position (T1 weighted images)

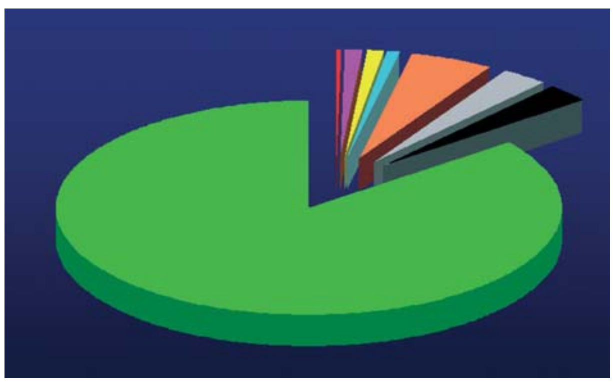

Fig. 5. Graphic representation of the complications (red: hemorrhage; violet: permanent neurological deficits, yellow: transient neurological deficits, cyan: postoperative seizures, brown: hardware removal, grey: hardware failure, black: electrodes migration, green: no complications)

generator was placed. This examem is merged with the preoperative planning in order to verify the electrode position [11] (Fig. 4).

## Results

### *Movement disorders*

Parkinson's disease: At a follow-up of $25.4 \pm 16.7$ months UPDRS in off-drug with stimulation is $26.4 \pm 11.7$, while in on-drug with stimulation is $15.4 \pm 9.1$. The variation off/off+ stimulation is $-52.1\%$ and variation on/on + stimulation is $-19.1\%$.

Dystonia: All patients showed a clinical improvement, as evaluated by the BMFDRS scales, that ranged between 27 and 88%. The improvement was progressive over a period of 3–6 months after surgery, and persisted during the follow-up (4–48 months). Our results demonstrate that DBS is an effective treatment for dystonia, with no remarkable side effects, even in childhood. In tardive dystonia the results are higher than 90% with immediate effects.

Tremor: All patients regained autonomous self feeding and personal care at 12–36 months follow-up with continuous high frequency stimulation. All Vim, Voa-Vop-Zi targets showed efficacious results but the latter allowed a better control of the ataxic component.

### *Chronic pain*

Cluster headache: At four years follow-up the percentage of the total number of days free from pain attacks improved from up to 78% and 10 patients of this series had a complete and persistent pain-free state.

SUNCT: At 18 months follow-up the patient had complete pain relief.

Neurogenic facial pain: Neurostimulation procedure was absolutely unsuccessful.

### *Disruptive behaviour*

Stable improvement with a 12 months follow-up was obtained and a marked reduction in sedative drugs was achieved allowing us to stop the contentive hospital procedures.

### *Epilepsy*

At 15 months follow-up the only operated patient reported a 60% dramatic reduction of seizures.

## Complications

Massive brain haemorrhage occurred in one case of STN implant (0.4%); permanent neurological deficits due to deep haemorrhage occurred in four patients of which one was a Vim implant and the other STN implants (1%). Transient neurological deficits due to deep haemorrhage occurred in five patients (1.2%); postoperative seizures occurred in three patients (0.7%); hardware removal due to infection occurred in twenty-two cases (5.4%) one of which had cerebral abscess at the origin of the stereotactic trajectory; hardware failure occurred in twelve patients (2.9%); late electrode migration occurred in twelve patients (2.9%) of which eight were under fourteen years old.

Risk rate is referred to single electrode implant surgery, patients who need more than one electrode implant may expect a higher risk rate.

## Discussion

### *Movement disorders*

Parkinson's disease: As far as the field of movement disorders is concerned, advanced Parkinson's disease remains the main indication for DBS. Drug treatment of parkinsonian symptoms unfortunately cannot avoid disability in an advanced course of disease since long-term levodopa therapy often results in invalidating motor fluctuations and dyskinesias. In the 1980s, the side effects and limits of chronic L-dopa therapy became obvious and led to reintroduction of the surgical treatment of motor symptoms in Parkinson's disease (PD). Advances in stereotactic surgery, neuroimaging [15, 16], electrophysiologic recordings and the possibility to obtain therapeutic responses by high-frequency deep brain stimulation (DBS) have renewed interest in the surgical treatment of PD. During the last 10 years, several groups have demonstrated that chronic DBS of the VIM, subthalamic nucleus (STN), or globus pallidus internus is an effective treatment for disabling pharmacotherapy-resistant motor symptoms (tremor, rigidity, bradykinesia) in PD. Increasingly evidence in favour of the subthalamic nucleus (STN) as the target of choice has been collected [4–6]. The experimental data in MPTP monkeys along with clinical results in human PD patients after both STN lesion or high frequency stimulation, point toward a major role of STN hyperactivity in the pathophysiology of PD. Deep brain stimulation seems to produce a functional inhibition of the neurons in the targeted structure that mimics the result of lesioning. The main advantage of this procedure versus lesioning is related to the reversibility and adjustability of its effects without any cerebral permanent damage. The parameters of stimulation can be changed to increase efficacy or to reduce side effects. In the future a more oriented choice between the available targets (Vim-Zi-STN-Gpi-CM) will further improve clinical outcome.

Dystonia: Dystonia is a neurological syndrome characterized by abnormal postures and involuntary movements.

The physiopathologic basis of dystonia has not yet been completely clarified, however, the cortical-subcortical network and the globus pallidus internus (Gpi) are the structures primarily involved. Pharmacological treatment of dystonia is sometimes disappointing.

The practice of lesioning in dystonic patients was very common in the 1950s and 1960s, since at that time it was essentially the only available treatment for severe cases. These procedures, performed 50 years ago, were reported to have results not always satisfying, sometimes with severe side effects. By the 1980s, brain surgery for dystonia was abandoned. However, the increased understanding of the pathophysiology of movement disorders and the availability of DBS technology led to a resurgence of interest in the surgical treatment of dystonia; with globus pallidus internus (GPi) still the favourite target [9, 13, 21]. The timing of clinical improvement observed in dystonia is different from that observed in Parkinson's disease. In fact, days, weeks and most often months are required and, moreover, the improvement continues for years, suggesting a phenomenon of neuronal plasticity rather than a simple transitory functional inhibition of a pool of neurons.

Tardive dystonia (TDt) affects about 15% of patients treated by long term neuroleptics therapy and has the potential of becoming irreversible and untreatable in 1–4% of these patients. According to results from literature, when drug therapy is ineffective, thalamotomy can be applied with good but sometimes transient results. Side effects such as dysarthria, dysphonia, and motor disturbances have been described, particularly when thalamotomy is bilateral. The three patients we selected for surgical treatment presented with the typical features of drug resistant TDt: they were young males, TDt onset was observed after a long period of neuroleptics treatment, dystonia persisted after withdrawal of the causative drug with resistance to any medical treatment. Tottemberg [20] was the first surgeon to use DBS for TDt: he investigated the effect of two different targets, VIM and GPi, on the same patient. While VIM did not result in any improvement of movement control, GPi did. Therefore, we treated our patients with bilateral GPi high frequency stimulation. Stimulation started the first day after surgery and immediate improvement could be obtained, differently from what can be generally observed in dystonia of different origin. In our TDt patients neuroleptic drug administration was not discontinued: GPi neurostimulation was found to act as a sort of protection against this particular drug related side effect. High frequency chronic GPi stimulation was found to be safe, highly and promptly effective in these patients, and GPi stimulation has the potential to become the elective treatment of TDt, however these results has to be validated by larger series.

Tremor: The impressive reduction of tremor obtained either immediately during the surgical procedure or at long term follow-up in Parkinson's disease, lead to propose neurostimulation as a suitable treatment of symptomatic tremor in multiple sclerosis patients. The first reported cases of midbrain electrical stimulation on multiple sclerosis patients (MS) with ataxic tremor were reported by Brice and Mc Lellan in 1980. The four patients of our preliminary series were selected on the basis of major impairment provoked by intentional and at rest upper limb tremor. These findings raise the possibility that ataxic tremor could benefit from chronic high frequency Voa-Vop-Zi electrical stimulation.

### *Pain*

Pain represents one of the most challenging issues for neurosurgeons. DBS and other neuromodulation procedures may offer a valid alternative to ablative procedures, which always produce a permanent damage that sometimes can give rise to neuropathic pain. Cluster headache (CH) in particular has been the first indication in the field of chronic pain: it was recognized starting from metabolic and functional neuroimaging which pointed to the postero medial hypothalamus. CH is a painful syndrome of the face often characterized also by symptoms of more general hypothalamic involvement such as psychomotor agitation. Recent imaging studies (PET and fMRI) demonstrated hypothalamic asymmetry and activation during pain attacks [13, 14, 19]. In line with these studies, suggesting the hypothalamus as the origin of pain attacks, we tried to interfere with the supposed hypothalamic hyperactivity through DBS.

### *Disruptive behaviour*

Aggressive behaviour may be associated with different psychotic diseases and/or severe oligophrenic conditions. Control of aggressiveness in most cases may be obtained by drugs including phenothiazines and neuroleptics. Nevertheless, in selected cases, control of aggressive behaviour may be problematic due to the need of high dosages of drugs producing major side effects and sedation, which made caring for these patients even more distressing. In the sixties several neurosurgical procedures have been proposed and performed to treat the aggressiveness in psychotic patients, but the danger of irreversible lesions to CNS structures involved in the control of cognitive functions and mood put such surgery in conflict with ethics. Also, electroconvulsive therapy (ECT) was progressively decried in the seventies due to evidence of irreversible brain damage inflicted by repeated procedures. On the other hand, the last three decades have provided a huge amount of data and knowledge about the neurophysiological mechanisms of aggressive behaviour since the first experience of Delgado on animals with neurostimulators implanted in the limbic system. Since the last decade the Delgado experience and similar experimental studies have inspired more science fiction writers than neurosurgeons.

Bilateral stereotactic lesion of the posteromedial hypothalamus was first reported by Sano in the sixties. This kind of surgery, also known as sedative neurosurgery, found little diffusion for fear of irreversible effects. Our recent experience of chronic hypothalamic stimulation for the treatment of intractable cluster headache demonstrated the feasibility and safety of this procedure and renewed our interest in this target. Deep brain stimulation (DBS) of the posterior hypothalamus was then performed in two patients [13]. DBS of the posterior hypothalamus could lead to a resurgence of interest in the treatment of severe behavioural disorders.

### *Epilepsy*

Although surgical resection of the seizure focus is the treatment of choice of refractory epilepsy, DBS may be an alternative procedure when the focus involves eloquent, unresectable areas. Stimulation of different brain structures such as the cerebellum (Cooper *et al.* 1973), the locus coeruleus (Faber and Vladyka, 1983), the thalamic centromedian nucleus (Velasco *et al.* 2000) and the STN-SN (Benabid *et al.*) has been effective in reducing seizure rate in humans [1, 9, 11, 17]. Several experimental data strongly suggested that basal ganglia and striatal pathways are involved in epileptic seizures threshold and diffusion.

Our results obtained in a young patient (26 yrs) submitted to DBS procedure of the SN-pars posteromedialis. Confirm the literature data and support application of DBS for the treatment of rolandic post-traumatic seizures.

## Conclusions

The reported series of patients extend the use of DBS beyond the field of PD to new fields such as cluster headache, distruptive behaviour, SUNCT, epilepsy and tardive dystonia.

The low complication rate, the reversibility of the procedure and the available image guided surgery tools will further increase the therapeutic applications of DBS. New therapeutical applications are expected for this functional scalpel.

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# Feed-forward control of post-stroke movement disorders by on-demand type stimulation of the thalamus and motor cortex

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## Summary

Deep brain stimulation (DBS) of the thalamus (Vo/Vim) has become popular as a means of controlling involuntary movements, including post-stroke movement disorders. We have also found that post-stroke movement disorders and motor weakness can sometimes be controlled by motor cortex stimulation (MCS). In some forms of movement disorders, motor dysfunction becomes evident only when patients intend to move their body. We have developed an on-demand type stimulation system which triggers stimulation by detecting intrinsic signals of intention to move. Such a system represents feed-forward control (FFC) of involuntary movements. We report here our experience of DBS and MCS for controlling post-stroke movement disorders, and discuss the value of FFC. Excellent control of post-stroke movement disorders was achieved by conventional DBS and/or MCS in 20 of 28 patients with hemichoreoathetosis, hemiballism tremor, and motor weakness. FFC was tested in 6 patients who demonstrated excellent control of post-stroke postural tremor or motor weakness by conventional DBS or MCS. The on-demand stimulation provided satisfactory FFC in 4 of 4 patients with postural tremor and 2 of 2 patients with motor weakness, when the activity of muscles involved in posturing or intention to move was fed into the system. These findings justify further clinical studies on DBS and MCS in patients with post-stroke movement disorders. The on-demand type stimulation system may also be useful for overcoming various post-stroke movement disorders.

*Keywords:* Movement disorders; involuntary movement; stroke; deep brain stimulation; motor cortex; thalamus.

## Introduction

During the last decade, deep brain stimulation (DBS) has become popular as a means of controlling involuntary movements. We have treated more than 400 patients with involuntary movements by DBS since 1989 [4–7, 10–12], including post-stroke movement disorders [6]. We have also found that involuntary movements can sometimes be attenuated in post-stroke patients undergoing motor cortex stimulation (MCS) for pain control [3, 5, 8]. This observation suggested that MCS may represent another useful option for controlling involuntary movements.

In some forms of movement disorders, involuntary movements are induced only when patients intend to move their body. We have developed an on-demand type stimulation system which triggers DBS or MCS by detecting intrinsic signals of intention to move. Such a system represents feed-forward control (FFC) of involuntary movements. In cases of postural tremor, for example, the tremor mechanism is activated by certain posturing. Signals related to posturing can therefore be used for FFC of the tremor. We report here our experience of DBS of the thalamus (Vo/Vim) and MCS for controlling post-stroke movement disorders, and discuss the value of FFC based on a preliminary study.

## Materials and methods

A total of 28 patients with post-stroke movement disorders, including hemichoreoathetosis, hemiballism, tremor and motor weakness, underwent DBS and/or MCS. We employed DBS of the thalamus (Vo/Vim) for controlling the hemichoreoathetosis, hemiballism or tremor. In some patients with hemichoreoathetosis and/or tremor, the effects of MCS were tested separately before or after the subjects underwent Vo/Vim-DBS. MCS was also performed in 3 patients for the primary purpose of improving motor weakness. The stimulation intensity of the MCS was carefully restricted to below the threshold for muscle contraction. The stimulation frequency employed for the long-term use of MCS was limited to below 50 Hz.

We are currently employing the electromyographic (EMG) activity of appropriate muscles as an intrinsic signal to trigger DBS or MCS for the on-demand stimulation system. We first developed an on-demand type stimulation system, by connecting the system to the externalized leads during the test stimulation period before internalization. An external pulse generator is triggered by the EMG activity which is involved in tremor-inducing posture. We next developed an on-demand type stimulation system, which triggers an implanted pulse generator through a console programmer by detecting the appropriate combination of multiple EMG activities which best represents tremor-inducing posture. The implanted pulse generator is activated transcutaneously. We tested whether or not tremor is controlled satisfactorily in 4 patients with

Table 1. *Effects of conventional and on-demand type stimulation of the thalamus and motor cortex in patients with post-stroke movement disorders*

| Movement disorders | n | Satisfactory control | |
|---|---|---|---|
| | | Conventional stimulation | On-demand stimulation |
| *DBS* | | | |
| Hemiballism | 3 | 3 | 0 |
| Hemichoreoathetosis | 8 | 5 | 0 |
| Resting tremor | 7 | 7 | 0 |
| Postural tremor | 7 | 4 | 4 |
| *MCS* | | | |
| Motor weakness | 3 | 2 | 2 |
| Total | 28 | 21 (75%) | 6 |

post-stroke postural tremor by using these systems. In 2 patients with post-stroke motor weakness, MCS was triggered by EMG activity for intention to move, and the effect of stimulation on motor performance was evaluated subjectively. The above 6 patients comprised those who demonstrated excellent control of post-stroke postural tremor or motor weakness by conventional DBS or MCS.

## Results

Excellent control of post-stroke involuntary movement was achieved by conventional DBS or MCS in 21 of the 28 patients (Table 1). In 2 patients, dual-lead DBS for stimulation of wide areas of the Vo/Vim was required to achieve satisfactory control. Some patients with post-stroke tremor preferred MCS to Vo/Vim-DBS. They underwent internalization of electrodes for MCS as well as DBS, and have so far used MCS to control their tremor for more than 8 years. The effects on tremor occurred at an intensity below the threshold for muscle contraction and at a relatively high frequency range. The inhibition of tremor was partial when the frequency was limited to below 50 Hz. The tremor under off-stimulation conditions disappeared in one patient after continuous MCS for more than 3 years. The on-demand stimulation system provided satisfactory FFC in 4 of the 4 patients with postural tremor and 2 of the 2 patients with motor weakness, when the EMG activities involved in posturing or intention to move were fed into the system.

## Discussion

The present data confirm the benefits of MCS for controlling tremor in post-stroke patients. Post-stroke involuntary movements, especially those in thalamic syndrome, are sometimes associated with central pain. Vo/Vim-DBS could elicit opposite effects in these disorders. Involuntary movements can be attenuated, but the pain of the same patients may be exacerbated. MCS might represent the therapy of choice under such circumstances [2, 5].

We have found that patients who underwent MCS for pain control sometimes report subjective improvement of their motor performance, which had been impaired in association with motor weakness. It has also been reported that stimulation of the posterior limb of the internal capsule can attenuate motor deficits caused by cortical injury [1]. Such an effect is not attributable to objectively detectable muscle strength and appears to have resulted from an inhibition of the muscle rigidity.

DBS and MCS, if used with the on-demand type stimulation system, may also be useful for controlling other motor symptoms in post-stroke patients and for improving their overall motor performance. The present findings justify further clinical studies on DBS and MCS in patients with post-stroke movement disorders. The on-demand type stimulation system could be regarded as a first step towards the development of hybrid electric neural circuits to overcome various post-stroke movement disorders.

## Conclusion

Future studies on cortical stimulation, including MCS and on-demand type stimulation systems, should clarify the clinical value of these techniques in controlling movement disorders. The present work was supported by a Grant-in-aid for Scientific Research (No. A12307029 and A15209047) from the Ministry of Science and Culture, Japan.

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# Pallidal high-frequency deep brain stimulation for camptocormia: an experience of three cases

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## Summary

*Introduction.* The term "camptocormia" describes a forward-flexed posture. It is a condition characterized by severe frontal flexion of the trunk. Recently, camptocormia has been regarded as a form of abdominal segmental dystonia. Deep brain stimulation (DBS) is a promising therapeutic approach to various types of movement disorders. The authors report the neurological effects of DBS to the bilateral globus pallidum (GPi) in three cases of disabling camptocormia.

*Methods.* Of the 36 patients with dystonia, three had symptoms similar to that of camptocormia, and all of these patients underwent GPi-DBS. The site of DBS electrode placement was verified by magnetic resonance imaging (MRI). The Burke Fahn and Marsden dystonia rating scale (BFMDRS) was employed to evaluate the severity of dystonic symptoms preoperatively and postoperatively.

*Results.* Significant functional improvement following GPi-DBS was noted in the majority of dystonia cases. At a follow-up observation after more than six months, the overall improvement rate was $71.2 \pm 27.0\%$, in all dystonia cases who underwent the GPi-DBS. In contrast, the improvement rate of the three camptocormia cases was $92.2 \pm 5.3\%$. It was confirmed that the improvement rate for camptocormia was much higher than for other types of dystonia.

*Conclusion.* According to our experience, a patient with a forward-bent dystonic posture indicative of camptocormia is a good candidate for GPi-DBS. The findings of this study add further support to GPi-DBS as an effective treatment for dystonia, and provide the information on predictors of a good outcome.

*Keywords:* Camptocormia; GPi-DBS; dystonia.

## Introduction

The term camptocormia is derived from two Greek words: kamptos (to bend, to crook) and kormos (trunk). A forced posture with a forward-bent trunk was termed camptocormia by the French neurologist Souques in 1915 [10]. It is a condition characterized by severe frontal flexion of the trunk, with passive dropping of both arms. Recently, camptocormia has been reported to occur in association with various other neurological conditions, including primary dystonia. The cause of this pathological condition remains unknown, and appropriate treatment has not been established.

Deep brain stimulation (DBS) has been regarded as a promising therapeutic approach for various types of movement disorders. The authors report the neurological effects of deep brain stimulation to the bilateral globus pallidum (GPi-DBS) in three cases of disabling camptocormia.

## Methods

We analyzed follow-up data obtained from a consecutive series of 36 patients with dystonia who underwent functional stereotactic neurosurgical treatment. We have so far undertaken GPi-DBS in 36 patients with primary and secondary dystonias. The main inclusion criterion for DBS therapy for dystonia was that the patient was diagnosed as having dystonia refractory to any medications. The exclusion criteria included significant cognitive dysfunction, active psychiatric symptoms, and evidence of other central nervous system disease or other systemic medical disorders. Of the 36 patients, three patients had symptoms similar to that of camptocormia, and these three patients underwent GPi-DBS.

The methods of magnetic resonance imaging (MRI) and microelectrode-guided stereotaxy, and electrode implantation were performed in a similar way to previous reports [6, 7]. No sedation was employed during the surgery. The boundaries of the GPi were identified by MRI and confirmed by the recording of spontaneous neural activity using semimicroelectrodes (impedance: 0.2–0.5 Mohm). The trajectory of the semimicroelectrode was directed from the frontal burr hole at an angle of 45–60 degrees from the horizontal plane. A DBS electrode for chronic stimulation (Medtronic; Minneapolis, MN) was implanted into the trajectory, which had been confirmed to be appropriate.

The DBS electrode, which has 4 contact points numbered 0–3 sequentially from the most distal contact (0) to the most proximal contact (3), was placed in such a way. The site of DBS electrode placement was verified by postoperative MRI. When DBS was found to be useful during the test stimulation period for a week, an implantable pulse generator (Soletora, Medtronic; Minneapolis, MN) was implanted into the subclavian region and connected to the DBS electrode. The stimulation parameters and contact points used for GPi-DBS were modified at each follow-up visit of the patients to our clinic on the basis of the results of neurological examination as well as patients' reports concerning the activity of daily life.

The BFMDRS (Burke Fahn and Marsden dystonia rating scale; maximum = 120) was employed to evaluate the severity of dystonic symptoms. In addition, an abdominal activity of selected muscle groups was studied by surface electromyography at rest and during the execution of simple tasks. These clinical studies were performed in each patient before surgery, at 6 months and every year after the surgery.

## Case report

### *History*

A right handed 46-year-old male who experienced a gradual onset and worsening of his forward bent dystonic posture was referred to our hospital. He was otherwise in good health. Neuroradiological examination including MRI showed normal findings. His abnormal forward bent dystonic posture and involuntary movements on his neck and abdomen were resistant to various medical treatments. His cognitive function was completely normal. He had no motor palsy and no obvious sensory deficit. His trunk was severely bent forward and continuous dystonic movements occurred mainly in the neck. When he walked, action-induced bending of the trunk markedly interfered with his gait. Electromyography before surgery demonstrated highly abnormal contractions of various muscles, particularly the rectus abdominis muscle. His score on the BMFDRS was 32 points before surgery.

### *Operation*

The patient underwent MRI-guided stereotactic bilateral implantation of DBS electrodes targeted to the posteroventral segment of the GPi. DBS electrodes were implanted, placing contact point 0 at 4.5 mm below the midpoint between the anterior and posterior commissures, and 20 mm lateral to the midline. No surgical complications were encountered.

### *Postoperative course*

A dramatic reduction in the abnormal muscular tone of the trunk and neck was noted immediately after the initiation of a high frequency stimulation to GPi (Fig. 1). Within several months after surgery, additional progressive improvements were noted. The maximum improvement was observed at 6 months after surgery. His score on the BMFDRS was 4 points at 6 months after surgery. No stimulation-related side effects were induced at stimulation intensity required for maximum effect. The maximum improvements have continued for more than 4 years to date.

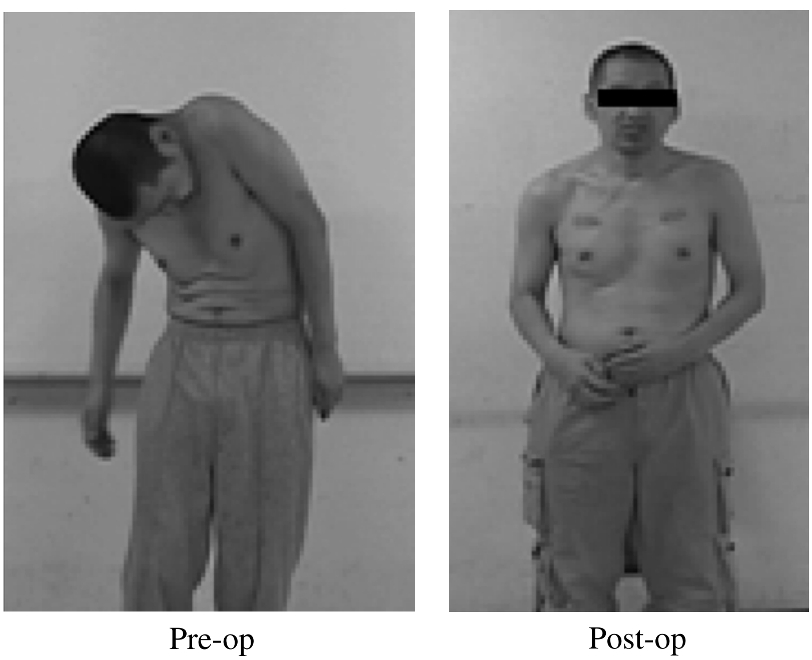


Fig. 1. A dramatic reduction in abnormal muscular tone of the abdomen was observed immediately after the initiation of high frequency stimulation to GPi

Table 1. *Changes in BMFDRS by GPi-DBS at the patients with camptocormia*

| Case | Sex | Age | Onset age | Etiology | Score pre. | Score post. | Imp. rate |
|---|---|---|---|---|---|---|---|
| 1 | M | 17y | 13y | primary | 50 | 0 | 100% |
| 2 | M | 46y | 45y | primary | 32 | 4 | 91% |
| 3 | M | 49y | 44y | primary | 48 | 32 | 83% |
| Mean improvement rate 92.2% | | | | | | | |

## Results

Significant functional improvements following GPi-DBS were noted in the majority of dystonia cases. There were no surgical complications or uncontrollable stimulation-related adverse effects. At a follow-up observation after more than 6 months, the overall improvement rate was $71.2 \pm 27.0\%$, as evaluated using the BFMDRS, in all dystonia cases that underwent the GPi-DBS. In contrast, the improvement rate of the three camptocormia cases was $92.2 \pm 5.3\%$ (Table 1). These findings suggest that the improvement rate for camptocormia, regarded as a form of abdominal segmental dystonia, was much higher than those of the other types of dystonia.

## Discussion

The forced forward-bent trunk posture was termed camptocormia by French neurologist Souques in 1915 [10]. He presented four patients from the military hospital in France. Similar case reports are published as a psychogenic illness occurring among soldiers in World War I [4] and II [9].

Such pathological condition has been reported to occur in association with various other neurological conditions. In recent times, camptocormia has been regarded as a form of abdominal segmental dystonia. The following features were noted in patients suffering from camptocormia [5].

A curvature in the lumbar region only occurred in a sitting or standing position.

In the horizontal bodily position, this curvature entirely disappeared. In a prone position, even a hyperextension of the trunk could be achieved without pain by raising the legs passively.

The proper reflexes and sensitivity were normal, and pyramidal tract signs could not be found.

Radiographs of the spine were normal.

It is suggested that such movement disorder has been responsive to electrotherapy or to corticosteroids medications in some patients, whereas in others the disorder has been refractory to all attempted treatment strategies [5].

Chronic high-frequency DBS has been shown to improve functional status in a number of movement disorders of various causes. Especially, the effects of GPi-DBS on various forms of dystonia were reported previously by several authors [2, 3, 7, 11]. The improvement rates in score on the BMFDRS of various types of dystonia including primary or secondary as well as generalized or focal varieties reported in the literature have a wide range.

An excellent effect was reported especially in DYT1 [1]. Eltahawy HA and his colleagues [3] indicated that primary dystonia responds much better than secondary dystonia to pallidal procedure. Also, they mentioned that the presence of basal ganglia abnormalities demonstrated by preoperative MRI is an indicator of a poor response to pallidal intervention for dystonia. The use of GPi-DBS for treating dystonia is rapidly increasing and preliminary evidence suggests that dystonia linked to genetic mutation and other primary early-onset dystonias respond most dramatically to treatment by pallidal procedure [2, 11], whereas secondary dystonia tends to show a poor response [3].

The advantages of DBS include its relatively nondestructive nature, its adjustability and reversibility, and its capacity to be used bilaterally in a safe manner. Nandi and his colleagues [8] first reported the neurological effects of long-term bilateral palidal high-frequency DBS in a patient with disabling camptocormia. They obtained significant functional improvement following long-term pallidal stimulation, and some improvements were also noted in neurological scores.

Our report also shows the remarkable benefits of the application of GPi-DBS for camptocormia. From the results of our three camptocormia cases, such type of abdominal segmental dystonia is a good candidate for GPi-DBS. The findings of this study add further support to GPi-DBS as an effective treatment for dystonia, and provide the information on predictors of a good outcome.

## Conclusion

According to our experience, a patient with a forward-bent dystonic posture indicative of camptocormia is a good candidate for GPi-DBS. This knowledge is important for providing an accurate prognostic information on the effect of GPi-DBS to patients and clinicians.

## Acknowledgment

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# Multimodal neurosurgical strategies for the management of dystonias

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## Summary

Dystonia have many subtypes, and is classified as focal, segmental and generalized. As for focal dystonia, spasmodic torticollis (cervical dystonia) and writer's cramp are most common. Cervical dystonia is mainly treated effectively with selective peripheral denervation, and task specific focal dystonia of the hand (writer's cramp) is effectively alleviated by stereotactic ventro-oral thalamotomy. Generalized dystonia is dramatically improved with deep brain stimulation of the globus pallidus interna. Because the majority of dystonia is medically refractory and surgical treatment results in marked improvement, the authors strongly believe that dystonia should be regarded as a definite neurosurgical indication. Based on personal experience of nearly 200 cases of dystonia surgery, the authors describe a multimodal approach to various types of dystonias. Also we discuss possible relation between dystonias and psychiatric conditions, and future new indication of dystonia surgery.

*Keywords:* Dystonia; torticollis; writer's cramp; peripheral denervation; thalamotomy; deep brain stimulation.

## Introduction

The term "dystonia" is used both as a name of disorder and a specific symptom. The range of symptoms is very wide and whether the underlying pathophysiology of various types of dystonia is uniform or not is not well known. In neurosurgical clinical practice, it is convenient to classify dystonias into pure cervical dystonia, task-specific focal hand dystonia, segmental and generalized dystonia. Because symptoms, signs, etiology, age, and so on differ greatly from patient to patient, we have to face various types of treatment modalities. We would like to introduce our consecutive experience of surgical management of these different types of dystonias.

## Segmental and generalized dystonia

For segmental and generalized dystonia, the treatment of choice at present is bilateral globus pallidum interna (GPi) deep brain stimulation as in most other centers. When I started pallidal surgery for dystonia about six years ago, the electrical stimulation devices were not readily available. Therefore, I used to perform sequential bilateral pallidotomy, and then I moved unilateral pallidotomy (right side) and contralateral (left side) pallidal DBS. However, since 3 years ago, it has become our routine to implant bilateral pallidal DBS for generalized and segmental dystonia. Our method does not differ from those of other centers; MRI/CT fusion stereotaxi. Initially we used intravenous propofol sedation to control intraoperatively unnecessary movements and found that the dystonia symptoms worsened in some patients with light propofol anesthesia [2, 10]. We then found several reports that dystonia is induced by propofol anesthesia, and since then we have been using intravenous dexmedetomidine hydrochloride that is generally used for sedation in the intensive care unit.

In Japan, DYT-1 dystonia is not common because of genetic and racial factors, and the majority of our cases are adult onset idiopathic dystonia without family history. Some of them had a history of psychiatric problems treated with antipsychotic medication, and the symptoms may be classified as tardive dyskinesia, but response to pallidal DBS is generally the same as those without such a psychiatric history. We also experienced some cases of dystonias due to hereditary metabolic disorders such as Lesch-Nyhan syndrome and Hallervorden-Spatz syndrome with favorable results [9].

Although it is evident that the optimal target for dystonia lies in the GPi, it is not known whether the traditional GPi target used for control of Parkinson's disease (PD) is best for dystonia. Also many of the patients with dystonia tend to be obsessive or in an excessive anxiety state, which indicates that the background pathophysiology of dystonia also involves limbic pallidum that is anterior to the GPi target for control of motor symptoms. To explore a better stimulation area and to find any psychological changes with DBS in the more anterior pallidum, we usually implant two DBS electrodes on one side, resulting in four electrodes implanted in the brain. The posterior electrode is in the traditional GPi for PD, and the anterior electrode is placed 3 mm anteriorly. We generally externalized the lead and perform trial stimulation over three weeks to find the best motor effect and to see psychological changes. The details of this investigation will be published in the near future. After GPi stimulation, involuntary dystonic movements improve within hours, but abnormal fixed postures of the trunk, neck, and extremities tend to respond much later.

The indication or the role of GPi DBS for cervical dystonias (CD) has not yet been established [4]. However, based on our experience of 132 CD patients treated with selective peripheral denervation, we strongly believe that GPi DBS is definitely indicated in the complex type of CD. Complex type of CD is characterized by irregular involuntary head and neck movements and diffuse bilateral involvement of the neck muscles.

## Cervical dystonia

Neurosurgical treatment of CD has a long history. In the beginning, the sternocleidomastoid muscle (SCM) and the accessory nerve were the target of surgical intervention. Then the importance of the posterior neck muscles, mainly the splenius muscle (SPL), was recognized. In order to denervate the accessory and cervical spinal nerves innervating to SCM and SPL, intradural rhizotomy was started, with some benefit. But inadequate denervation of SPL and complications due to denervation of normal muscles, turned out to be a problem. Some performed spinal cord stimulation to mimic sensory trick phenomenon. Bertrand [1] started and established selective peripheral denervation in which selective and complete denervation of the posterior neck muscles was accomplished by denervating the extradural dorsal rami of C1–C6 spinal nerves. This is now regarded as the safest and most effective neurosurgical treatment for the majority of CD. We modified this procedure to further minimize the side effects [6]. It is important to remember that the levator scapulae muscle is also involved in some CD patients resulting in lateral tilt of the head and elevation of the shoulder. In such cases, selective denervation of the levator scapulae muscle is safely performed [8]. Although peripheral denervation is a symptomatic treatment, many of the patients can enjoy symptom free life afterwards as if background pathophysiology was completely cured. As mentioned previously, in some complex type of CD and CD with extracervical symptoms, our preference is GPi DBS.

## Task-specific focal hand dystonia

The most common type of task-specific focal hand dystonia is writer's cramp and musician's cramp. Such condition is very miserable, especially when the symptom is related with the patient's profession. As there have been some case reports on thalamotomy for writer's cramp, we started ventrooral thalamotomy for task-specific focal hand dystonia about five years ago [7]. This was because botulinum toxin injection is not approved in Japan for symptoms other than neck and face dystonias. The ventrooral nucleus of the thalamus receives inputs from GPi and forms part of the thalamo-cortical-basal ganglia loop. Task-specific focal hand dystonia is regarded as the result of oscillation of this cerebral circuit, and making a small lesion in this loop to de-sensitize the loop is the theoretical background of this treatment. So far we have treated 22 patients with writer's cramp and four with musician's cramp. Immediately after the operation, the effect is generally dramatic, but the problem is that recurrence rate is about 15% of patients. Such recurrence seems to be due to inadequate lesioning, because true lesioning and temporary thermal effect are difficult to distinguish during surgery. However, it is evident from our experience that we can cure writer's cramp and musician's cramp with ventrooral thalamotomy with minimal risk. There have been no permanent complications, though transient (2–3 weeks) mild limb weakness and dysarthria were seen in a few patients. One may argue why we do not perform DBS instead of lesioning. This is of course debatable, but the main reason is that DBS merely leads to suppression of the symptom, but thalamotomy can result in permanent cure. DBS itself has disadvantages in terms of hardware complications and psychological burden on the patients; they are living with a device and the disease itself is not cured. Patients with focal hand dystonia are generally young (32 years old on average in our series), and the risk of thalamotomy is supposed to be lower than in aged population as in PD patients. Recovery from complications, if any, is considered faster and more complete.

Recently we found task-specific focal "foot" dystonias among semi-professional speed skaters. The symptom appears only when they skate, and the foot moves at the ankle joint laterally like valgus. This condition is well-known among Olympic level skaters in Japan and they call it Burabura (floppy) disease in slang.

### Issue on dystonia and psychiatric conditions

It is well known that patients with dystonia tend to have a particular psychological or mental character. Patients with CD are often depressive, aggressive, but occasionally obedient. Focal hand dystonia patients are often obsessive, and perfect and impeccable pursuit. Those with DYT-1 dystonia are almost always bright, clever, intelligent. Patients with dystonias may develop psychiatric problems even after treatment of the physical symptoms, and it is also well known that psychiatric disorders are sometimes followed by movement disorders called tardive dyskinesia and dystonia. Thus movement disorders, especially dystonia, seem to be closely related with psychiatric or mental conditions. Dystonia is regarded as an expression of dysfunction of the thalamo-cortical-basal ganglia motor loop, but there are many other loop circuits in the brain and dysfunction of some of these loops are responsible for psychiatric disorders such as depression and obsessive disorders. The motor and mental functions of the brain are basically the output (efferent) system. Therefore, as there are many motor disorders as shown in Table 1, there must be corresponding psychiatric disorders such as mental tremor, mental dystonia, mental spasticity, mental dyskinesia, and so on. We assume these conditions are generally and traditionally called psychiatric disorders such as depression, obsession, compulsion, anxiety, and so on. Therefore, it is reasonable that surgical treatment of intractable psychiatric problems now attracts many functional neurosurgeons in a similar way as movement disorder surgery.

Table 1

| Motor symptoms | Possible mental symptoms | Traditional mental and psychiatric symptoms |
|---|---|---|
| Tremor | mental tremor | depression |
| Ataxia | mental ataxia | obsession |
| Dystonia | mental dystonia | compulsion |
| Chorea | mental chorea | anxiety |
| Ballism | mental ballism | mania |
| Dysmetry | mental dysmetry | schizophrenia |
| Spasticity | mental spasticity | personality disorder |
| Apraxia | mental apraxia | mental retardation |
| Palsy | mental palsy | etc |
| etc | etc | |

### New possible indication of dystonia surgery

There are some mysterious and unsolved movement or posture problems that are often regarded as due to hysteria or mental instability. One is stuttering and another is idiopathic scoliosis. There is a report that scoliosis may be linked to the occurrence of cervical dystonia, perhaps as a forme fruste of a genetic dystonic predisposition [3]. Stuttering is also suggested as a type of dystonia [5]. We may in future become able to solve such difficult but important problems based on the knowledge of neurosurgical treatment of dystonia.

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# Detection of boundaries of subthalamic nucleus by multiple-cell spike density analysis in deep brain stimulation for Parkinson's disease

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## Summary

When microelectrode recording of single cell activity is employed for targeting the subthalamic nucleus (STN), multiple sampling of single cells is needed to determine whether the electrode has passed through the ventral boundaries of the STN. In contrast, stepwise recording of multiple cell activities by a semimicroelectrode reveals robust changes in such activities at the dorsal and ventral boundaries. We attempted to quantify changes in multiple cell activities by computing multiple-cell spike density (MSD). We analyzed MSD in 60 sides of 30 patients with Parkinson's disease. Neural noise level was defined as the lowest cut-off level at which neural noise is separated from larger amplitude spikes. MSD was analyzed at cut-off levels ranging from 1.2 to 2.0-fold the neural noise level in the white matter in each trajectory. Both the dorsal and ventral boundaries were clearly identified by an increase and a decrease ($p < 0.0001$) in MSD, respectively, in all the 60 sides. The cut-off level of 1.2-fold showed the clearest change in MSD between the STN and the pars reticulata of substantia nigra. MSD analysis by semimicroelectrode recording represents the most practical means of identifying the boundaries of STN.

*Keywords:* Parkinson's disease; deep brain stimulation; subthalamic nucleus; substantia nigra, microelectrode; semimicroelectrode.

## Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) affords great benefits to the daily activities in patients with advanced Parkinson's disease (PD) [4, 5, 7]. Most of recent reports have placed emphasis on microelectrode recording of single cell activity for refining the anatomical targeting of the STN during surgery [1, 2, 8–10]. The ventral boundary of the STN is, however, sometimes unclear [9]. Because a microelectrode detects only electrical events arising from a small area, multiple sampling of single cell activity is needed by changing the location of the electrode tip to determine whether the electrode has passed through the ventral boundary of the STN and entered the pars reticulata of substantia nigra (SNr).

We have been employing semimicroelectrode recording [4, 6, 11, 12] for many years to refine anatomical targeting. A semimicroelectrode could detect electrical events arising from a relatively wide area. This method results in stable recordings of spikes and neural noise generated by multiple cells at any locations of the electrode tip.

Semimicroelectrode recording of multiple cell activities reveals robust changes in such activities at the dorsal and ventral boundaries, and therefore appears to be more practical and time-saving. Little has yet been reported, however, regarding the standardization of such a technique. In this study, we attempted to quantify changes in multiple cell activities by computing multiple-cell spike density (MSD).

## Materials and methods

We analyzed data obtained from semimicroelectrode recording in 30 patients of Parkinson's disease, who underwent single stage surgery for bilateral STN-DBS. These patients were diagnosed as having idiopathic PD; they demonstrated past evidence of a good response to levodopa, but showed severe motor symptoms despite medications at tolerable doses and appropriate schedule. The patients' Hoehn and Yahr stage with medication was within the range from Stage III to V during the off-period, and from Stage II to IV during the on-period. The patients and their families gave informed consent for all procedures.

Indirect magnetic resonance (MR) imaging-based anatomic targeting was used. Employing Leksell SurgiPlan® (Elekta Instruments AB, Stockholm, Sweden), the MR images were reconstructed, and both the anterior commissure (AC) and the posterior commissure (PC) were identified. AtlasSpace® (Elekta Instruments AB, Stockholm, Sweden) could superimpose the digitized version of the Schaltenbrand-Wahren atlas on patient's MR images. The tentative target was defined as the posterolateral STN. A burr hole was made 30–35 mm anterior to the coronal suture and 20–25 mm lateral to the midline [11–13]. The STN

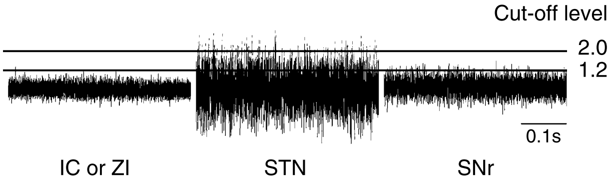


Fig. 1. Cut-off levels for analyzing the MSD were set in the ranging from 1.2, 1.4, 1.6, 1.8, and 2.0-fold the neural noise level in IC or ZI. This is because as the electrode enters the STN, neural noise level increased more than 2.0-fold of the level in the IC or ZI, MSD within the STN reflects both spikes and sharp compound waves, although spikes are predominantly represented at higher cut-off levels. *IC* Internal capsule; *ZI* zona incerta; *STN* subthalamic nucleus; *SNr* pars reticulata of substantia nigra; *MSD* multiple-cell spike density

was approached from the burr hole at an angle of 40–50 degrees to the horizontal plane parallel to the AC-PC line and 0–12.5 degrees to the sagittal plane.

Neural activities were recorded with a pencil-shaped bipolar concentric type semimicroelectrode (Unique Medical Co., Tokyo, Japan). The diameter of exposed tip was approximately 0.1 mm, and the interpolar distance was 0.5 mm with an electrical resistance of 0.2 Mohm at 1000 Hz. The catheter needle was first inserted and advanced to a point 10 mm above the tentative target, and the tip of the semimicroelectrode was advanced in consecutive 0.25 mm increments from a depth of 10 mm above the tentative target by employing a hydraulic microdrive (Narishige Co., Tokyo, Japan). The recording first yielded the anterior thalamic nucleus or the internal capsule (IC), and this was always followed by the zona incerta (ZI) and Forel H fields before entering the STN. In addition, the semimicroelectrode was further advanced 3 mm from the tentative target to confirm the border between the STN and the SNr. Signals were amplified, filtered (300 Hz–10 kHz), displayed on an oscilloscope, played on an audio monitor, and stored in a data recorder.

Electrical events recorded by the semimicroelectrode included spikes with variable amplitudes arising from multiple cells as well as neural noise, i.e., the fluctuation in field potentials generated by various neural elements. Large amplitude spikes could be separated from neural noise by setting an appropriate cut-off level of amplitude. However, it was not always possible to separate small or medium-sized spikes from sharp compound waves, which are contained in the neural noise. We therefore computed the density of spikes and sharp compound waves together, as MSD, counting their occurrence at various cut-off levels.

In the final tracking by semimicroelectrode recording, we determined neural noise level in the IC or ZI. Neural noise level was defined as the lowest cut-off level at which neural noise is separated from larger amplitude spikes. MSD at a given recording site was analyzed at cut-off levels ranging from 1.2 to 2.0-fold the neural noise level in the IC or ZI (Fig. 1). Because MSD within the STN reflects both spikes and sharp compound waves, differences in MSD at all 0.25 mm increments of the electrode were compared for the detection of the dorsal and ventral boundaries of the STN. Also, MSD recorded at every 0.25 mm increment was averaged in each structure, and used for the comparison between the IC or ZI, the STN, and the SNr.

The data are expressed as the mean ± standard deviation. For statistical analysis, Mann-Whitney's U test was used for comparison of MSD. If the probability value was less than 0.05, the difference was considered to be significant. This study was approved by the institutional committee for clinical research on humans.

## Results

When the electrode enters the STN, neural noise level raised more than 2.0-fold the level in the IC or ZI,

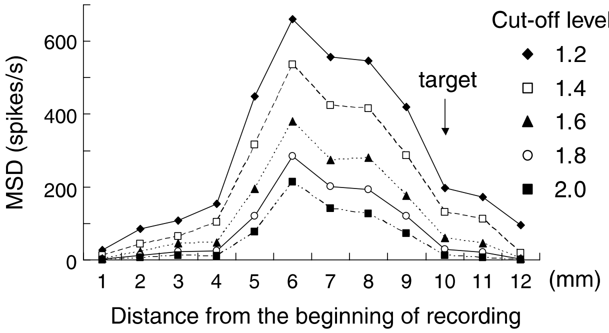


Fig. 2. Representative example of changes in the MSD at STN. Cut-off level was varied from 1.2 to 2.0-fold the neural noise level at the IC. The MSD increased at 5 mm from the point where recording was initiated, and decreased at the tentative target point (10 mm)

and spikes are predominantly observed at higher cut-off levels. MSD clearly increased when the electrode crossed the dorsal boundary of the STN, and decreased when the electrode passed through the ventral boundary of the STN and entered the SNr. MSD within the STN was larger than MSD in IC or ZI and MSD in the SNr at any cut-off levels ranging from 1.2 to 2.0-fold (Fig. 2). The cut-off level of 1.2-fold showed the largest increase in MSD in the STN (584 ± 195 spikes/s), which was markedly higher than MSD in IC or ZI (16 ± 9 spikes/s; $p < 0.0001$, $n = 60$) and SNr (94.1 ± 80.8 spikes/s; $p < 0.0001$, $n = 60$; Fig. 3) at this cut-off level. The dorsal and ventral boundaries of the STN were clearly identified by the increase and decrease in MSD, respectively, in all the 60 sides.

Immediately after the stereotactic operation was completed, we performed MR imaging again, and the location of contact points of the DBS electrode was confirmed. The mean distance of the DBS electrode from the midline in

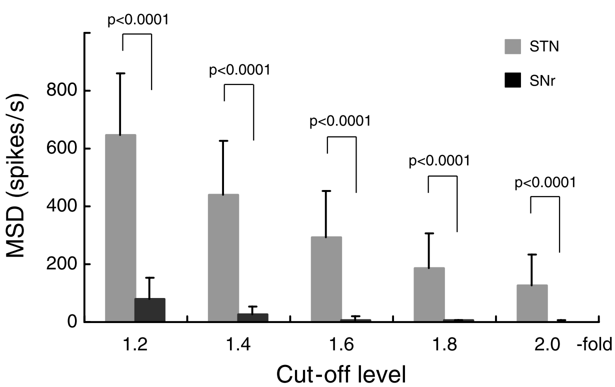


Fig. 3. Graphs demonstrate the comparison of MSD between STN and SNr at each cut-off level. The cut-off level of 1.2-fold showed the most obvious changes. MSD recorded in STN are significantly higher than MSD in SNr ($p < 0.0001$). *MSD* Multiple-cell spike density; *STN* subthalamic nucleus; *SNr* pars reticulata of substantia nigra

the present series of patients is 11.3 mm, which is the same as the distance reported previously (11–12 mm) [2, 9].

## Discussion

In this study, we demonstrated that MSD clearly increased when the electrode entered the STN. In the typical recording within the STN reported by Starr *et al.* [9], large amplitude spikes from multiple cells and elevated neural noise level were observed. The increase in MSD at the dorsal boundary of the STN is consistent with these findings.

The discharge rate of STN cells is approximately half of the discharge rate of SNr cells if analyzed as single cell activity by microelectrode recording. Hutchison *et al.* [3] reported that, although STN cells show discharge with an irregular pattern at varying rate ranging from 25 to 45 Hz ($37 \pm 17$ Hz), SNr cells exhibit a discharge with more regular pattern at a much faster rate ($71 \pm 23$ Hz). Their results indicate that background multiple cell activities are higher in the SNr than in the STN. Starr *et al.* [9] also reported that cells in the SNr show a discharge at faster rate ($86 \pm 16$ Hz) as compared to cells in the STN ($34 \pm 14$ Hz).

In contrast to these previous reports on microelectrode recording, MSD was always higher in the STN than in the SNr in this study. Background multiple cell activities may vary in microelectrode recording depending on the location of the electrode tip. The discrepancy in spike density (discharge rate) between studies employing microelectrodes and semimicroelectrodes appears to reflect the difference in the capability of detecting information regarding cell density in addition to the discharge rate of cells in average.

In this study, the lowest cut-off level of 1.2-fold showed the largest changes. This is obviously because MSD at such a cut-off level includes fluctuation in field potential which becomes larger in amplitudes within the STN. Since an increase in amplitude in field potential may also reflect increases in multiple cell activities as well as the cell density, the significance of MSD analysis may not differ at any cut-off level for determining the boundaries of the STN.

In conclusion, this study demonstrated that MSD analysis by semimicroelectrode recording represents the most practical means of identifying the boundaries of STN.

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# Follow-up of bilateral subthalamic deep brain stimulation for Parkinson's disease

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## Summary

*Purpose.* To demonstrate the effects of bilateral subthalamic deep brain stimulation (STN-DBS) in the treatment of Parkinson's disease (PD) after 4–45 months' follow-up.

*Method.* Between 04/01 and 12/04, 46 PD patients were operated on with bilateral STN-DBS. All of them were evaluated with Unified Parkinson's Disease Rating Scale (UPDRS) parts II–V before surgery and 4–45 months after surgery. The amelioration of miscellaneous symptoms and decrease of medication dose, respectively, were compared. Main side effects were observed.

*Findings.* After surgery, both the score of activities of daily living (ADL) and the UPDRS motor score decreased significantly ($p < 0.001$). Among the PD symptoms, tremor was improved best. Rigidity, bradykinesia, axial symptoms, facial expression and dyskinesia were all improved, although to a lesser extent, while speech was not improved. Medication dose was decreased significantly ($p < 0.001$). According to the time of follow-up, 4 groups were classified (4–12 months, 13–24 months, 25–36 months and 37–45 months group). ADL, UPDRS motor score and dyskinesia subscore improvement were compared among these groups. No significant difference existed. No life threatening complications occurred. Main side effects included hypophonia, dyskinesia, confusion, depression.

*Conclusions.* Bilateral STN-DBS is a satisfying surgical method for the treatment of advanced PD. It can improve the cardinal PD symptoms up to 45 months. Complications and side effects were rare and usually temporary or reversible.

*Keywords:* Deep brain stimulation; subthalamic nucleus; follow-up.

## Introduction

In the past few years, deep brain stimulation (DBS) has become an accepted treatment modality for Parkinson's disease (PD) patients who experience disabling motor fluctuations and dyskinesia as a result of dopaminergic therapy, and some follow-up data have been published, including short-term follow-up for 3–6 months and long-term follow-up for up to 5 years. The selected targets varied from subthalamic nucleus (STN) to globus pallidus internus (GPi) [2, 4, 12, 14, 20]. The objective of our study was to demonstrate the effects of bilateral STN-DBS in the treatment of PD after 4–45 months' follow-up. To our knowledge, this is one of the several largest series study in this field.

## Materials and methods

### *Patient selection*

Forty six idiopathic PD patients were admitted to Beijing Tiantan Hospital between 04/01 and 12/04. There were 31 men and 15 women. Their age ranged from 42 to 78 years, averaging $63.8 \pm 7.8$ years. Average duration of PD until surgery was $11.31 \pm 3.63$ years (ranging from 4 to 18 years). Inclusion and exclusion criteria followed international recommendations (Core Assessment Program for Surgical International Therapies; CAPSIT). All cases had preserved levodopa effectiveness, but with severe motor fluctuations and dyskinesias and prolonged Off states. Hoehn-Yahr Scale of the patients before surgery was: Grade II: 10 cases, Grade III: 18 cases, Grade IV: 13 cases, Grade V: 5 cases. Before surgery, the Unified Parkinson's Disease Rating Scale (UPDRS) motor score, activities of daily living (ADL), dyskinesia were evaluated in both medication off and on states. Total equivalent dose of levodopa was calculated according to the accepted equivalence among different dopaminergic medications.

### *Surgical procedure*

The surgical procedure coincided with those from other literature. Briefly, the patient was fixed with a Leksell stereotactic headframe on the morning of surgery and transferred to MRI suite to take MRI (3.0 Tesla) examination. The image data was then transferred to the Surgiplan workstation in the operation room. STN was 2–3 mm posterior to the midcommissural point, 12–13 mm lateral to the midplane of the third ventricle and 4–6 mm below the intercommissural line. The anatomical boundary of STN was easily distinguishable on the T2 and

Flair weighted images and the coordinates were calculated automatically by Surgiplan system. The patient was operated on under local anesthesia. Intraoperative microelectrode recording was used to verify the firing pattern of STN. Quadripolor electrodes (Medtronic Inc., electrode 3389) were implanted bilaterally in STN. Intraoperative physiological test ensured the appropriate response of the patient and no obvious adverse effect. Then under general anesthesia, implanted pulse generator (IPG, Medtronic Inc., Kinetra) was implanted subcutaneously in the subclavicular region. The stimulator started to work 2–3 weeks later and was programmed several times till the most ideal effects occurred.

*Follow-up of patients*

From 04/05 to 07/05, we carried out follow-up throughout China. The follow-up time ranged from 4 to 45 months, averaging $19.26 \pm 8.35$ months. The items of evaluation were the same as those before surgery, except that four states of the patient were assessed, including medication off/stimulation off ($Med_{off}/Stim_{off}$), medication off/stimulation on ($Med_{off}/Stim_{on}$), medication on/stimulation off ($Med_{on}/Stim_{off}$) state and medication on/stimulation on ($Med_{on}/Stim_{on}$). The equivalent dose of levodopa was also calculated.

*Statistics*

In comparison of ADL, UPDRS motor score and subscores, dyskinesia and levodopa equivalent daily dose (LEDD) in all patients, a paired *t* test was used. In comparison of their improvement after surgery among different time of follow-up, a one way ANOVA was firstly used. If significant difference existed, then an independent-samples *t* test was to be used. Normal distribution of all variables was verified before comparison. Statistics was processed using SPSS-12 for Windows.

## Results

### *Efficacy of bilateral STN-DBS*

Postoperatively, all patients showed an improvement in ADL, UPDRS motor score and subcores, as well as dyskinesia subscores. The values of these variables and their comparison were shown in Table 1.

Since both parts II and IV in UPDRS were interview-based, and some patients never turned off the stimulator in their daily life, so these data were collected only in $Stim_{on}$ states after surgery. Compared with the preoperative value, ADL was improved by 42.9% in $Med_{off}$ state ($p < 0.001$) and 29.1% in $Med_{on}$ state ($p < 0.001$) after surgery. UPDRS motor score was evaluated in two and four different states before and after surgery, respectively. We compared among the values in different states before and after surgery. In $Med_{off}$ states, stimulation could improve total motor score from $49.2 \pm 19.3$ to $29.7 \pm 13.7$ ($p < 0.001$, improvement rate 39.58%). The comparison of total motor score between $Med_{off}/Stim_{on}$ and $Med_{on}/Stim_{off}$ states showed no difference ($p = 0.094 > 0.05$), which meant no efficacy difference between medication and stimulation alone. $Stim_{on}/Med_{on}$ could further improve motor symptoms by 32.25% compared to $Stim_{on}/Med_{off}$ state ($Stim_{on}/Med_{off}$ $29.7 \pm 13.7$, $Stim_{on}/Med_{on}$ $20.2 \pm 13.6$, $p < 0.001$).

In order to demonstrate the alleviation extent of different motor symptoms, we compared tremor, rigidity, bradykinesia, axial symptoms, facial expression and speech separately. Among all these symptoms, tremor (items 20, 21) was improved best. In $Med_{off}$ state, stimulation improved tremor by 68.63%, $Med_{on}$ further improved tremor by 67.65%. Rigidity (item 22), bradykinesia (items 23–26), axial symptoms (items 27–30) and facial expression (item 19) were also improved prominently, although to a lesser extent than tremor. In $Med_{off}$ state, stimulation improved rigidity, bradykinesia, axial symptoms and facial expression by 52.09, 31.30, 24.07 and 14.76%. Medication further improved these symptoms by 41.69, 27.98, 25.89 and 18.99% respectively. In contrast, speech (item 18) subscore comparison between $Med_{off}$ state before surgery and $Med_{off}/Stim_{on}$ state after surgery showed no difference. Dyskinesia (items 32–35) was chiefly induced by dopaminergic

Table 1. *ADL, UPDRS score and subscores, dyskinesia scores comparison before surgery and at the time of follow-up (mean ± SD)*

| Article | Preop | | Postop | | | |
|---|---|---|---|---|---|---|
| | $Med_{off}$ | $Med_{on}$ | $Med_{off}/Stim_{off}$ | $Med_{off}/Stim_{on}$ | $Med_{on}/Stim_{off}$ | $Med_{on}/Stim_{on}$ |
| UPDRS ADL | $27.5 \pm 11.2$ | $13.4 \pm 6.9$ | – | $15.7 \pm 8.1^{b}$ | – | $9.5 \pm 6.0^{b}$ |
| UPDRS motor | $49.2 \pm 19.3$ | $33.2 \pm 23.2$ | $52.3 \pm 17.5$ | $29.7 \pm 13.7^{d}$ | $35.6 \pm 23.7$ | $20.2 \pm 13.6^{d}$ |
| Tremor | $10.8 \pm 6.9$ | $7.7 \pm 6.9$ | $12.8 \pm 7.3$ | $3.4 \pm 4.0^{d}$ | $7.0 \pm 8.0$ | $1.1 \pm 2.1^{d}$ |
| Rigidity | $7.9 \pm 5.0$ | $5.8 \pm 5.3$ | $6.5 \pm 5.4$ | $3.8 \pm 4.1^{d}$ | $5.1 \pm 5.5$ | $2.2 \pm 3.4^{c}$ |
| Bradykinesia | $17.2 \pm 7.1$ | $16.0 \pm 7.8$ | $21.2 \pm 8.5$ | $11.8 \pm 5.8^{d}$ | $13.0 \pm 8.1$ | $8.5 \pm 5.9^{d}$ |
| Axial symptoms | $7.0 \pm 3.9$ | $5.0 \pm 2.7$ | $7.2 \pm 3.3$ | $5.3 \pm 3.2^{d}$ | $5.4 \pm 3.8$ | $4.0 \pm 3.2^{c}$ |
| Facial expression | $2.1 \pm 1.1$ | $1.5 \pm 1.3$ | $2.1 \pm 1.7$ | $1.8 \pm 1.0^{c}$ | $1.7 \pm 1.0$ | $1.4 \pm 1.1^{c}$ |
| Speech | $1.9 \pm 1.1$ | $1.4 \pm 1.0$ | $1.8 \pm 1.2$ | $1.9 \pm 0.9^{e}$ | $1.6 \pm 0.9$ | $1.6 \pm 0.9$ |
| Dyskinesia | – | $3.6 \pm 1.3$ | – | – | – | $0.7 \pm 1.0^{b}$ |

Difference of ADL and dyskinesia between preoperative and postoperative states: $^{a}p < 0.05$, $^{b}p < 0.001$). Difference of UPDRS motor score and subscores between different states before and after surgery: $^{c}p < 0.05$, $^{d}p < 0.001$, $^{e}p > 0.05$.

Table 2. *UPDRS scores comparison among different time of follow-up after surgery. Comparison was among different groups in both $Med_{off}/Stim_{on}$ and $Med_{on}/Stim_{on}$ states*

| Article | 4–12 months ($n=11$) | | 13–24 months ($n=17$) | | 25–36 months ($n=10$) | | 37–45 months ($n=8$) | |
|---|---|---|---|---|---|---|---|---|
| | $Med_{off}/Stim_{on}$ | $Med_{on}/Stim_{on}$ | $Med_{off}/Stim_{on}$ | $Med_{on}/Stim_{on}$ | $Med_{off}/Stim_{on}$ | $Med_{on}/Stim_{on}$ | $Med_{off}/Stim_{on}$ | $Med_{on}/Stim_{on}$ |
| UPDRS ADL | 39.7 ± 12.9 | 61.3 ± 21.1 | 46.8 ± 15.8 | 67.9 ± 23.1 | 43.3 ± 17.4 | 64.3 ± 20.3 | 42.7 ± 11.6 | 63.3 ± 22.6 |
| UPDRS motor | 40.5 ± 17.9 | 62.6 ± 21.1 | 38.1 ± 29.7 | 58.3 ± 26.2 | 38.1 ± 4.6 | 51.4 ± 7.0 | 44.3 ± 8.0 | 66.9 ± 14.8 |
| Tremor | 66.0 ± 26.5 | 84.2 ± 29.0 | 57.1 ± 43.6 | 90.8 ± 18.8 | 75.5 ± 23.7 | 87.8 ± 14.1 | 90.0 ± 20.0 | 97.5 ± 50.0 |
| Rigidity | 40.1 ± 39.6 | 71.8 ± 37.6 | 63.5 ± 42.8 | 65.2 ± 63.1 | 46.9 ± 32.1 | 57.2 ± 42.3 | 42.4 ± 33.5 | 60.2 ± 45.6 |
| Bradykinesia | 30.0 ± 21.4 | 57.1 ± 27.8 | 39.9 ± 30.4 | 49.1 ± 34.3 | 22.7 ± 7.4 | 38.4 ± 13.4 | 30.2 ± 19.5 | 51.6 ± 26.8 |
| Axial symptoms | 28.0 ± 29.5 | 45.8 ± 31.6 | 18.0 ± 24.8 | 41.3 ± 33.5 | 38.7 ± 7.3 | 43.9 ± 6.3 | 24.2 ± 17.1 | 59.6 ± 17.3 |
| Facial expression | 26.2 ± 39.5 | 31.6 ± 48.3 | 7.1 ± 18.9 | 46.4 ± 46.6 | 14.6 ± 17.2 | 29.2 ± 21.0 | 33.3 ± 47.1 | 45.8 ± 41.7 |
| Speech | 0.0 ± 34.0 | 14.5 ± 40.7 | –33.3 ± 47.1 | 0.0 ± 0.0 | 13.5 ± 17.8 | 29.2 ± 21.0 | 20.8 ± 25.0 | 38.3 ± 43.3 |
| Dyskinesia | – | 78.3 ± 27.2 | – | 79.9 ± 20.1 | – | 83.3 ± 16.3 | – | 80.2 ± 19.3 |

medications, thus it was compared between $Med_{on}$ state before surgery and $Med_{on}/Stim_{on}$ state after surgery. The result showed a dramatic improvement by 80.6%. Meanwhile, LEDD (Levodopa equivalent daily dose) was decreased by 34.1%, its value 747.5 mg/d and 492.5 mg/d before and after surgery. The diminution was significant ($p<0.001$). Four cases ceased to take any antiparkinson medication any more.

According to the follow-up time after surgery, the 46 patients in our series were divided into four groups: patients followed up between 4 to 12, 13 to 24, 25 to 36 and 37 to 45 months. We then compared ADL, UPDRS motor score and subscores, dyskinesia improvement in order to evaluate the long-term efficacy of STN-DBS. The results were shown in Table 2.

All variables in different groups were compared with one way ANOVA . In $Med_{off}/Stim_{on}$ state, there was no difference in both ADL and UPDRS motor score among different groups (ADL: $p=0.634$, UPDRS motor score: $p=0.856$). Comparison among different subitems of UPDRS motor score showed similar results (tremor: $p=0.637$, rigidity: $p=0.842$, bradykinesia: $p=0.570$, axial symptoms: $p=0.986$, facial expression: $p=0.384$, speech: $p=0.622$). In $Med_{on}/Stim_{on}$ state, there was no difference in ADL, UPDRS motor score and dyskinesia among different groups (ADL: $p=0.723$, UPDRS motor score: $p=0.698$, dyskinesia subscore: $p=0.564$). Comparison among different subitems of UPDRS motor score also showed no difference (tremor: $p=0.766$, rigidity: $p=0.880$, bradykinesia: $p=0.460$, axial symptoms: $p=0.853$, facial expression: $p=0.329$, speech: $p=0.712$). Based on the above results, we did not further compare variables between different group by independent-samples $t$ test. In conclusion, the improvement of ADL, parkinsonian motor symptoms and dyskinesia by STN-DBS was kept stable for at least 45 months, whether in the $Med_{on}$ or $Med_{off}$ state.

*Complications and side effects*

In our series, there was no life threatening complications. Since postoperative MRI was not a routine examination, we could not exclude asymptomatic intracranial hematoma. Nonetheless, no symptomatic intracranial hematoma was encountered. Scalp ulceration due to lead abrasion occurred in 2 cases and was sutured subsequently. Side effects such as paraesthesia and eye movement disorder were usually transient and reversible. Seven cases complained of reversible hypophonia, accounting for 15.2% of all patients. Two patients had to stand up to dyskinesia when the parameters well controlled other parkinsonian symptoms. Adjustment of parameters led to disappearance of dyskinesia and recurrence of parkinsonian symptoms simultaneously. Other side effects included psychological disorders such as depression in 2 patients, confusion in 1 patient. Postoperative obesity was also complained in 3 patients although no accurate body weight comparison was available.

## Discussion

During the past few year, STN-DBS has been used worldwide in the treatment of PD. Some published data are now available, thus the results can be compared among different medical centers. In our series, ADL was improved by 42.9% and 29.1% in medication off and on states, respectively. UPDRS motor score was improved by 39.58% in medication off states. Medication further improved another 32.35%. Dyskinesia was improved by 80.6% compared to it before surgery. LEDD was reduced by 34.1% compared to that before surgery. As to the different motor symptoms, tremor was best improved by 68.63% in medication off state, followed in order by rigidity, bradykinesia, axial symptoms and facial expression, by 52.09, 31.30, 24.07 and 14.76%, respectively. Our results confirm the comprehensive efficacy of bilateral STN-DBS in the treatment of PD and demonstrate that combination of medication and STN-DBS could best improve motor symptoms. The results corroborate the outcome of other published studies. Previous studies showed motor disability improvement in the medication off state varied between 33 and 67% [2, 4, 6–8, 12, 14–17, 19, 20]. Reduction of the UPDRS part IV score varied between 80 and 92% [19]. The extent of diminution of LEDD ranged between 40 and 80.4% [9, 15, 17, 21]. The improvement of motor disability and dyskinesia in our series was within the range of other literature, while LEDD dimunition was not as ideal as other reports. We believe this is partly because the preoperative dose in our group is also lower than others, due to the insufficient medical therapy in our country. Although some authors [18, 19] completely replaced dopaminergic medication by STN-DBS in 50% of patients, only 4 patients in our group withdrew their medication completely. Thus we highly recommend the combination of medication and STN-DBS after surgery. We also compared the improvement of PD symptoms among different times of follow-up. No difference was present among the 4–12, 13–24, 25–36 and 37–45 months groups, confirming the long-term efficacy of STN-DBS. This is also in accordance with other reports.

The complications of STN-DBS surgery include device-related complications such as skin ulceration, lead fracture and displacement, as well as surgical complications, such as intracranial hematoma and infections. The absence of symptomatic intracranial hematoma in our series was attributed to careful manipulation during operation. Avoidance of sulcus in the electrode trajectories, prevention of CSF overdrainage, precise localization of the target to reduce repeating puncture were crucial. Microelectrode recording was routinely applied, with no obvious bleeding. Although theoretically the risk of bleeding was increased by microelectrode trajectories, the facilitation of localization made it worthy of utilization. In our group, 7 patients had hypophonia after surgery. Reduction of stimulating parameters could alleviate the symptom. Other authors have reported similar side effects, usually with a lower incidence [7, 21]. It may be caused by the current diffusion to the internal capsule. The relatively higher incidence of hypophonia in our series was due to electrode position. Another remarkable side effect in our series was DBS-related dyskinesia, which occurred in 2 patients. Although the incidence was rather low, it was very prominent and intolerable. Adjustment of parameters led to disappearance of dyskinesia and recurrence of parkinsonian symptoms simultaneously. Until the last follow-up, the appropriate parameter, medication and ideal outcome did not occur simultaneously in these patients. Many authors reported that stimulation-induced dyskinesia was a good predictive indicator of STN-DBS effectiveness and was reversible after reduction of stimulating parameters. However, the optimal parameter, medication and ideal outcome should be integrated together. Other side effects were usually psychiatric such as depression, confusion, and occurred in 2 and 1 patient in our series. The same problems have been widely discussed by other authors [10, 13]. The cause of postoperative depression is unclear. One explanation may be the addiction to dopaminergic treatment and subsequent reduction of medication dosages, with a negative affective withdrawal state. More attention should be paid to mood disorders after surgery.

Since the application of DBS in PD, GPi and STN have been the two most popular targets. Some clinical studies proved the efficacy of GPi-DBS in reducing off-period symptoms, dyskinesias, and motor fluctuation in advanced PD for 3–12 months. While a follow-up period of 5 years showed that although dyskinesia remained significantly reduced, the initial improvement of off-period motor symptoms and fluctuations gradually declined. Beneficial effects on ADL in the on- and off-period were lost after the first year [3, 5, 11]. Based on all these results, most authors believe that STN-DBS may be superior to GPi-DBS. Nonetheless, a recent randomized blinded pilot comparison of the safety and efficacy of STN and GPi stimulation in patients with advanced PD questions the above opinion. PD patients were randomized to implantation of bilateral GPi or STN stimulators. Off-period UPDRS motor scores, bradykinesia and LEDD were improved better by STN-DBS compared to GPi-DBS after 12 months, while dyskinesia was reduced better by GPi-DBS than by STN-DBS. Cognitive and behavioral complications were observed only in combination with STN stimulation [2]. In our opinion, these results might be caused by the relative short period of follow-up. Bilateral STN-DBS is still the first choice for advanced PD.

In conclusion, our study showed the high efficacy and safety of bilateral STN-DBS in the treatment of PD. It comprehensively improves all parkinsonian symptoms including tremor, rigidity, bradykinesia, posture and gait instability. ADL of the patients is also improved. Medication is significantly reduced at the mean time, thus levodopa induced dyskinesia could be relieved. In most patients, combination of stimulation and medication leads to the best result. Complications and side effects are few and should be considered with caution. The efficacy of DBS is kept stable during long-term up of up to 45 months.

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# Rapid subthalamic nucleus deep brain stimulation lead placement utilising CT/MRI fusion, microelectrode recording and test stimulation

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## Summary

Subthalamic nucleus (STN) deep brain stimulation (DBS) has become an established treatment strategy for patients with medically refractory Parkinson's disease (PD). There are however numerous strategies employed for STN lead placement. Variations include method of STN localisation, use of microelectrode recording, number of microelectrode recording passes and time taken for the procedure. We describe a relatively simple and rapid technique of STN lead placement utilising CT/MRI image fusion, microelectrode recording and test stimulation.

The first 58 consecutive patients undergoing STN DBS were assessed pre- and post-operatively. UPDRS scores, medication use and any surgical complication were assessed.

Bilateral STN DBS was an efficacious treatment option for medically refractory PD. We have described a technique which can be performed with effect and low morbidity, and in a time which is well tolerated by patients.

*Keywords:* Deep brain stimulation; movement disorder; Parkinson's disease; subthalamic nucleus.

## Introduction and aims

Subthalamic nucleus (STN) deep brain stimulation (DBS) has become an established treatment strategy for patients with medically refractory Parkinson's disease (PD). There are however numerous strategies employed for STN lead placement. Variations include method of STN localisation, use of microelectrode recording, number of microelectrode recording passes and time taken for the procedure. We describe a relatively simple and rapid technique of STN lead placement utilising CT/MRI image fusion, microelectrode recording and test stimulation, and present results of our first 58 consecutive patients.

## Methods

Our series employs a uniform technique, used in two units encompassing three community hospitals (two in Brisbane, one in Sydney).

*Procedure*

Surgery is carried out in the "off" state. General anaesthesia (propofol) is induced in the radiology suite, and a CRW stereotactic frame affixed to the patient's head. After CT scanning the patient is transferred to the operating room and the headframe attached to the operating table. The frontal scalp is prepared and draped. A small bifrontal scalp flap is raised, and bifrontal burrholes are made, approximately 3 cm from the midline, but placed to avoid ventricular violation by the microelectrode or lead.

The ventromedial STN is directly targeted by visualisation on fused CT/MRI images. We use FLAIR sequences obtained on 1.5 or 3.0 Tesla scanners (usually obtained 1–2 days prior to surgery), with CT/MRI fusion carried out on Radionics, Stealth (Medtronics-Sofamor Danek) or BrainLab workstations. The target can be refined by additional visualisation on the Schaltenbrand atlases on the workstations, which can be "morphed" to fit the individual patient.

A 500 micron tungsten microelectrode (Fred Hayer Corporation) is passed via a microdrive attached to the headframe to 5 mm above the selected target. Microelectrode recordings are obtained at 1 mm steps through the STN to the substantia nigra (SN). Recordings are audibly and visually displayed on a Medtronics Leadpoint computer. White matter ("quiet areas") and characteristic STN and SN signals are confirmed.

With target confirmation by microelectrode recording, further confirmation is carried out by test stimulation. The 500 micron tip is withdrawn, and the distal outside sheath of the probe is used to provide stimulation at 130 Hz with a pulse width of 60 microseconds. The patient is examined for effect on clinical signs (dyskinesia, tremor, rigidity, bradykinesia) and absence of adverse effects.

After this step the microelectrode is withdrawn and the permanent DBS lead (Medtronic 3387) is placed through the same guidetube. The lead is fixed to the skull with a suture and bone cement.

After bilateral lead placement the patient is again anaesthetised. External connecting leads (Medtronic) are attached to the DBS leads and brought out through retroauricular stab incisions. The scalp wound is sutured and a head bandage applied.

Over the next several days lead placement in each STN is confirmed with an MRI scan (with appropriate safety protocols) and test stimulation via the external leads (Fig. 1). Internal pulse generators (Medtronic Soletra) are placed in infraclavicular pockets under general anaesthesia at logistically convenient time.

The first 58 consecutive patients undergoing STN DBS were assessed pre- and post-operatively. UPDRS scores, medication use and any surgical complication were assessed.

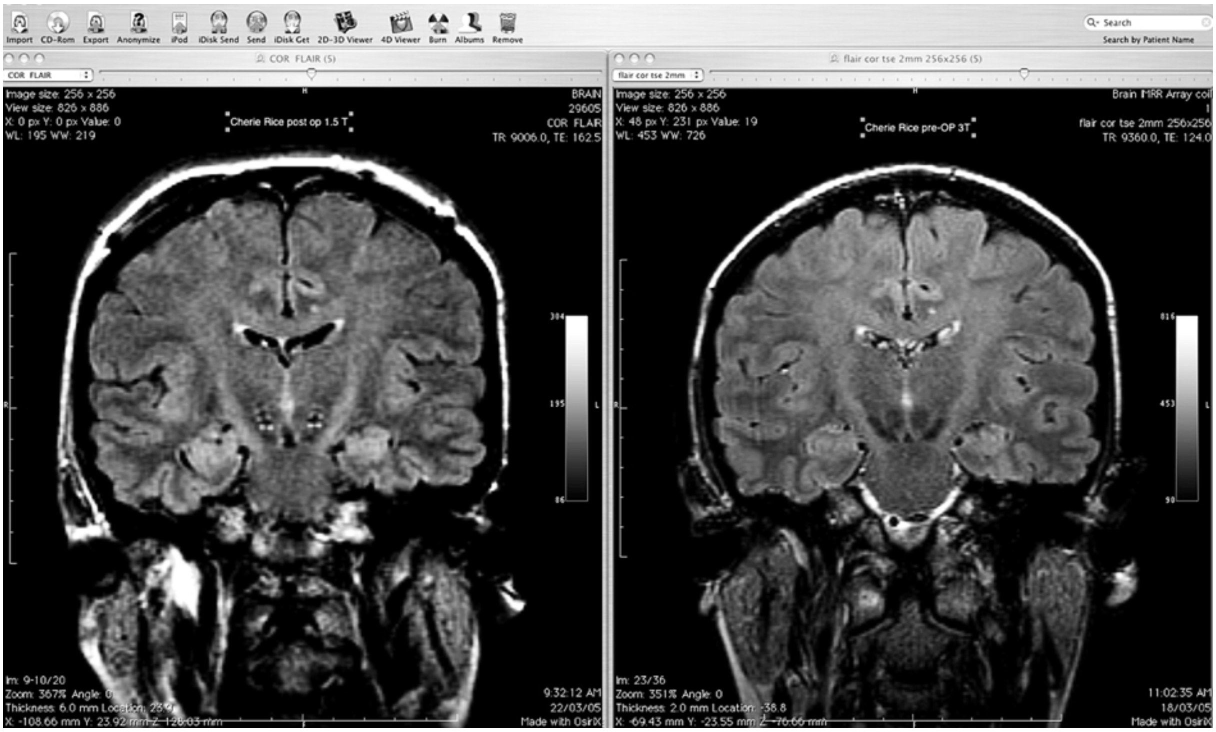


Fig. 1. Coronal FLAIR images showing STN – pre-operative image on right, post-operative image on left, showing satisfactory lead placement

## Results

The 58 patients were assessed at $10 \pm 6$ months post-operatively. The patients underwent surgery during the period mid 2002–end 2004.

110/116 lead placements were performed with a single microelectrode pass. Average elapsed time from application of the stereotactic headframe to departing the operating room after bilateral lead insertion was 3 hours.

Table 1 demonstrates mean reduction in the unified Parkinson's disease rating scale (UPDRS) from best "on-medication" pre-operatively compared to best "on-stimulation" post-operatively, with or without medication.

Mean daily Levodopa equivalent in the population group was 1487 mg pre-operatively, and 471 mg post-operatively. This was a 68% reduction ($p < 0.0005$). 14/58 (24%) of patients became totally drug free, and another 17/58 (30%) were able to come off Levodopa.

Complications are listed in Table 2.

Table 1

| | Mean reduction | 95% confidence interval | *P* value |
|---|---|---|---|
| UPDRS Part I | 2.4 (75%) | 1.7–3.1 | <0.0005 |
| II | 4.3 (38%) | 2.4–6.2 | <0.0005 |
| III | 9.9 (44%) | 7.7–12.2 | <0.0005 |
| IV | 6.1 (88%) | 4.7–7.4 | <0.0005 |
| Total score | 22.7 (52%) | 19.3–26.1 | <0.0005 |

Table 2

| |
|---|
| Mortality – 0 |
| Morbidity |
| 5/116 (4%) leads not ideally placed and revised |
| Change in speech volume or fluency – 5 patients |
| Deep venous thrombosis – 1 patient |
| Symptomatic Haemorrhage – 0 |
| Infection – 0 |

## Conclusion

Bilateral STN DBS was an efficacious treatment option for medically refractory PD. We have described a technique which can be performed with effect and low morbidity, and in a time which is well tolerated by patients.

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# FDG-PET study of the bilateral subthalamic nucleus stimulation effects on the regional cerebral metabolism in advanced Parkinson disease

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## Summary

The aim of the study was to evaluate the changes in regional cerebral metabolic rate of glucose (rCMRGlu) induced by bilateral subthalamic nucleurs (STN) stimulation in advanced Parkinson's disease (PD). $^{18}$F-Fluorodeoxyglucose (FDG) PET data obtained before and one month after stimulation were analyzed with statistical parametric mapping (SPM). As a result of clinically effective bilateral STN stimulation, rCMRGlu increased in lateral globus pallidus (GP), upper brain stem, dorsolateral prefrontal cortex (DLPFC) and posterior parietal-occipital cortex, and decreased in the orbital frontal cortex and parahippocampus gyrus ($p < 0.001$). We conclude that the alleviation of clinical symptoms in advanced PD by bilateral STN stimulation may be the result of activation of both ascending and descending pathways from STN and of restoration of the impaired higher-order cortex functions.

*Keywords:* Parkinson's disease; subthalamic nucleus; deep brain stimulation; PET; $^{18}$F-fluorodeoxyglucose.

## Introduction

Stimulation of the subthalamic nucleus (STN), especially bilateral stimulation, may improve all cardinal motor signs of the Parkinson's disease (PD), and has become an effective treatment option in advanced medically intractable PD patients. However, the underlying mechanisms are still poorly understood. To elucidate the functional anatomic substrate involved in the clinical effect of STN stimulation, we investigated the changes in regional cerebral metabolic rate of glucose (rCMRGlu) with $^{18}$F-fluorodeoxyglucose (FDG) PET examinations in PD patients under clinically effective bilateral STN stimulation.

## Materials and methods

### *Patients*

Five patients with insufficient symptom control by medication of advanced PD, all levodopa responsive, were selected for this study. The patients had a clear diagnosis of idiopathic PD with bilateral symptoms, disabling motor fluctuations despite adequate pharmacotherapy, no brain pathology as assessed by MRI, and no dementia symptoms. Bilateral STN electrodes (Medtronic model 3389; Medtronic, Minneapolis, MN) were implanted under local anesthesia using magnetic resonance imaging (MRI)-guided target identification and intraoperative macrostimulation. The electrodes were permanently connected to impulse generators (Soletra, Medtronic) and lead extensions in the same surgical session. The clinical characteristics of the patients are presented in Table 1.

### *Study design*

Written informed consent was obtained from each subject before entering the study. All patients were scanned twice with FDG/PET. Preoperative imaging took place on the operation day just before mounting the frame and then one month after surgery. The patients fasted overnight prior to the scannings and antiparkinsonian medications had been discontinued at least 12 hrs. The STN stimulation was on at least 12 hrs prior to the postoperative PET imaging. Before the PET imaging, patients were rated according to the motor portion of Unified Parkinson's Disease Rating Scale (UPDRS III).

### *Positron emission tomography*

The PET examinations were performed with an ECAT EXACT HR+ scanner (Siemens-CTI, Knoxville, USA) with the patient supine in resting state having the eyes covered and the ears plugged. In the three-dimensional mode, the scanner acquires oblique sinograms with a maximum cross-coincidence of $\pm 11$ rings. A 10 min transmission scan with three rotating $^{68}$Ge/$^{68}$Ga sources was performed for attenuation correction. The scanning was started 30 min after an intravenous bolus injection of 5 mCi of FDG and lasted for 10 min.

### *Data analysis*

The data on rCMRGlu were analyzed with statistical parametric mapping (SPM 99, Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab 6.1 (Mathworks Inc., Sherborn, MA). The scans from each subject were aligned, stereotaxically normalized, and proportionately scaled. Metabolic measurements obtained pre- and postoperatively were compared on a voxel basis using the paired *t*-test option

Table 1. *Clinical characteristics of the PD patients 1 month after bilateral STN stimulation*

| Patient no./sex/age | Disease duration yrs | UPDRS motor score (off drug) | | Dopaminergic treatment (mg/24 h) | |
|---|---|---|---|---|---|
| | | Pre-operation | 1 month post-op | Pre-operation | 1 month post-op |
| 1/M/63 | 12 | 65 | 25 | 1200 | 1100 |
| 2/M/57 | 8 | 39 | 18 | 850 | 700 |
| 3/M/58 | 6 | 38 | 16 | 750 | 500 |
| 4/M/66 | 5.5 | 42 | 20 | 700 | 400 |
| 5/F/64 | 5 | 49 | 21 | 1650 | 800 |
| Mean ± SD | 7.3 ± 2.8 | 46.6 ± 11.1 | 20 ± 3.4 | 1030 ± 397.8 | 700 ± 273.9 |

Dopa equivalent: 100 mg L-dopa = 133 mg released L-dopa = 10 mg Bromocriptine = 1 mg Selegiline.

in SPM99. Operative changes were considered significant for $p < 0.001$ at cluster level over the entire volume in the brain analyzed.

## Results

### *Clinical outcome*

After one month of bilateral STN stimulation, UPDRS motor scores improved by 57.1% in the off medication state ($p < 0.005$). The mean dose of levodopa was decreased by 32% as compared to the preoperative condition.

### *Effects of bilateral STN stimulation on regional brain metabolism*

Significant changes of the cerebral metabolic activity following clinically effective STN stimulation are summarized in Table 2 and Figs. 1 and 2. During the stimulation, FDG/PET showed a significantly *increased* rCMRGlu in the left lateral globus pallidus (GP), mid-

Table 2. *Areas with changes in resting-state cerebral metabolism in PD patients with bilateral STN stimulation*

| Areas | Side (L/R) | Talairach coordinates x | y | z | t score | *p* |
|---|---|---|---|---|---|---|
| *Enhanced activation* | | | | | | |
| Occipital lobe, | L | −24 | −78 | −8 | 40.53 | 0.0001 |
| Lingual gyrus (BA18) | R | 4 | −94 | −14 | 26.89 | 0.0001 |
| Parietal lobe, | L | −18 | −54 | 56 | 9.02 | 0.001 |
| Precuneus (BA7) | L | −12 | −58 | 48 | 8.57 | 0.001 |
| Middle frontal cortex (BA10) | R | 46 | 52 | −2 | 27.97 | 0.0001 |
| Lateral globus pallidus | L | −14 | −4 | 4 | 7.59 | 0.001 |
| Brainstem, midbrain | R | 14 | −22 | −18 | 8.04 | 0.001 |
| | R | 12 | −26 | −16 | 7.91 | 0.001 |
| *Reduced activation* | | | | | | |
| Inferior frontal cortex | R | 42 | 20 | 10 | 8.71 | 0.001 |
| (BA45, BA47) | L | −44 | 30 | −14 | 14.31 | 0.001 |
| Parahippocampal gyrus | L | −28 | −4 | −18 | 15.52 | 0.001 |

*BA* Brodmann area.

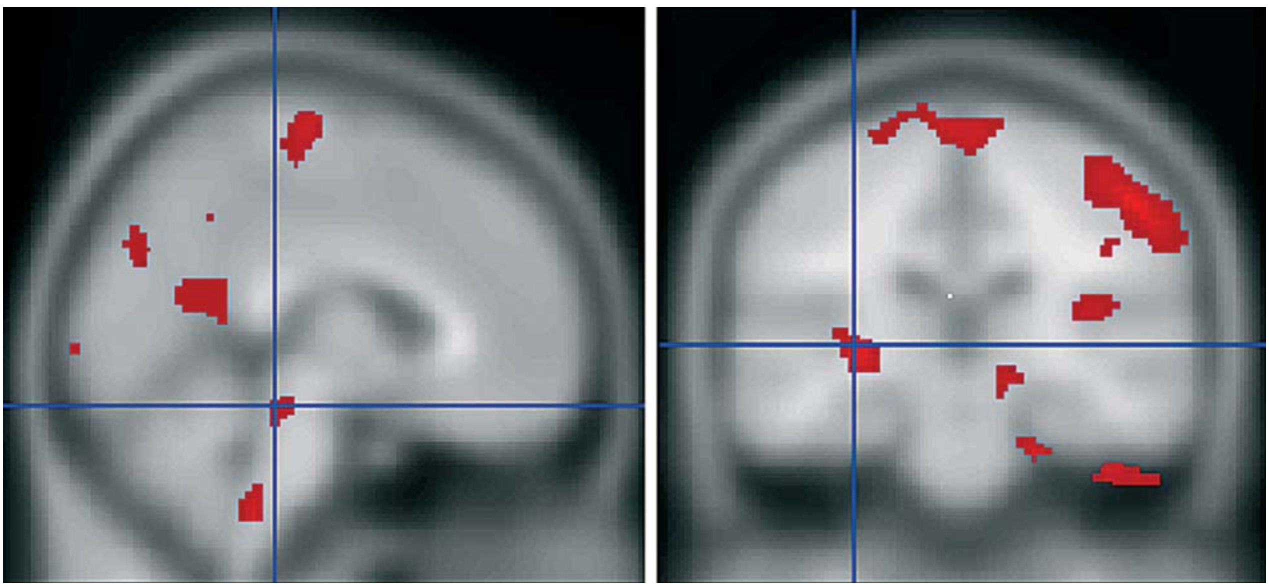

Fig. 1. Relative increase of activation in midbrain, globus pallidus and parietal-occipital cortex

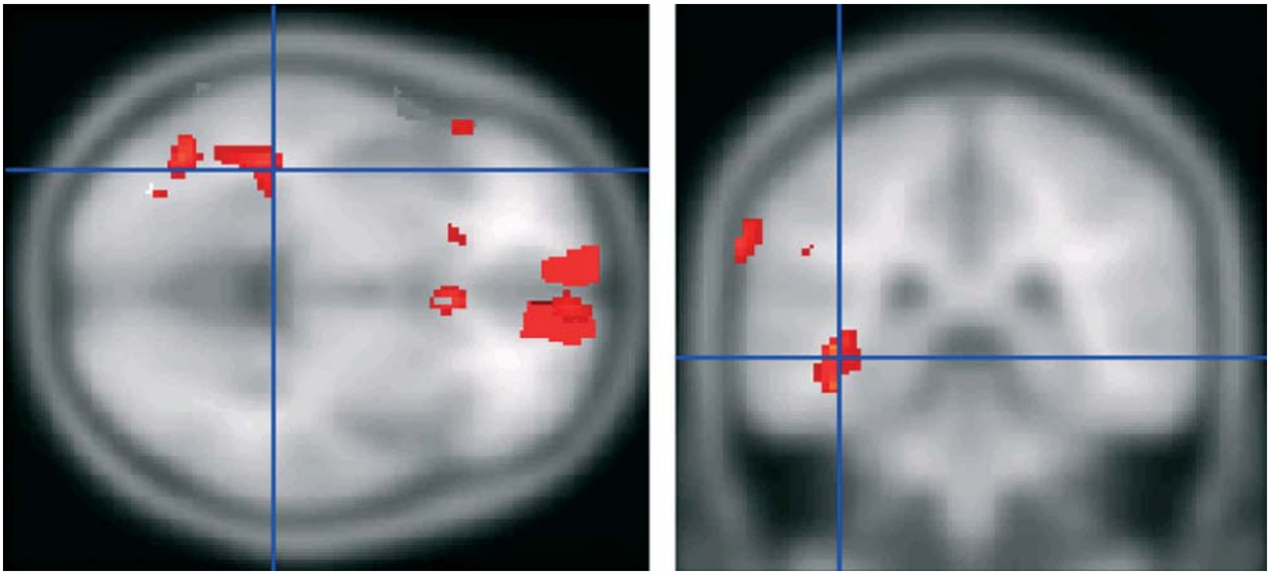

Fig. 2. Relative decrease of activation in orbital frontal cortex and left parahippocampus gyrus

brain, right dorsal lateral prefrontal cortex (DLPFC) and bilaterally in the posterior parietal-occipital cortex (BA7, 18). Significant *reductions* in glucose utilization were present in the bilateral orbitalfrontal cortices and in the parahippocampal gyrus.

## Discussion

Resting state measurement of regional glucose utilization using FDG/PET can be applied for localizing the effects of stereotaxic surgical procedures on brain function. A previous resting state FDG/PET study has demonstrated that PD is characterized by lentiform, thalamic and pontine hypermetabolism associated with metabolic reductions in the lateral premotor, DLPFC and parietal-occipital association cortical regions [3].

The main findings in our study were the activation of lateral GP and the upper brain stem during bilateral STN stimulation. This is in contrast to the effects of subthalamotomy, which is reported to cause a decrease in the glucose metabolism in the lentiform nucleus, thalamus and the pons [6]. Since STN is reciprocally interconnected with lateral GP (GPe), the activation of that latter structure may be the result of orthodromatic activation of STN efferent or antidromatic activation of Gpe afferent fibers. This finding is consistent with a previous cerebral blood flow PET study after bilateral STN stimulation [7]. The activation of STN efferent destined to the pedunculopontine nucleus (PPN) in the upper brain stem is presumably part of the reason for the increased rCMRGlu in this area. Since the activation of PPN can improve akinesia, gait dysfunction and postural abnormalities as demonstrated in a primate PD model [4], this activation may also be a basis for the improvement of the axial symptoms in PD patients subjected to bilateral STN stimulation.

STN stimulation also influenced areas remote from the stimulation sites including DLPFC and bilateral parietal-occipital cortices. DLPFC is mostly involved in cognitive function such as motor planning or working memory, and the posterior parietal-occipital areas serve as higher-order sensory convergent areas for perception; they are also assumed to be involved in other higher brain functions such as self-initiated movements, which are typically impaired in PD patients [1, 2]. Clinically effective bilateral STN stimulation appears to restore these functionally deficient cerebral cortices in PD.

Another finding of STN stimulation was a decrease of FDG uptake in both orbitalfrontal cortices and the parahippocampal gyrus. Our findings may indicate that the depression observed in some patients treated with STN stimulation reflects a specific interference of the stimulation with limbic functions rather than being a sequel of postoperative levodopa reduction. In a previous neuropsychological study, it has been demonstrated that bilateral STN stimulation has a negative impact on various aspects of frontal executive capacity [5]. That observation may well correspond to our finding that the metabolism of the orbitalfrontal cortices is significantly reduced.

The present study demonstrates that STN high-frequency stimulation activates both ascending and descending pathways resulting in either excitation or inhibition and in restoration of impaired higher-order cortex function in advanced PD patients.

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