

Università degli Studi di Trieste

Corso di Laurea Magistrale in
INGEGNERIA CLINICA

**DEEP BRAIN
STIMULATION E
NEUROSEGNALI DI
PROFONDITÀ**

**Corso di Complementi di Analisi di
Segnali Biomedici**

Modulo NEUROSEGNALI

Docente Sara Renata Francesca MARCEGLIA

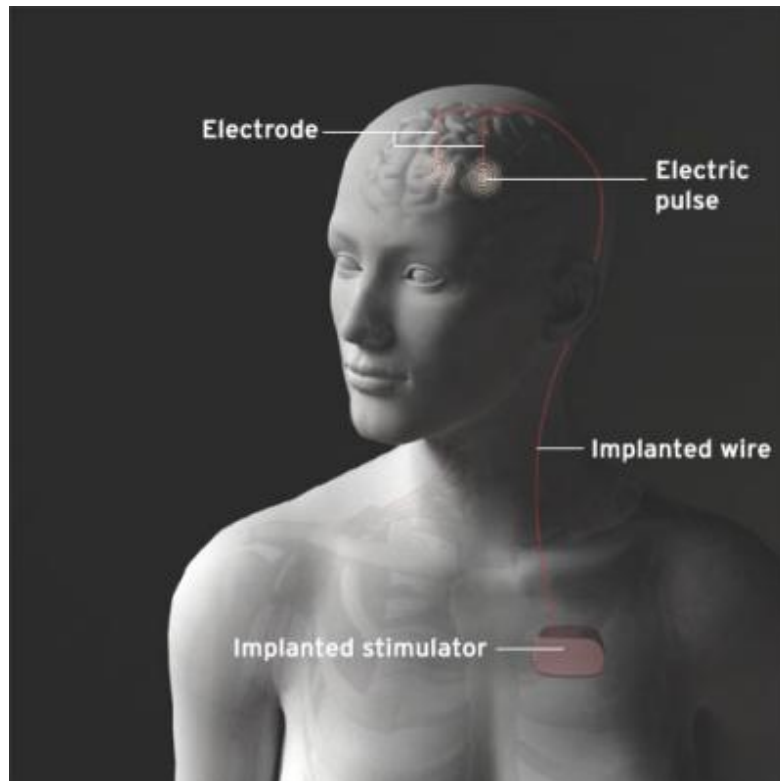


Dipartimento di Ingegneria e Architettura



**UNIVERSITÀ
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CHE COS'È LA DBS

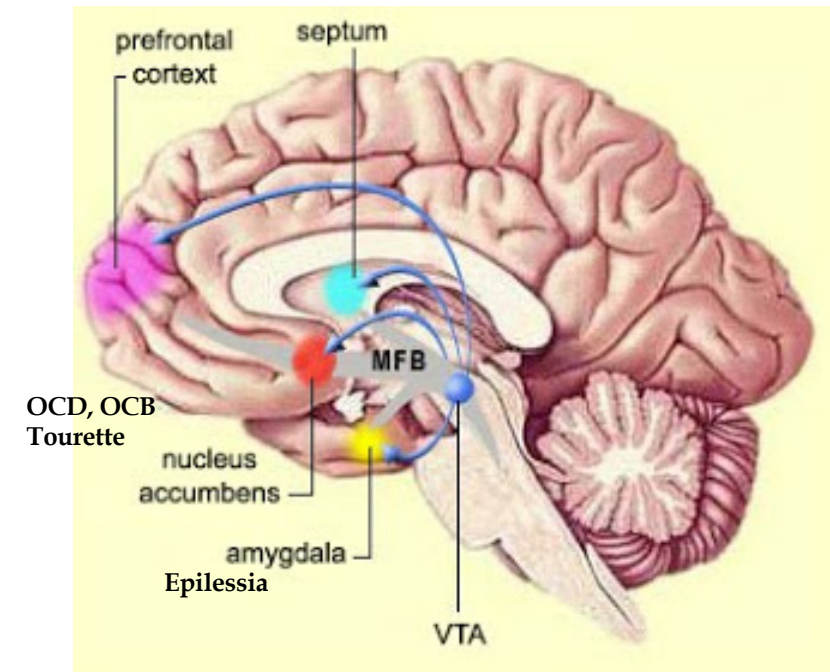
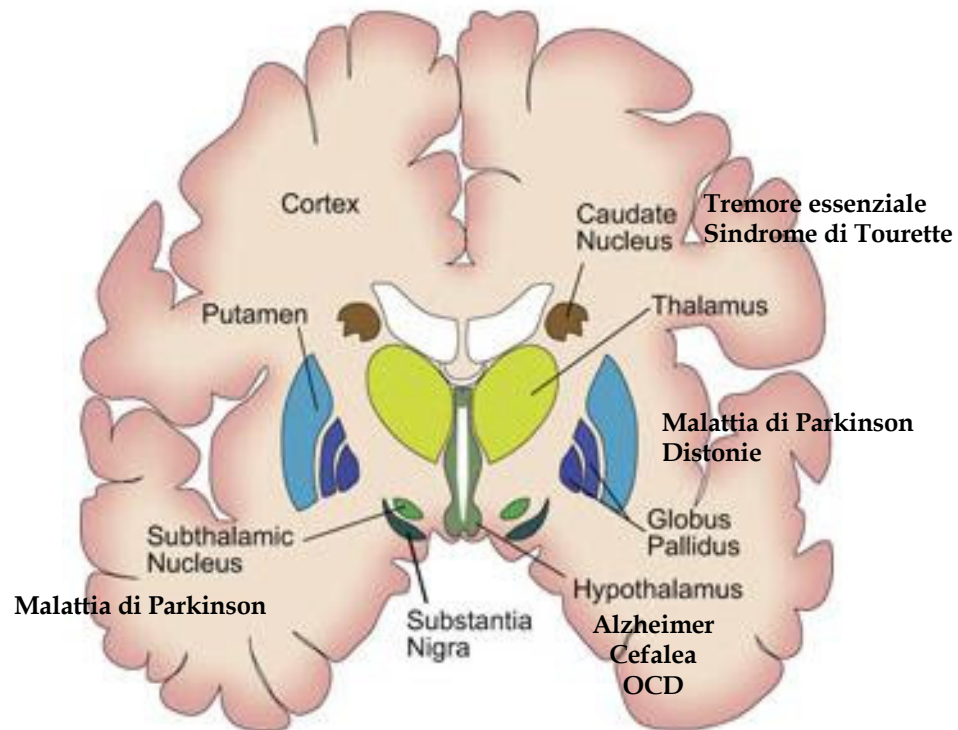


- ✓ Stimolazione elettrica ad alta frequenza (biologica) di strutture target sottocorticali
- ✓ Elettrocateri stimolatori posizionati mediante chirurgia stereotassica
- ✓ Stimolatore sottocutaneo



Frequenza	100-180 Hz
Durata dell'impulso	60-150 us
Ampiezza (in V)	2-5 V
Ampiezza (in I)	1-5 mA

I TARGET DELLA DBS

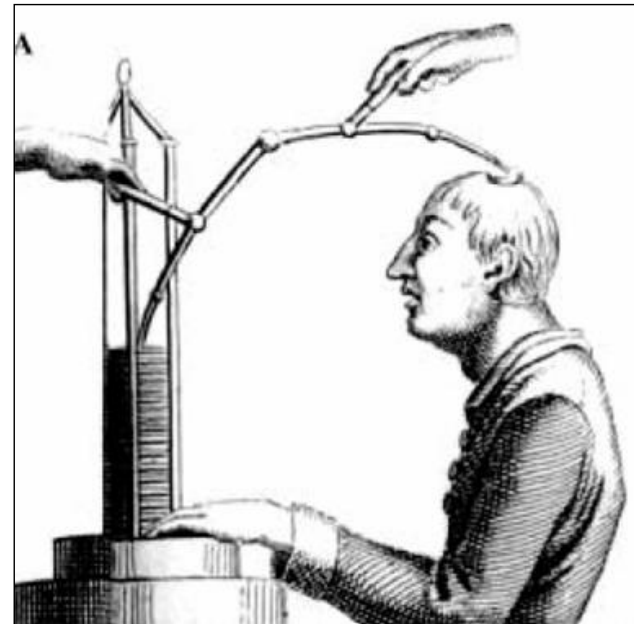


I PRECURSORI DELLA DBS



Giovanni Aldini
(1762-1834)

Giovanni Aldini, nipote di Galvani, si dedicò alle applicazioni elettroterapiche focalizzandosi sull'uso dell'elettricità per guarire malattie mentali. Fece uso della pila di Volta.



Trattamento con la pila voltaica eseguito su Lanzarini (sindrome depressiva, 17 maggio 1801, Ospedale Sant'Orsola di Bologna).



DBS: LA STORIA

- La DBS come tecnica chirurgica nasce con la stereotassia
- **1952 → J. Delgado:**
 - **Primi esperimenti sugli animali**
 - **In seguito implanta 25 pazienti epilettici e schizofrenici**
- 1963 → N. Bechtereva
 - Impianto di pazienti con disturbi ipercinetici
 - Articolo in russo, poco conosciuto
- 1970 → impianti in pazienti con dolore cronico
- 1978 → Cooper:
 - 200 pazienti epilettici impiantati nel cervelletto e nel talamo

From the State Hospital for Mental Diseases, Howard, Rhode Island, Department of Medicine and Neurosurgical Service, Massachusetts General Hospital, Department of Medicine and Surgery, Harvard Medical School and Department of Physiology, Yale University School of Medicine.

Technique of Intracranial Electrode Implantation for Recording and Stimulation and its Possible Therapeutic Value in Psychotic Patients

by

JOSE M. R. DELGADO, HANNIBAL HAMLIN and
WILLIAM P. CHAPMAN



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Proc. 6th Symp. Int. Soc. Res. Stereotaxotomy, Tokyo 1973, part II
Confinia neurol. 37: 136–140 (1975)

Method of Electrostimulation of the Deep Brain Structures in Treatment of Some Chronic Diseases

N. P. BECHTEREVA, A. N. BONDARTCHUK, V. M. SMIRNOV,
L. A. MELIUTCHEVA and A. N. SHANDURINA

Institute of Experimental Medicine, Academy of Medical Sciences of the USSR,
Leningrad



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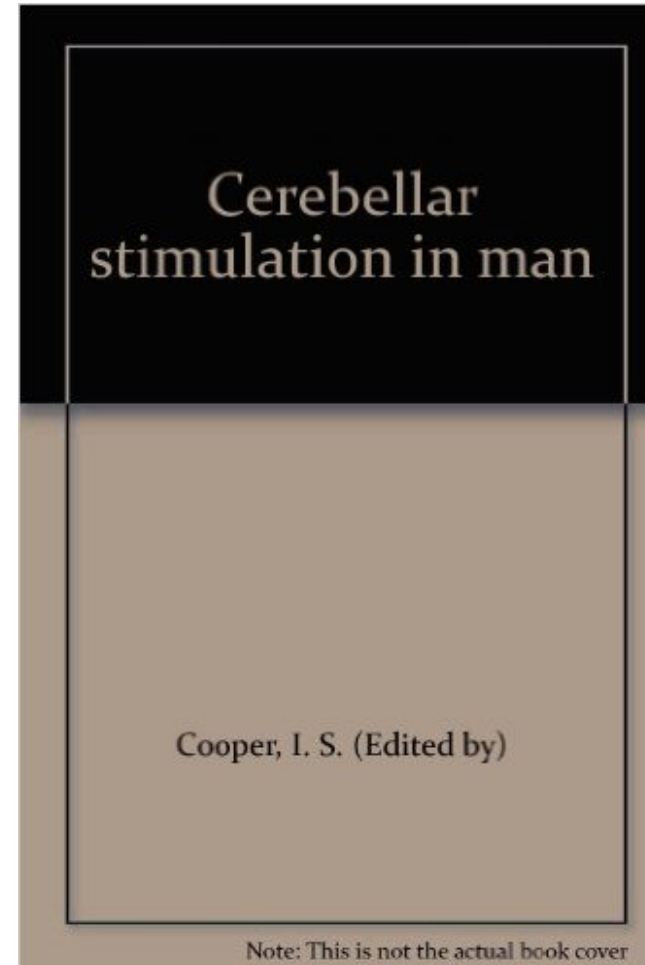
September 1973

Chronic Thalamic Stimulation for the Control of Facial Anesthesia Dolorosa

Yoshio Hosobuchi, MD; John E. Adams, MD; Burt Rutkin, MS

DBS: LA STORIA

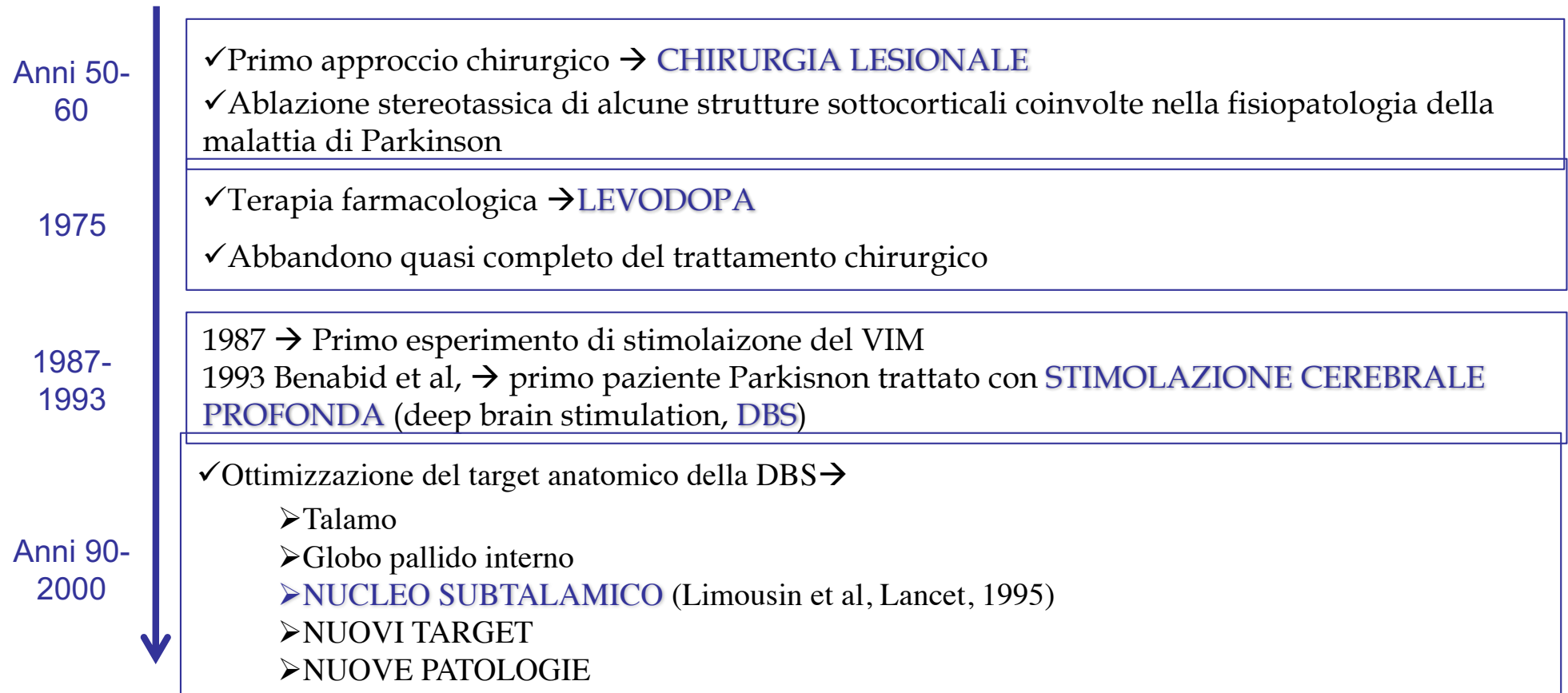
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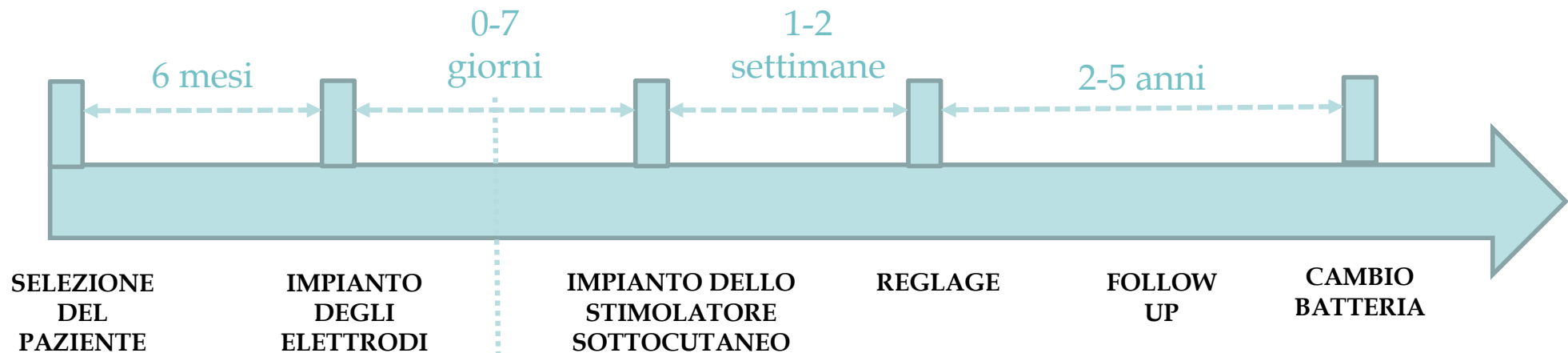
DBS E MALATTIA DI PARKINSON



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LA PROCEDURA



Finestra temporale per lo studio dei segnali elettrofisiologici dagli elettrodi impiantati

Gli stimolatori non ricaricabili hanno un tempo di vita di 2-5 anni e poi vengono sostituiti

LA CHIRURGIA STEREOTASSICA



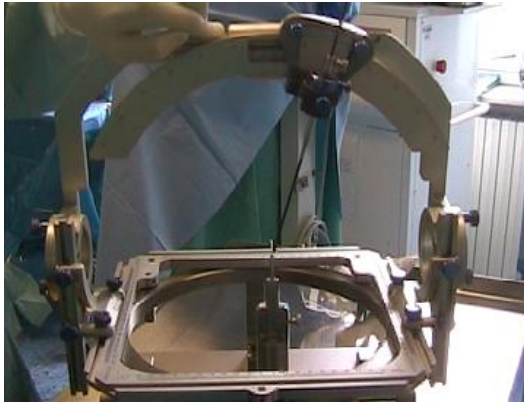
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LA CHIRURGIA STEREOTASSICA



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Preparazione del casco
stereotassico

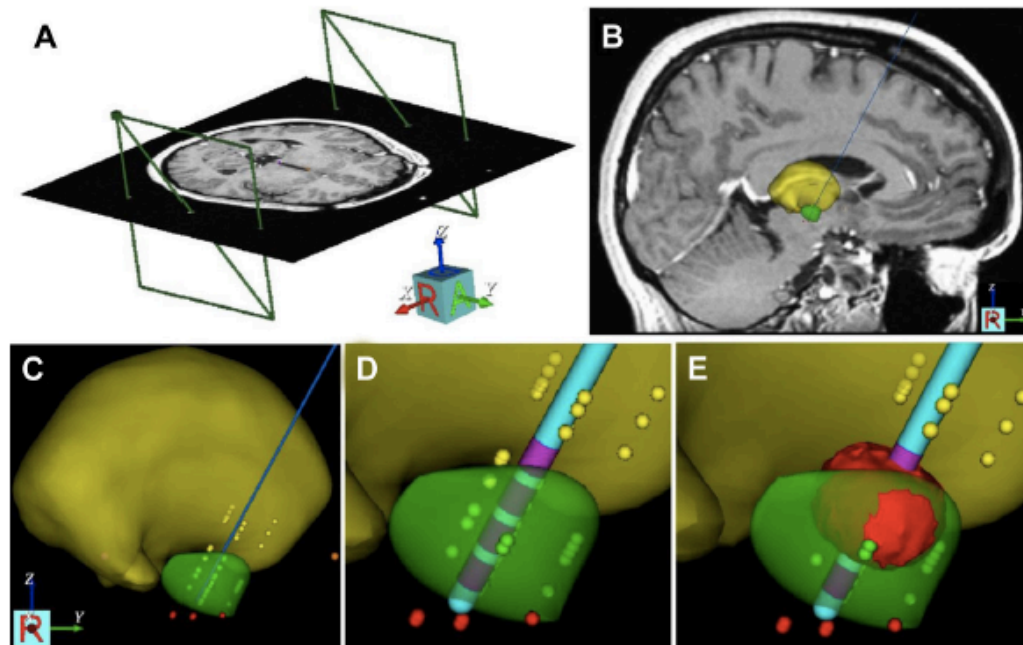


Il casco stereotassico montato
sul paziente

LA CHIRURGIA STEREOTASSICA



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Planning preoperatorio per
la definizione di :

posizione del target

traiettoria di ingresso

Figure 1. Deep brain stimulation. A) Stereotactic coordinate system is defined relative to the patient imaging data using the frame fiducial markers displayed in green. B) Atlas representations of anatomical nuclei are used to help identify the target (yellow volume – thalamus; green volume – subthalamic nucleus (STN)). The blue line represents the intended surgical trajectory. C) Stereotactic location of microelectrode recording data (thalamic cells – yellow dots; STN cells – green dots; substantia nigra cells – red dots). D) DBS electrode placement. Purple cylinders represent the electrode contacts. E) Red volume simulates the volume of tissue activated during therapeutic DBS. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

LA CHIRURGIA STEREOTASSICA



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Foratura della teca
cranica (trapanatura)

LA CHIRURGIA STEREOTASSICA



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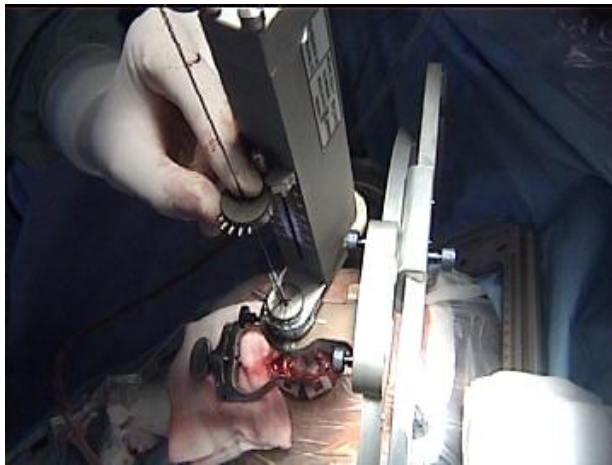


Preparazione della
microguida

LA CHIRURGIA STEREOTASSICA



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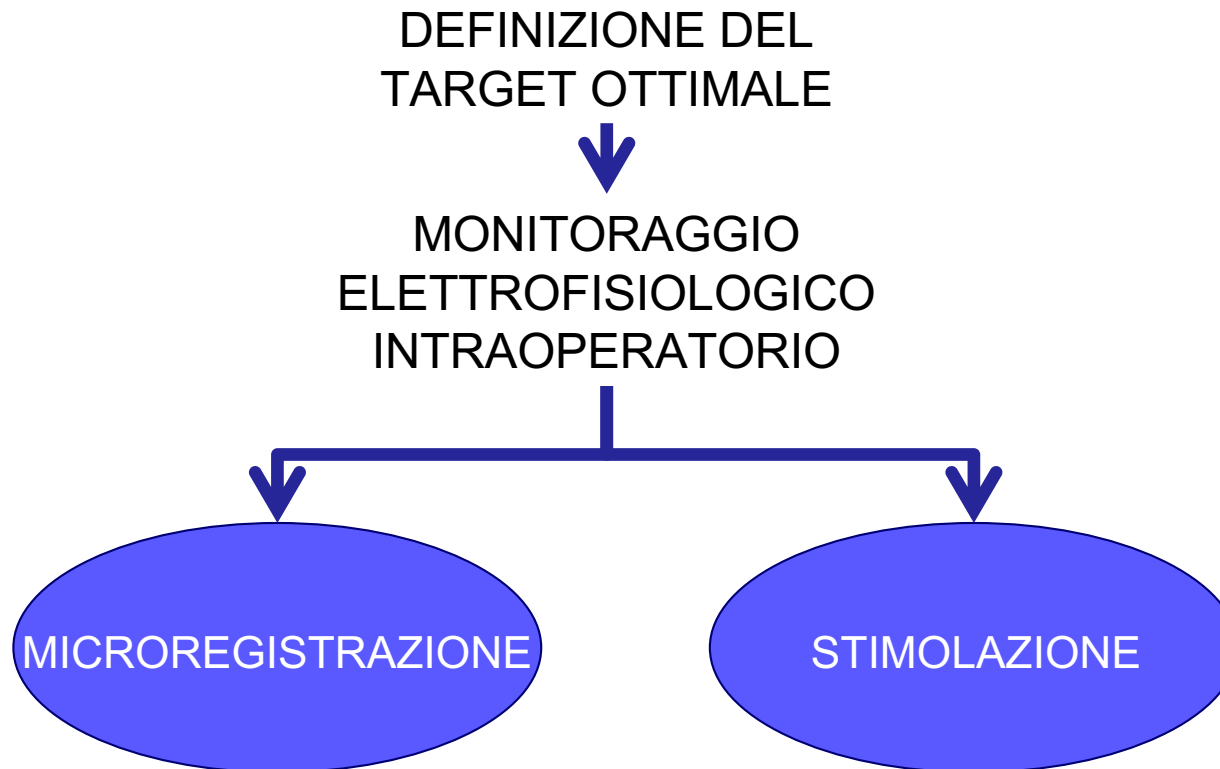


Inserimento dei microelettrodi
esploratori

LA CHIRURGIA STEREOTASSICA

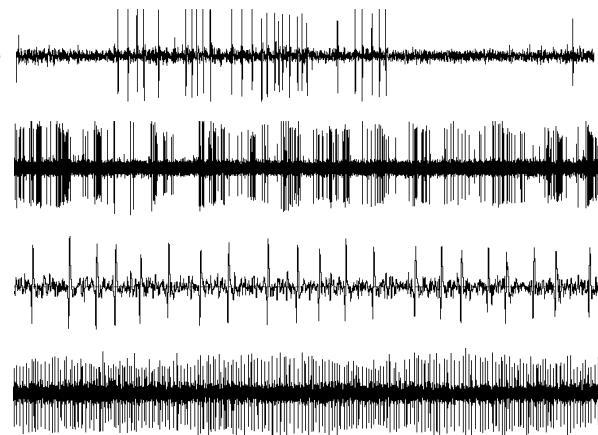
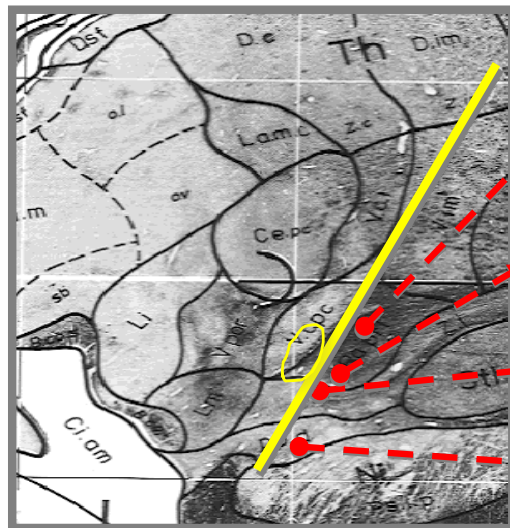
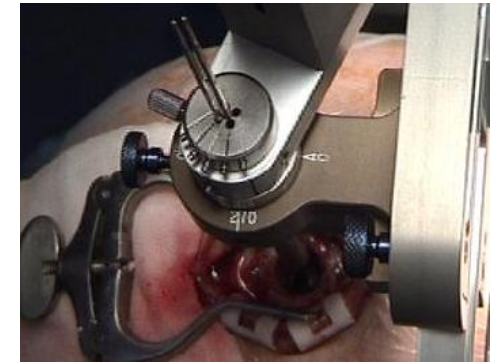


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LA MICROREGISTRAZIONE

- RegISTRAZIONI elettrofisiologiche utilizzate per migliorare il posizionamento degli elettrodi.
- Inserimento di 2/3 microelettrodi ($\sim 1\text{ M}\Omega$) in parallelo per la registrazione della attività cellulare (2-3 cellule)



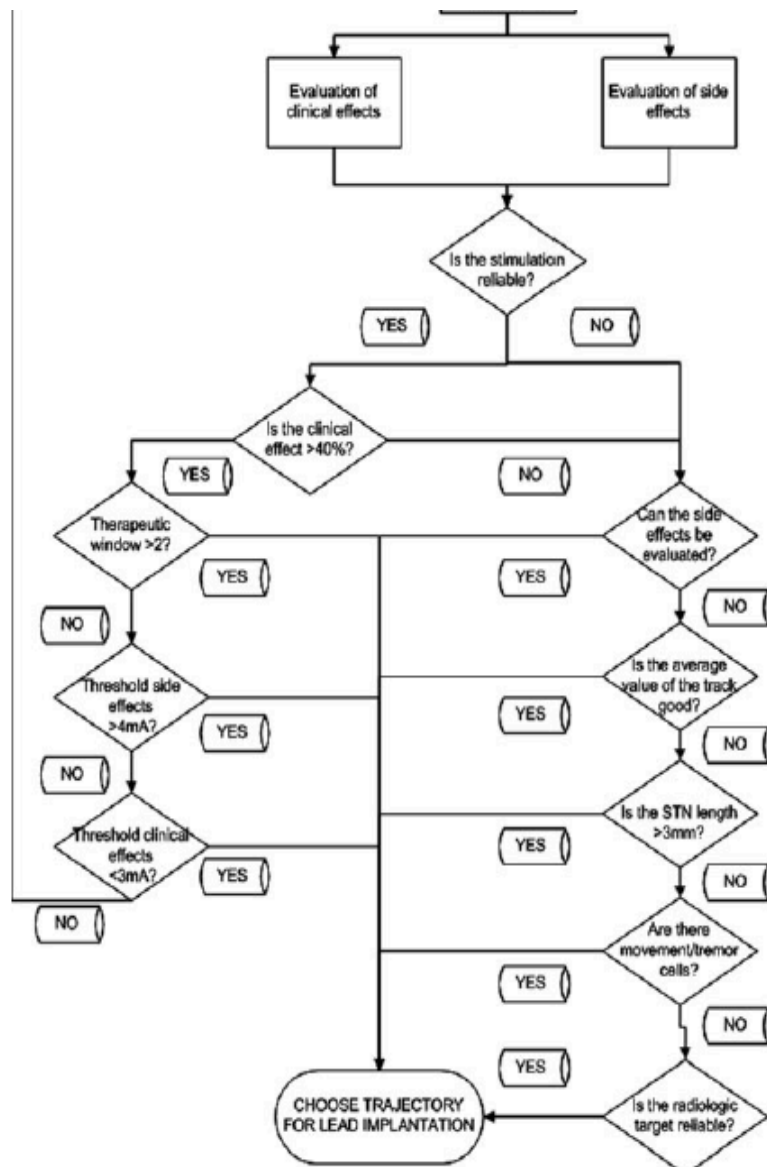
Confine

Centro

Zona incerta

Sostanza nera

LA STIMOLAZIONE INTRAOPERATORIA



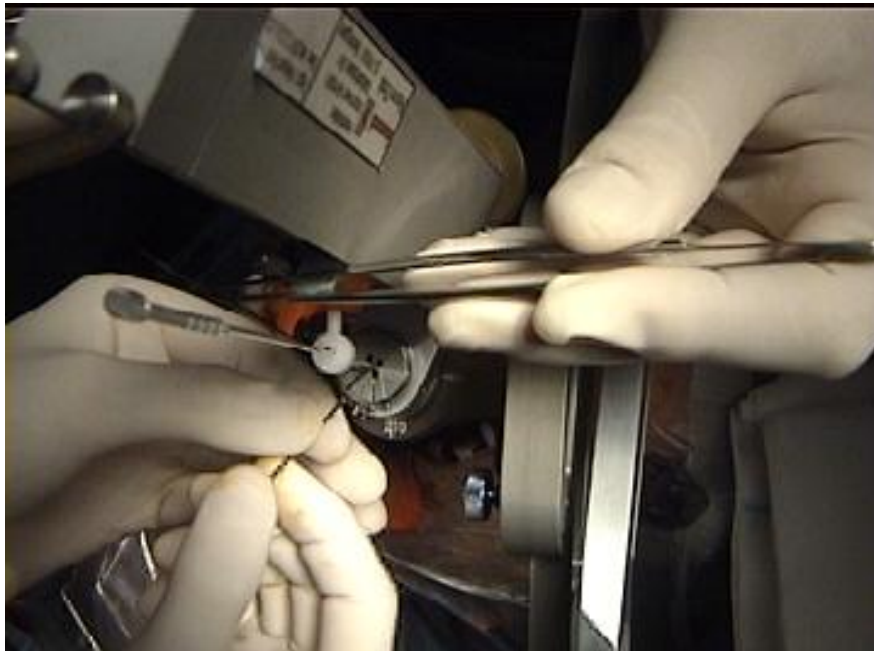
- Valutazione del livello di collaborazione del paziente
- Valutazione dell'effetto clinico → Ampiezza minima che consente una diminuzione della rigidità >50%
- Valutazione degli effetti collaterali → Ampiezza massima che consente la stimolazione senza effetti collaterali

$$\text{Therapeutic window} = \frac{\text{Threshold for side effects (mA)}}{\text{Threshold for clinical effects (mA)}} > 2.$$

IMPIANTO DELL'ELETTRODO DEFINITIVO



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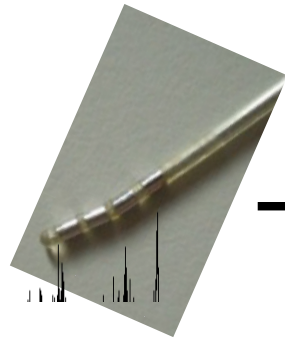
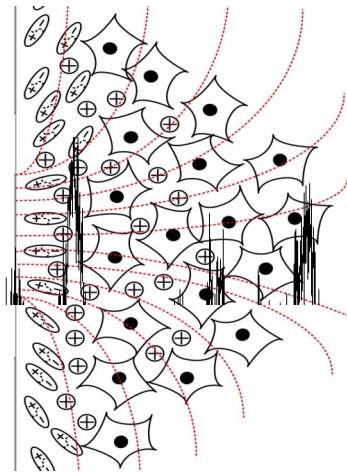
- ✓ L' elettrodo definitivo viene impiantato
- ✓ L' elettrodo **non viene collegato** allo stimolatore sottocutaneo
- ✓ Lo **stimolatore** sottocutaneo viene impiantato in un **intervento successivo**

INTASCAMENTO DELLO STIMOLATORE



- L'operazione di connessione degli elettrodi alle estensioni, tunnellizzazione e connessione allo stimolatore può avvenire:
 - Immediatamente dopo il posizionamento degli elettrodi
 - Alcuni (3-7) giorni dopo la chirurgia stereotassica → gli elettrodi impiantati vengono esternalizzati e consentono la registrazione dei biopotenziali locali (local field potentials, LFPs)
- L'operazione avviene in anestesia generale

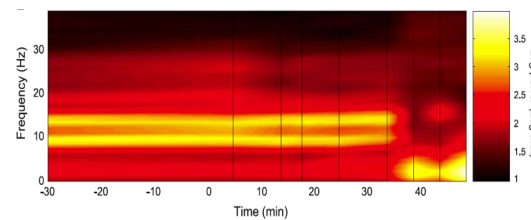
I LOCAL FIELD POTENTIALS



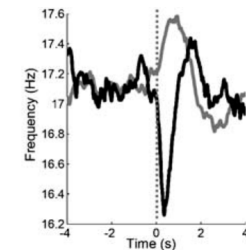
ANALISI DELLE
OSCILLAZIONI IN
DIVERSE CONDIZIONI
SPERIMENTALI

Attività sincrona presinaptica e postsinaptica di ampie popolazioni di neuroni → EEG di profondità – local field potentials (LFPs)

Modulazioni di
ampiezza



Modulazioni di
frequenza



IMPIANTO DEFINITIVO



4 cylindrical metal contacts of
Platinum-Iridium (30%) of 6
mm² area

(1.27 mm diameter, 1.5 mm width,
spaced by 0.5 mm)



*Medtronic Activa PC
and
Extension cable*

REGLAGE E FOLLOW UP

- Reglage →
 - Procedura di ottimizzazione dei parametri di stimolazione
 - Viene effettuata manualmente da un neurologo esperto per trail-and-error
 - Dopo circa 1-2 settimane dall'impianto
- Follow up →
 - La stimolazione attuale prevede parametri costanti che vengono verificati solo durante visite di follow-up
 - 6-12 mesi
 - In alcuni casi al paziente è fornito un programmatore per verificare il livello della batteria



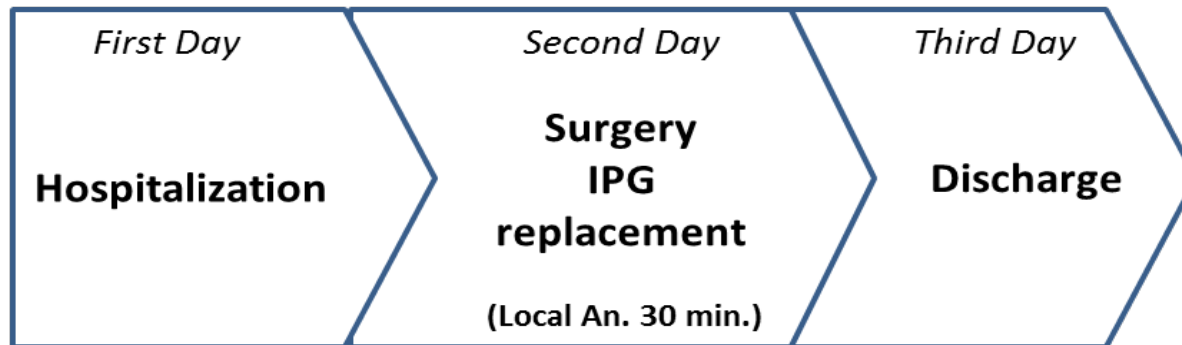
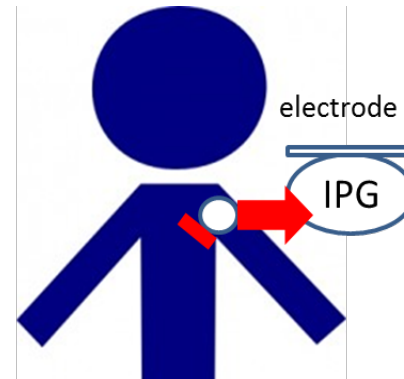
*Medtronic
Programmatore
per il clinico*



*Medtronic
Programmatore
per il paziente*

CAMBIO BATTERIA

Routine surgery for IPG replacement





RISCHI

- Rischi connessi alla procedura chirurgica:
 - Emorragia cerebrale → severa (morte o coma) nel 1-2% dei casi
 - Ictus, seizures, infezioni
- Rischi connessi all'impianto
 - Infezioni → incidenza da meta-analisi 4-5%
 - Problemi connessi agli elettrodi e/o stimolatore → 2-3%
- Rischi connessi alla stimolazione di per sè
 - rischi reversibili con il cambio di programmazione
 - 19% dei pazienti



The Neurostimulation Appropriateness Consensus Committee (NACC) Safety Guidelines for the Reduction of Severe Neurological Injury

Deep Brain Stimulation

The placement of a lead into the targets in the substance of the brain lends to the potential of brain injury from direct trauma, bleeding, and infection. The complications rates are detailed in Table 6.

Table 6. Neurological Complication Rates: Deep Brain Stimulation.

	Percentage
Hemorrhage	1.8%
Infection	1.4–8.5%
Infection/erosion	6.7–20%

COMPLICAZIONI



La disattivazione del IPG non comporta rischio di vita

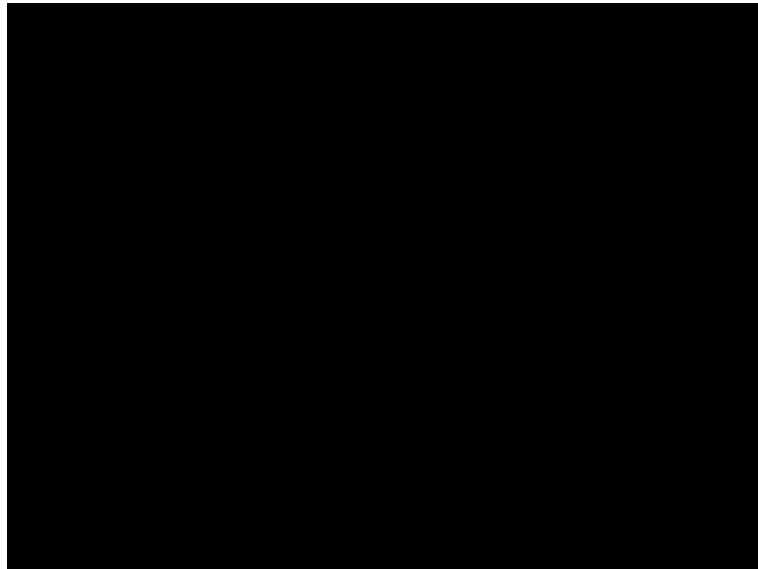
TO THE EDITOR

A Canadian Winter Indirectly Inactivates a Deep Brain Stimulation System

Keywords: Deep brain stimulation, Implantable pulse generator, Electromagnetic interference, Movement disorders

Neodymium magnets are polyvalent in the fashion and technology industries. In our patient, small hidden fashion magnets caused his IPG to inactivate, but only once positioned in very close proximity, complicating our search for an EMI device. Miniature magnets (8 mm) can interfere with implantable cardioverter-defibrillators if positioned within 3 cm of the generator.² Magnets from tablet computers can also modify programmable shunt valve settings.³ As illustrated by this case, education about EMI alerted our patient to the possibility of interference but did little to help him rapidly resolve his problem.

BENEFICI (1)



***preop.
med ON***

BENEFICI (2)



***3 mesi
med OFF
stim ON***

MECCANISMI D'AZIONE

- I meccanismi d'azione della DBS non sono ancora stati chiariti
- L'area di attivazione attorno all'elettrodo dipende dalla densità di corrente
- Gli effetti sui neuroni circostanti sono molteplici

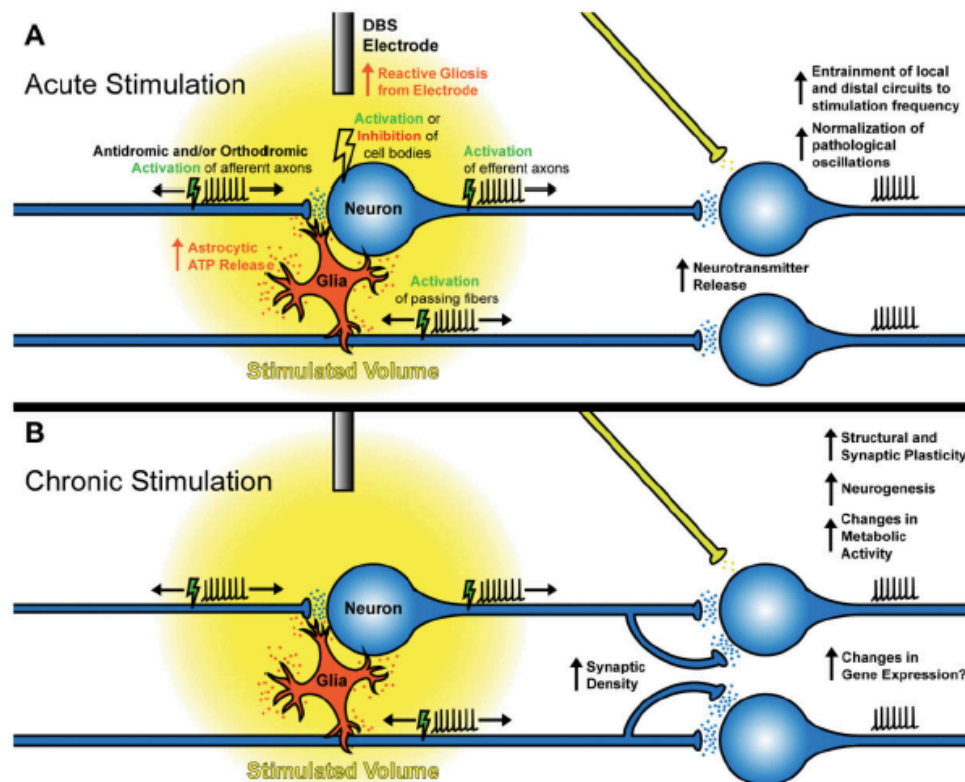
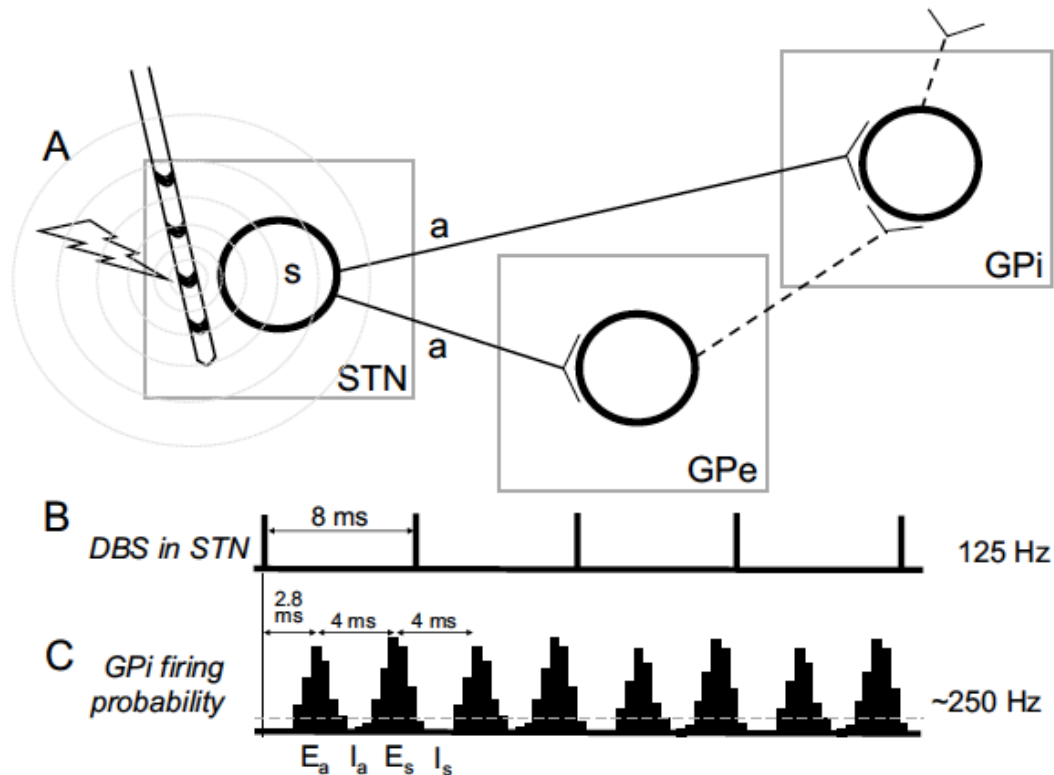


Figure 1. General cellular mechanisms of DBS

(A) Acute stimulation results in complex effects in local, upstream, and downstream circuits. Insertion of the electrode itself promotes an inflammatory response resulting in reactive gliosis over the course of days. Upon stimulation, DBS stimulates neural cell bodies, axons, and glia, entraining neural activity to the stimulation frequency. Effects on cell bodies are variable and both activation and inhibition of firing rates have been reported. DBS preferentially modulates myelinated axons rather than cell bodies, resulting in antidromic and/or orthodromic stimulation of afferent axons, efferent axons, and passing fibers. How and when antidromic vs. orthodromic activation is elicited is unknown. Modulation of upstream and downstream projections can normalize pathological oscillations in distal regions by entraining activity to the stimulation frequency (frequency jamming), and can result in enhanced neurotransmitter release. (B) The effects of chronic stimulation are less well-understood but neuroplastic mechanisms are evident. Stable metabolic changes and synaptic plasticity occur in the stimulated area and distally modulated regions, as well as neurogenesis and progenitor proliferation. Structural plasticity in the form of changes in intrinsic excitability, synaptic density, and synaptic reorganization can occur as well, possibly driven by activity-induced changes in gene expression. These adaptations may reinforce the effects of acute stimulation.

EFFETTI DI RETE (1)



- La stimolazione a 130 Hz potrebbe portare alla ricostituzione di un ritmo “veloce” (250-300 Hz) a causa della duplice azione del STN sul GPi (diretta e mediata dal GPe)
- Questo fenomeno è riconducibile al concetto di “jamming” → reset dei pattern oscillatori indotto dalla stimolazione a livello dell’intero circuito corteccia-gangli della base-talamo-corteccia

EFFETTI DI RETE (2)

Gli effetti di rete derivano da diversi meccanismi contemporanei di attivazione/inibizione

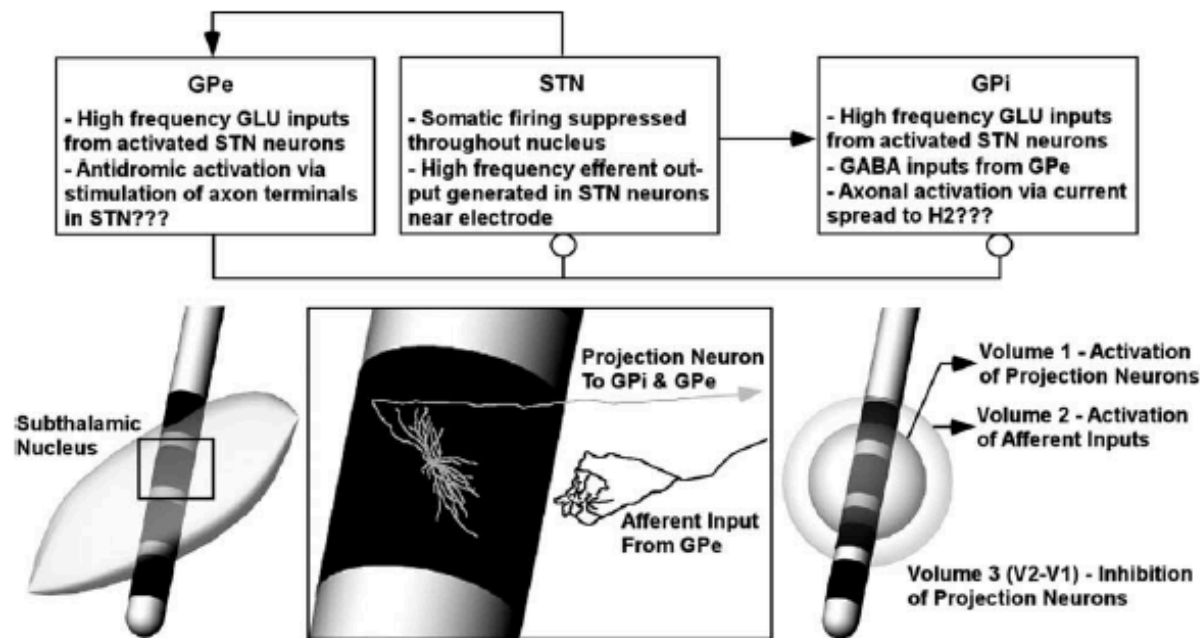


Fig. 7. Hypothetical summary of the effects of STN DBS. See text for details. (Top) network summary of stimulation effects induced in the subthalamic nucleus (STN), external segment of the globus pallidus (GPe), and the internal segment of the globus pallidus (GPi). This list is highly simplified and not exhaustive of present knowledge. (Bottom) pictorial summary of the stimulation effects generated in STN.

APPLICAZIONI CLINICHE

INDICAZIONI D'USO

Malattia di Parkinson

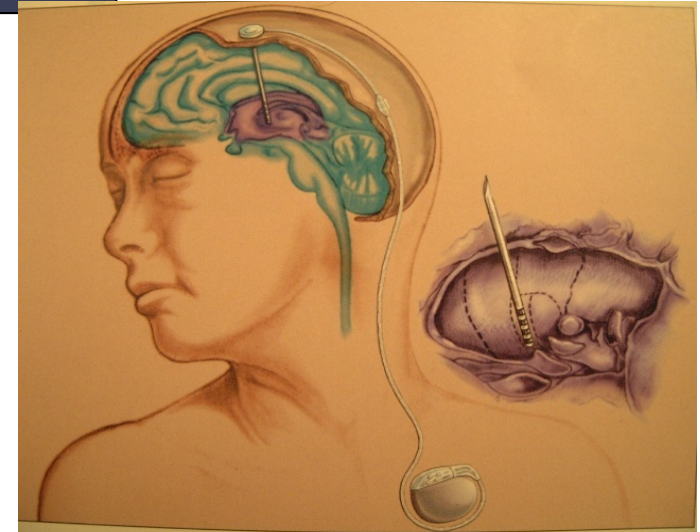
Distonie

Tremore Essenziale

APPLICAZIONI OFF-LABEL

Sindrome di Tourette

Obsessive Compulsive Disorders



APPLICAZIONI SPERIMENTALI

NEUROPSICHIATRIA

Depressione

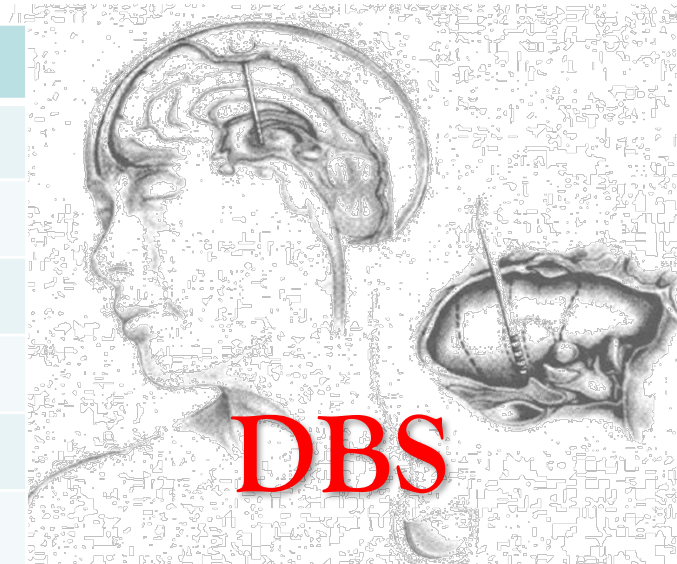
Schizofrenia

Anedonia

Dipendenze

Anoressia

Controllo degli Impulsi



NEUROLOGIA

Alzheimer

Sclerosi Multipla

Autismo

Dolore Cronico

Tinnito

Epilessia

Stato vegetativo/coma

Restless Leg Syndrome

CARDIOLOGIA/MALATTIE METABOLICHE

Iipertensione

Obesità



MALATTIA DI PARKINSON

TARGET

STN – nucleo subtalamico	Target maggiormente utilizzato
GPI – globo pallido interno	Preferibile in pazienti con ipercinesie
Vim- ventral intermediate nucleus (talamo)	Preferibile in pazienti con tremore
PPN – nucleo peduncolopontino	Nucleo sperimentale – per migliorare instabilità posturale e cammino

PARAMETRI CLINICI

Frequenza	130 Hz
Ampiezza	2-5V
Durata dell'impulso	60 us

EFFETTI CLINICI PRINCIPALI

- *Effetto immediato all'accensione*
- UPDRS III OFF – miglioramento del 48-71% a 12 mesi
- Off time – Riduzione del 35-65%
- LEDD – Diminuzione del 65%
- Discinesie – Riduzione del 68%

COMPLICANZE PRINCIPALI

- Peggioramento nel tempo dei sintomi assiali: parlato, cammino, equilibrio, postura
- Declino delle funzioni esecutive
- Fluttuazioni motorie ancora presenti⁶

DISTONIA



TARGET

GPI – globo pallido interno	Target di elezione
STN – nucleo subtalamico	Target sperimentale testato anche in concomitanza con GPI (4 elettrodi impiantati)

PARAMETRI CLINICI

Frequenza	130 - 180 Hz
Ampiezza	2-5V
Durata dell'impulso	90-120 us

EFFETTI CLINICI PRINCIPALI

- *Effetto visibile dopo alcune settimane di accensione*
- Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) – miglioramento del 49%
- Disabilità – miglioramento del 30%
- Qualità della vita – miglioramento del 30%

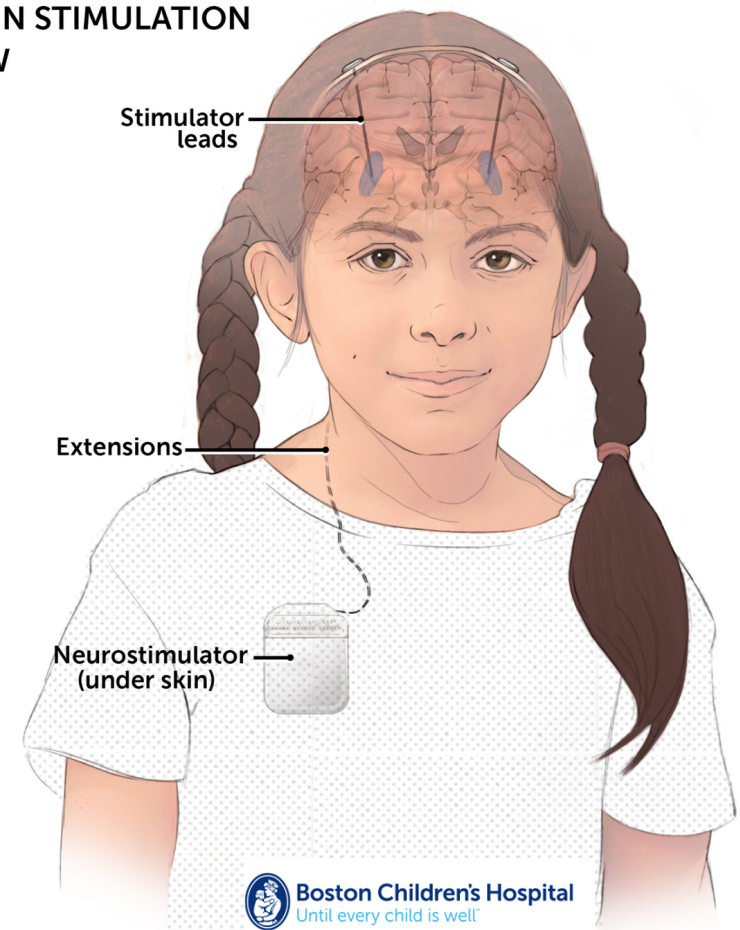
COMPLICANZE PRINCIPALI

- Disartria o acinesia che possono essere indotte dalla stimolazione (poco frequenti)

DBS PEDIATRICA

DEEP BRAIN STIMULATION OVERVIEW

- La DBS è utilizzata nei bambini affetti da distonia
- La DBS nei bambini non è ancora consolidata come negli adulti
- Il bambino dovrà portare l'impianto probabilmente per tutta la vita →
 - Maggiore attenzione all'educazione dei genitori
 - Maggiore attenzione nella procedura chirurgica per evitare infezioni e altre complicanze
 - Importanza di mantenere dei registri della DBS in questi pazienti





TREMORE ESSENZIALE

TARGET

Vim- ventral intermediate nucleus (talamo)	Target di elezione
--	--------------------

PARAMETRI CLINICI

Frequenza	130 Hz
Ampiezza	2-5V
Durata dell'impulso	60 us

EFFETTI CLINICI PRINCIPALI

- *Effetto immediato all'accensione*
- 40-100% riduzione del tremore
- Miglioramento della disabilità
- Miglioramento della qualità della vita

COMPLICANZE PRINCIPALI

- Disartria
- Atassia, problemi nel cammino
- Si suggerisce di spegnere lo stimolatore nel sonno per diminuire la probabilità di diminuzione della tolleranza alla terapia nel tempo



SINDROME DI TOURETTE

TARGET

CM-Pf/VO – nucleo centromediano – parafascicolare/Ventrale Orale (talamo)	Target maggiormente utilizzato
GPI – globo pallido interno	Primo target testato (tic distonici)
Nucleus Accumbens	Pazienti con OCB
Capsula interna (lembo anteriore)capsule	Pazienti con OCB

PARAMETRI CLINICI

Frequenza	130 Hz
Ampiezza	2-9V
Durata dell'impulso	90-210 us

EFFETTI CLINICI PRINCIPALI

- *Effetto visibile dopo alcune settimane di accensione*
- Riduzione dei tic
- In base al target: riduzione dei comportamenti ossessivi e dell'ansietà

COMPLICANZE PRINCIPALI

- Aumento del rischio di infezioni (pazienti con self injuring behaviours - SIB)
- La compliance alla terapia è una controindicazione

OBSESSIVE COMPULSIVE DISORDERS (OCD)



TARGET

Nucleus Accumbens	Primo target testato
Ventral Capsula/Ventral Striatum	Target utilizzato in alcuni pazienti con successo

PARAMETRI CLINICI

Frequenza	130 - 135 Hz
Ampiezza	2-9V
Durata dell'impulso	90 – 210 us

EFFETTI CLINICI PRINCIPALI

- *Effetto visibile dopo alcune settimane di accensione*
- Yale Brown Obsessive Compulsive Score (YBOCS) miglioramento >25% dopo 12 mesi
- Miglioramento ansietà e sintomi depressivi nella maggioranza dei pazienti

COMPLICANZE PRINCIPALI

- Pochi studi di lungo termine

MALATTIA DI ALZHEIMER

Deep brain stimulation of the ventromedial prefrontal cortex causes reorganization of neuronal processes and vasculature

M. Mallar Chakravarty^{a,h,c,*}, Clement Hamani^{c,f,1}, Alonso Martinez-Canabal^g, Jacob Ellegood^h, Christine Laliberté^h, José N. Nobrega^{d,f}, Tejas Sankar^{e,j}, Andres M. Lozano^e, Paul W. Frankland^{g,k,l,m}, Jason P. Lerch^{g,h,j}

Journal of Neurosurgery
Jul 2016 / Vol. 125 / No. 1 / Pages 75-84

Bilateral deep brain stimulation of the fornix for Alzheimer's disease: surgical safety in the ADvance trial

Francisco A. Ponce, MD^{1,*}, Wael F. Asaad, MD, PhD^{2,3}, Kelly D. Foote, MD⁴, William S. Anderson, MD, PhD⁵, G. Rees Cosgrove, MD², Gordon H. Baltuch, MD, PhD⁶, Kara Beasley, DO, MBE⁷, Donald E. Reymers⁸, Esther S. Oh, MD^{9,10}, Steven D. Targum, MD⁸, Gwenn S. Smith, PhD¹⁰, Constantine G. Lyketsos, MD, MHS¹⁰, and Andres M. Lozano, MD, PhD¹¹ for The ADvance Research Group

Surgical Neurology International

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Editor: J. Roberto A. F. Delgado, MD, University of California, Los Angeles, CA, USA

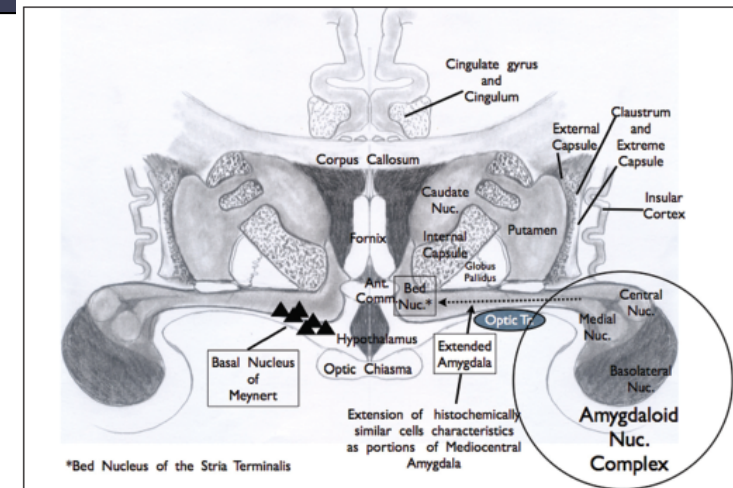
Alzheimer's disease: The role for neurosurgery

Julio Leonardo Barbosa Pereira¹, Angela Downes¹, Alessandra Gorgulho^{1,2}, Vishal Patel¹, Dennis Malkasian¹, Antonio De Salles^{1,2}

Table 1: Clinical trials involving deep brain stimulation for Alzheimer's disease

Study	Start date	Status	Responsible party
Advance DBS-f in patients with mild probable Alzheimer's disease	May 2012	Recruiting	Functional Neuromodulation Ltd
Deep brain stimulation of the NBM to treat cognitive deficits in light to moderate Alzheimer's disease	January 2010	Unknown	Sturm and Kuhn, University of Cologne
Deep brain stimulation for the treatment of Alzheimer's disease	March 2012	Recruiting	Rezai, The Ohio State University
Deep brain stimulation for Alzheimer's disease	March 2007	Unknown	Lozano, University of Toronto
Study of the brain stimulation effect on memory impairment in Alzheimer disease	August 2009	Unknown	Centre Hospitalier Universitaire de Nice
Chronic electrical stimulation of hypothalamus/fornix in Alzheimer's disease	June 2009	Unknown	Centre Hospitalier Universitaire de Nice

NBM: Nucleus basalis of Meynert



Based on these promising animal results and improved cognitive scores in one patient undergoing DBS for obesity, Dr. Laxton and colleagues recently conducted an **open-label study of DBS for AD**.^[20] Six patients with early AD were treated with **DBS of the fornix bilaterally**, over 1 year, monitoring both neuropsychological assessments and FDC-PET scans. Clinical evaluation with the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-COG) and the Mini Mental State Examination (MMSE) suggested a **decrease in the rate of cognitive decline**. The follow-up PET studies after 1 year demonstrated an **increase in cerebral glucose metabolism** that was subsequently associated with improved cognitive status. This result is rather encouraging, but it must be interpreted with caution as the study was a small phase I open-label trial conducted without placebo control.^[20]

ALTRE APPLICAZIONI



REVIEW

Deep brain stimulation and multiple sclerosis: Therapeutic applications

Holly A. Roy, Tipu Z. Aziz*

SCLEROSI MULTIPLA

Abstract

Deep brain stimulation is a neurosurgical technique that can be used to alleviate symptoms in a growing number of neurological conditions through modulating activity within brain networks. Certain applications of deep brain stimulation are relevant for the management of symptoms in multiple sclerosis. In this paper we discuss existing treatment options for tremor, facial pain and urinary dysfunction in multiple sclerosis and discuss evidence to support the potential use of deep brain stimulation for these symptoms.

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Published online 2016 Nov 14. doi: [10.4103/2152-7806.194156](#)

PMCID: PMC5134112

The impact of deep brain stimulation on tinnitus

TINNITO

[Jasper V. Smit](#),^{*} [Marcus L. F. Janssen](#),¹ [Malou Engelhard](#), [Rob M. A. de Bie](#),³ [P. Richard Schuurman](#),⁴ [Maria F. Contarino](#),⁵ [Arne Mosch](#),⁵ [Yasin Temel](#),² and [Robert J. Stokroos](#)

[Author information](#) ▶ [Article notes](#) ▶ [Copyright and License information](#) ▶

The THI decreased significantly during DBS compared to the situation prior to surgery (from 18.9 to 15.1, $P < .001$), which was only significant for DBS in the subthalamic nucleus (STN). The THI in the control group (36.9 to 35.5, $P = 0.50$) and other DBS targets did not change. The VAS loudness increased in the control group (5.4 to 6.0 $P < .01$).

EPILESSIA

The effects of deep brain stimulation (DBS) on pharmacoresistant epilepsy have been under scrutiny since the 1970s,⁴ and several structures have been targeted throughout the years.⁵ The efficacy of thalamic stimulation depends on the epilepsy type. Stimulation of the anterior nucleus has proved to be effective for focal epilepsy showing that 54% of patients had seizure reduction of at least 50% after a 2 year follow up (Stimulation of the Anterior Nucleus of Thalamus for Treatment of Refractory Epilepsy (SANTE) trial⁶). Other studies have showed that the centromedian nucleus stimulation appears to be effective in generalised epilepsies.^{7–9}

ALTRE APPLICAZIONI



ELSEVIER

Contents lists available at ScienceDirect

Sleep Medicine

RLS

journal homepage: www.elsevier.com/locate/sleep

Letter to the Editor

Deep brain stimulation (DBS) for severe restless legs syndrome: therapeutic and physiologic considerations

We implanted **bilateral GPI DBS in two subjects** with refractory idiopathic RLS. GPI was chosen because this site was never reported to worsen RLS associated with other conditions. It is also the major outflow of the basal ganglia and improves both "off" features of PD (hypodopaminergic state) and drug-induced dyskinesia in PD (hyperdopaminergic state). There is evidence supporting both scenarios in RLS [12].

Overall, **both subjects reported about 50% improvement and in hindsight would repeat the procedure, but neither had complete relief or eliminated RLS medications.** My impression is that this site may have a mitigating effect but is not the primary pathophysiologic pathway for RLS. That said, these are among the most severe of RLS sufferers and failed many treatments that usually benefit patients.

Acta Neurochir (2017) 159:137–143
DOI 10.1007/s00701-016-3002-2

AUTISMO

CASE REPORT - NEUROSURGICAL TECHNIQUES

Nucleus accumbens deep brain stimulation for a patient with self-injurious behavior and autism spectrum disorder: functional and structural changes of the brain: report of a case and review of literature

Hye Ran Park¹ · In Hyang Kim² · Hyejin Kang³ · Dong Soo Lee³ · Bung-Nyun Kim² · Dong Gyu Kim^{4,5} · Sun Ha Paek^{4,5}

Review

DBS for Obesity

OBESITÀ

Ruth Franco¹, Erich T. Fonoff², Pedro Alvarenga³, Antonio Carlos Lopes³, Eurípedes C. Miguel³, Manoel J. Teixeira², Durval Damiani¹ and Clement Hamani^{2,4,5,*}

Data from animal studies and **preliminary reports in humans suggest that DBS may be a promising alternative for the treatment of obesity.** Structures involved in mechanisms of feeding and rewarding aspects of food intake, namely the **hypothalamus and NAc**, have been considered as potential targets. Though surgery was shown to be safe in the few patients treated so far, further studies are still needed not only to better characterize the side effect profile of these procedures but also their actual efficacy.

Deep brain stimulation in addictive disorders **DIPENDENZE**

The published literature on DBS for the treatment of addictive disorders is sparse, and includes several case reports of patients with comorbid psychiatric disorders (Kuhn *et al.*, 2007a,b, 2009; Mantione *et al.*, 2010; De Ridder *et al.*, 2016). In the first, a patient was treated unsuccessfully for agoraphobia by **bilateral DBS of the NAc** but his comorbid alcohol dependence was ameliorated (Kuhn *et al.*, 2007a). The same group reported smoking cessation in 3 of 10 patients who underwent DBS of the NAc, for Tourette's syndrome, OCD or anxiety (Kuhn *et al.*, 2011). A similar observation was described by Mantione and colleagues (2010). Here, a patient who had undergone NAc DBS for treatment-refractory OCD quit smoking and lost weight post-surgery.



ALTRE APPLICAZIONI

REVIEW

Update on Neuromodulation for Treatment-Resistant Depression [version 1; referees: 3 approved]

Bettina Bewernick¹, Thomas E Schlaepfer^{1,2}

¹Department of Psychiatry and Psychotherapy, University Hospital, Bonn, Germany

²Departments of Psychiatry and Mental Health, Johns Hopkins University, Baltimore, USA

Efficacy. In small pilot studies, an antidepressant effect of DBS was described: a reduction of symptoms of greater than 50% was reached in about 50% of the patients after 12 months of DBS treatment^{70,74-78}. First results have found superior response rates in the sIMFB (more rapid effects and >70% response rates after 3 months⁷⁹ and after 12 months⁷⁹), but long-term data and larger samples are required for efficacy evaluation. First small studies with sham stimulation found conflicting results concerning placebo effects^{79,80} (see Table 1).

DEPRESSIONE

Ethical aspects. Few treatment approaches in psychiatry have initiated as much ethical debate as DBS. Major issues concerning patient autonomy are: the manipulation of human personality with DBS⁸¹, a sudden disruption of the patient's biography⁸², and the ability of patients with treatment-resistant depression to give informed consent⁸³.

7. Schizophrenia and deep brain stimulation: pre-clinical research

SCHIZOFRENIA

Ethically, many experts fear that there is not enough preliminary evidence to justify large clinical trials of DBS for schizophrenia. However, beneficial results from some early studies has resulted in limited FDA approval of DBS for OCD, which will only help to pave the way for potential use of DBS for schizophrenia. Financially, DBS costs approximately \$80,000 US dollars per patient [91]. In comparison to the social cost exacted by schizophrenia, this may make DBS a viable option for severe patients if deemed successful.

Neuromodulation: Technology at the Neural Interface

Received: August 22, 2016 Revised: October 2, 2016 Accepted: October 18, 2016

(onlinelibrary.wiley.com) DOI: 10.1111/ner.12551

STRESS POST TRAUMATICO

Posttraumatic Stress Disorder: Perspectives for the Use of Deep Brain Stimulation

Roman Reznikov, MSc* Clement Hamani, MD, PhD*†

NEUROSEGNALI E DBS

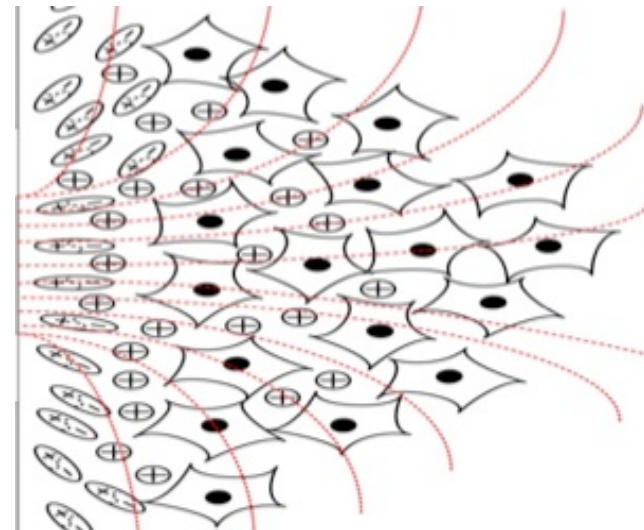
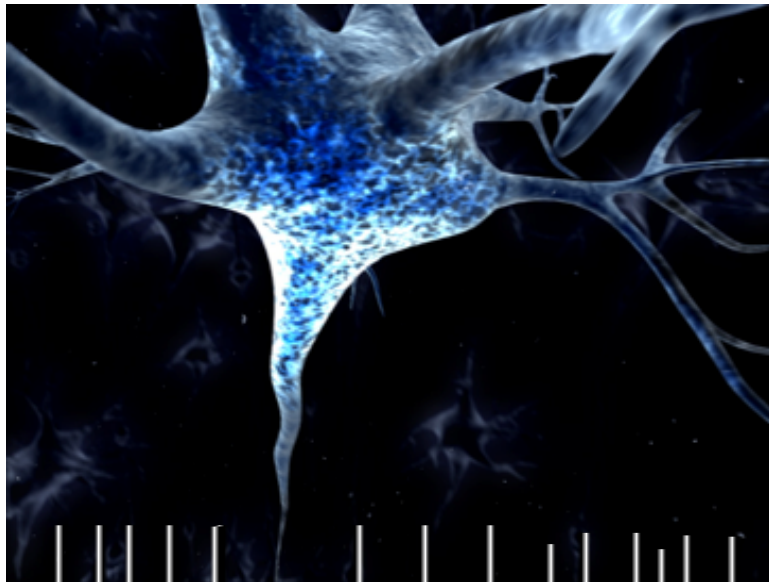
- Attività di **singole cellule**
- Registrazione Intraoperatoria**
- Attività di **popolazioni neuronali**
- Registrazione Postoperatoria**



SINGLE UNITS vs LFPs

Vantaggi dei local field potentials:

- Riflettono l'attività di una grande popolazione di neuroni
- Sono particolarmente sensibili all'attività oscillatoria
- Possono essere registrati in fase post-operatoria





OBIETTIVI

Individuazione del target
ottimale nella fase
intraoperatoria

Studio della fisiopatologia dei
circuiti sottocorticali
nell'uomo

Neurofisiologia nel
paziente con DBS

Ottimizzazione del
trattamento con DBS

Individuazione di alterazioni
specifiche nella attività
elettrica correlate alla
patologia trattata

LE REGISTRAZIONI INTRAOPERATORIE

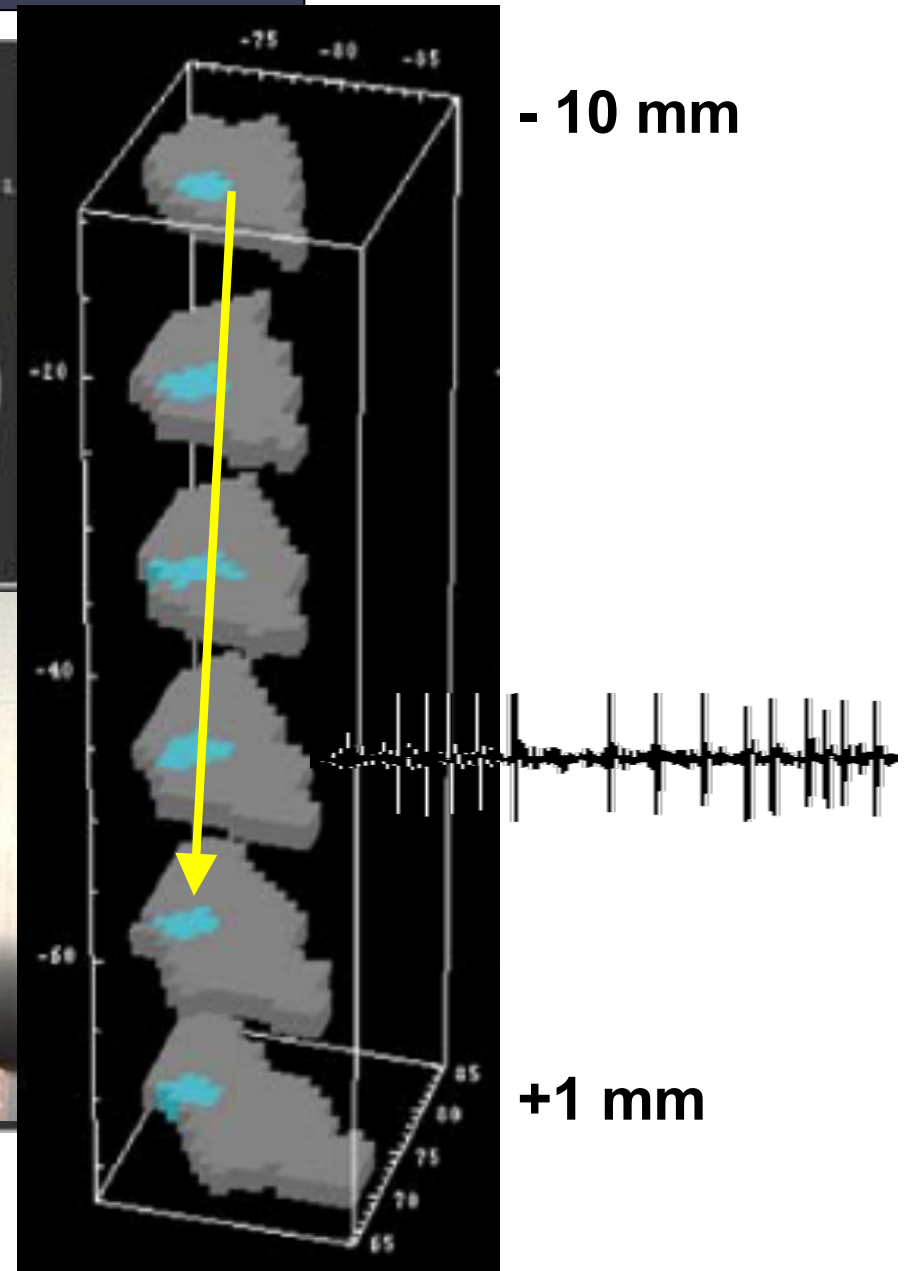
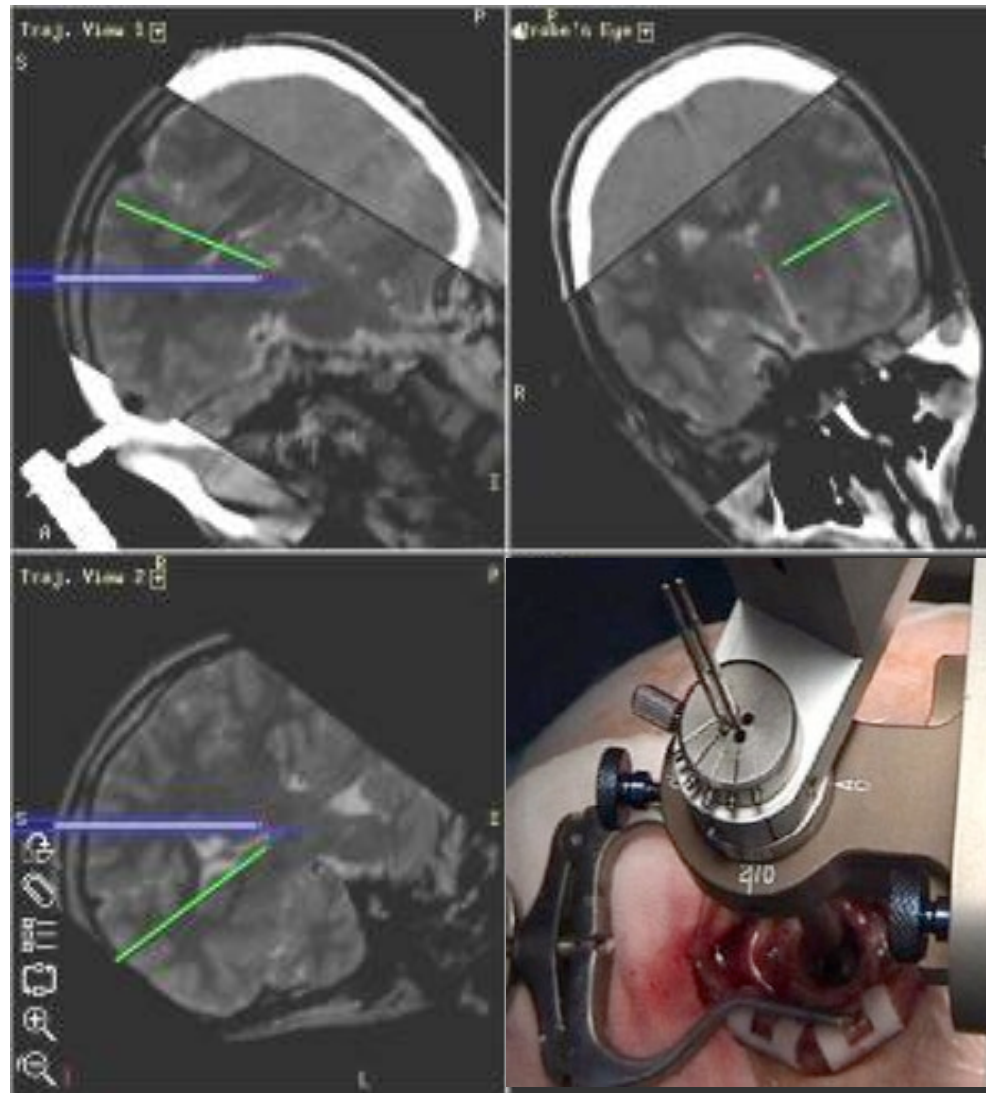


UNIVERSITÀ
DEGLI STUDI DI TRIESTE



Inserimento dei
microelettrodi esploranti
da cui si registra l'attività
cellulare (registrazioni
extracellulari)

MODALITÀ DI REGISTRAZIONE



- 10 mm

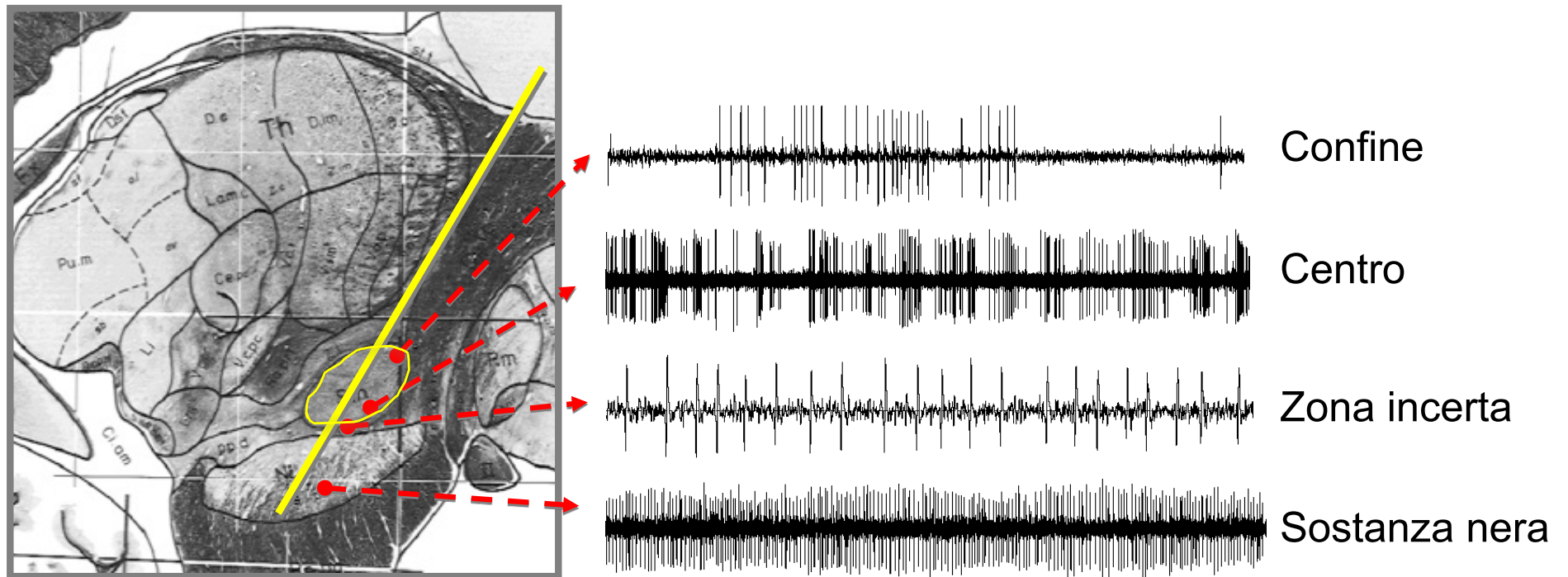
+1 mm

- Microelettrodo → impedenza $1M\Omega$
- 2-3 attività cellulari

MODALITÀ DI REGISTRAZIONE



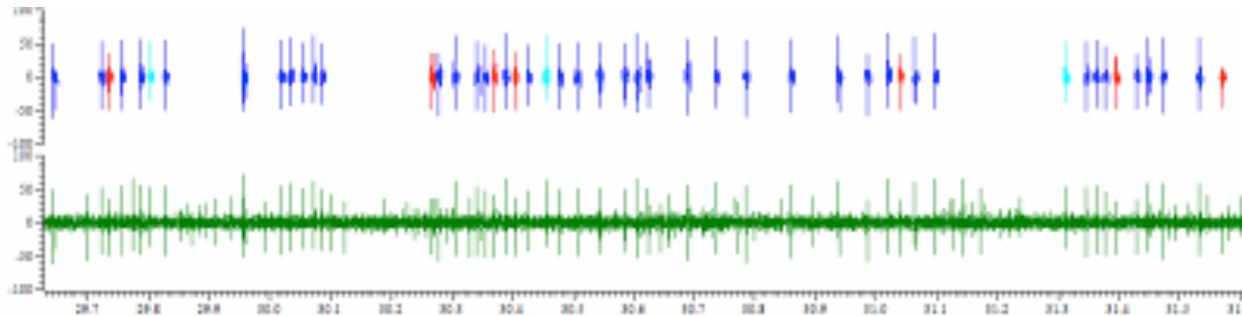
I pattern di scarica dei neuroni caratterizzano le strutture attraversate durante la discesa dell' elettrodo e danno informazioni utili per migliorare il posizionamento dell' elettrodo



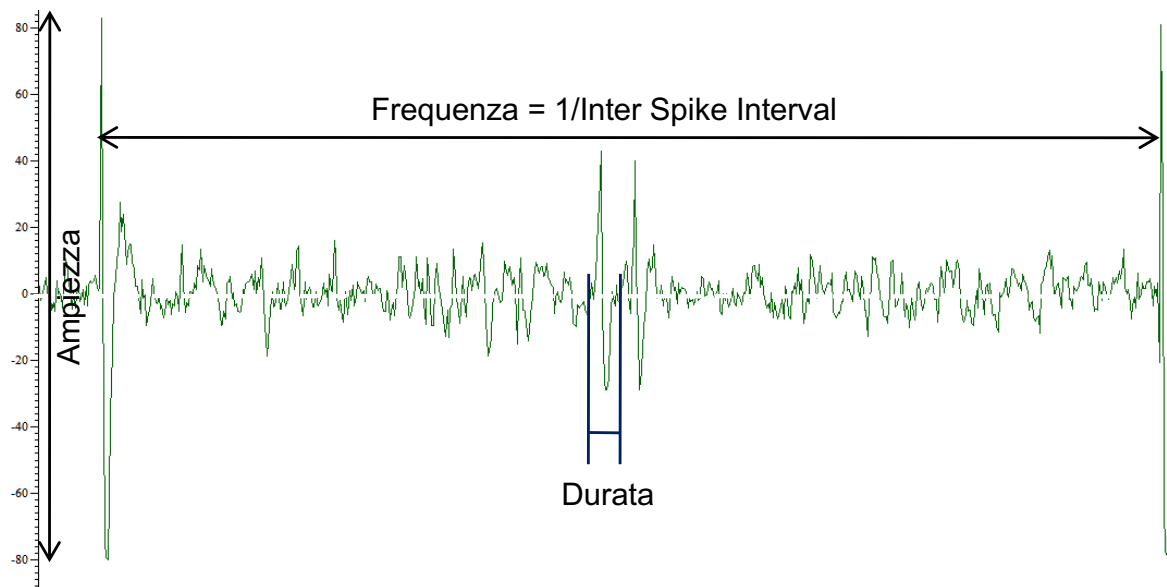
ANALISI DEI SEGNALI INTRAOPERATORI



1. Individuazione dei potenziali d'azione



- Frequenza media
- Caratteristiche medie degli spike per ogni posizione

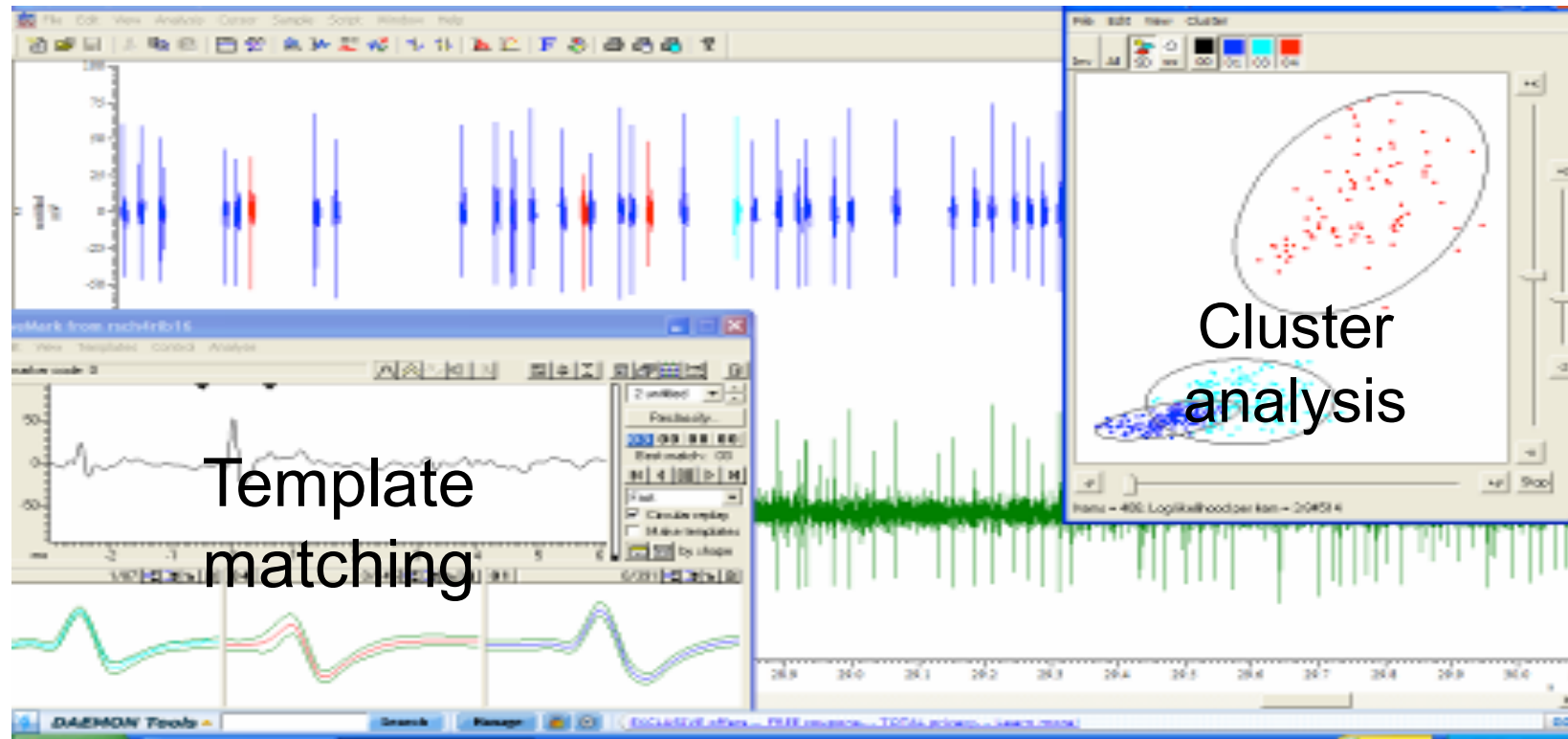


ANALISI DEI SEGNALI INTRAOPERATORI



UNIVERSITÀ
DEGLI STUDI DI TRIESTE

2. Discriminazione delle singole attività cellulari



- Frequenza singola
- Caratteristiche degli spike

ATTIVITÀ SINGLE-UNIT NELLA DISTONIA

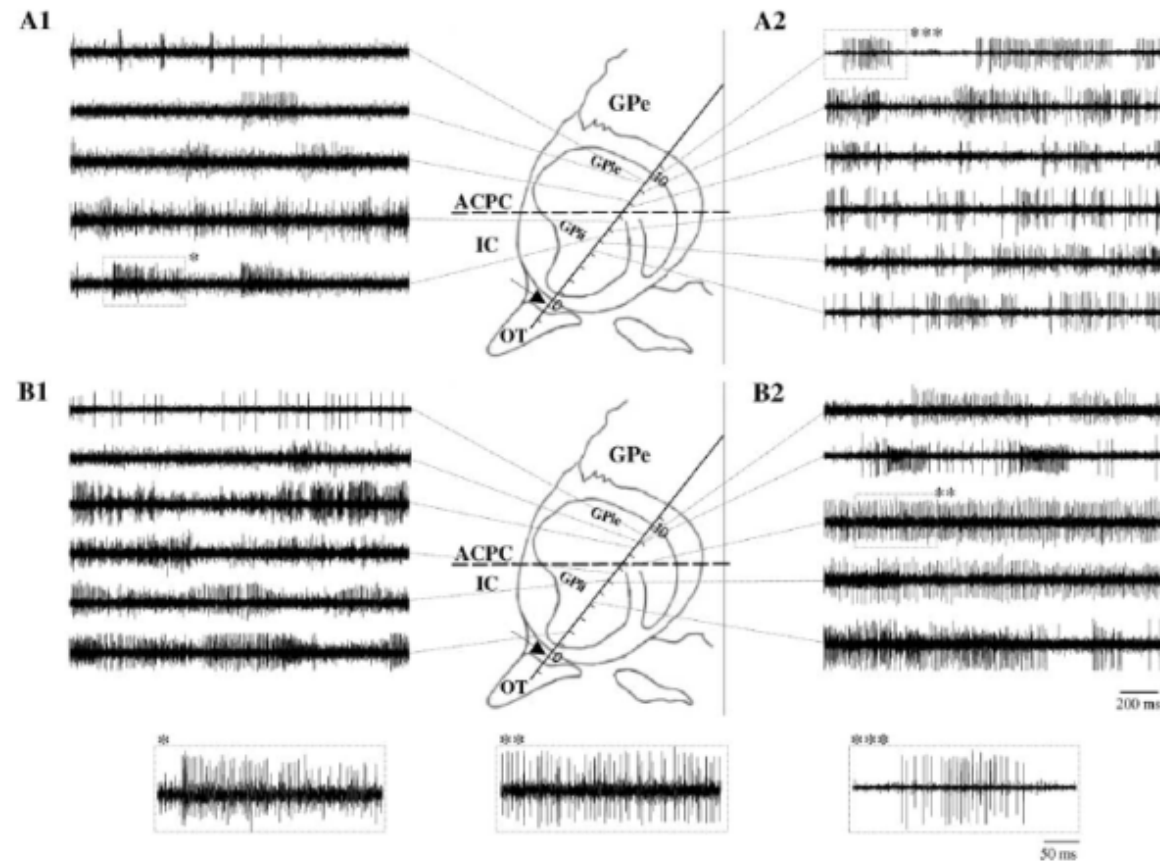
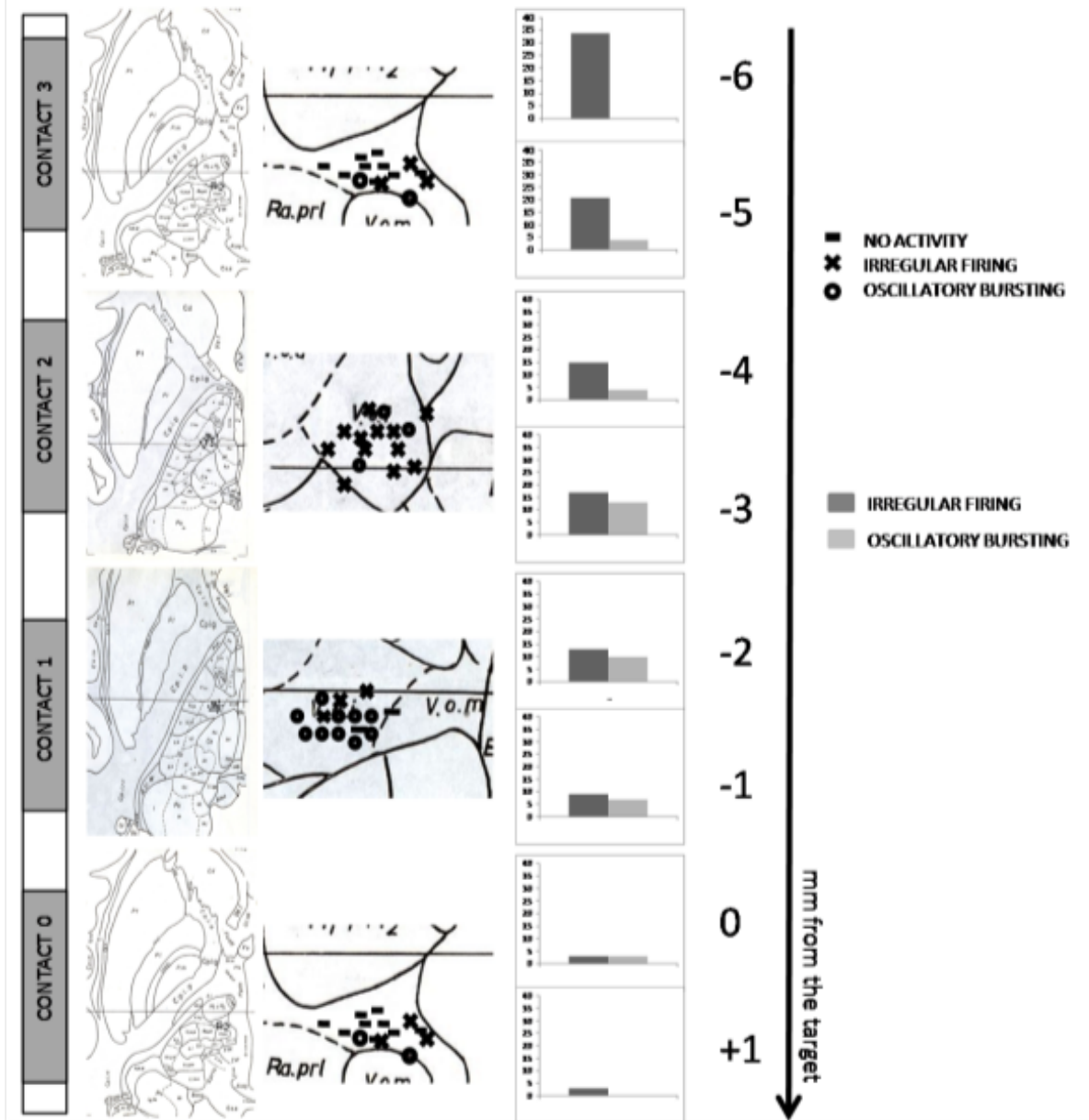


Fig. 2. Discharge patterns of GPi neuronal activity in dystonia. Patterns of discharge representative of most of the neurons in the GPi in the patients with dystonia. Location of a typical trajectory plotted on a sagittal map 20 mm from midline of human globus pallidus from the Schaltenbrand and Wahren atlas (Schaltenbrand and Wahren, 1977) is in the middle of the figure. Each small division on the scale is 1 mm. IC: internal capsule; ACPC: anterior commissure and posterior commissure; OT: optic tract; GPe: the external segment of the globus pallidus; GPi, GPii: the external and internal segment of the GPi, respectively. The neuronal activity within the squares of the dash-lines are expanded at the bottom and demonstrate three types of GPi discharge: grouped neuronal activity (*); rapid tonic neuronal activity (**) and sensory discharge in burst (***). The data collected come from 4 patients: A1: primary generalized dystonia (0a1204); A2: primary focal dystonia (0b0823); B1: secondary spasmodic torticollis (0b1224); B2: hemidystonia (0a0823).

ATTIVITÀ SINGLE-UNIT NELLA SINDROME DI TOURETTE



Lungo la traccia in avvicinamento al target si possono identificare pattern localizzati

- Irregular firing 6-4 mm sopra il target
- Oscillatory bursting 3-1 mm sopra il target
- Silent zone a target.

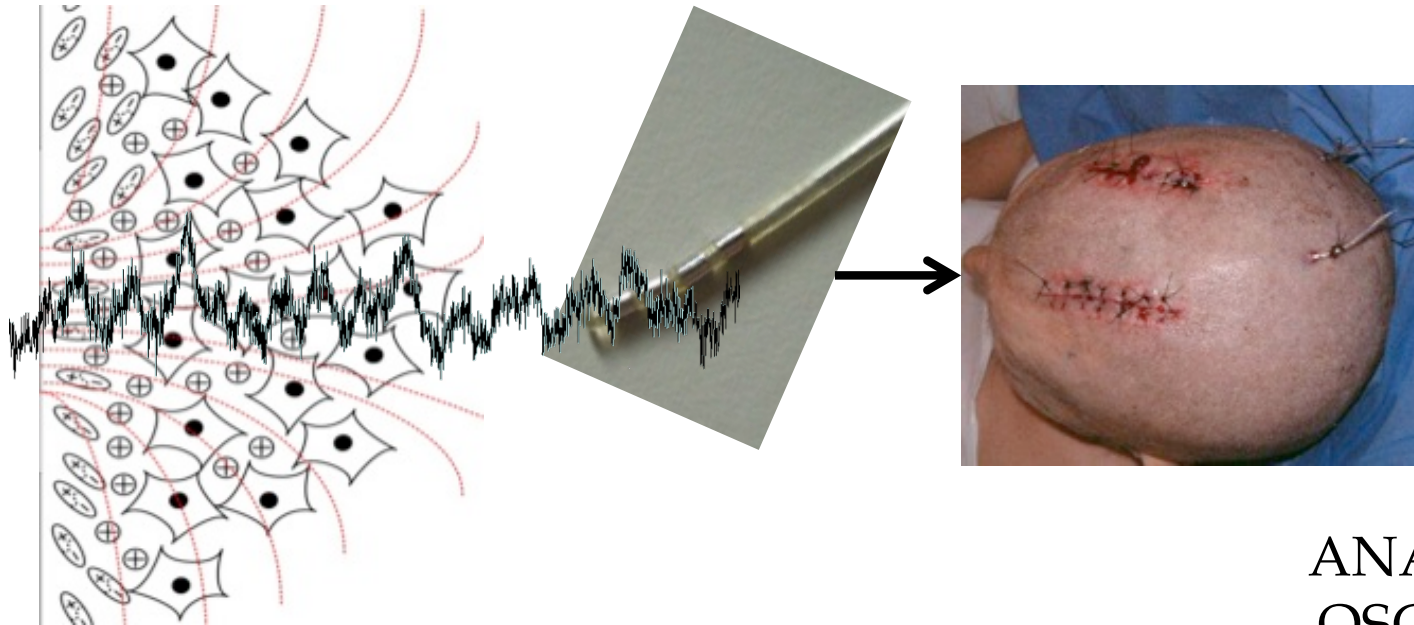


IDENTIFICAZIONE TARGET

LE REGISTRAZIONI POSTOPERATORIE



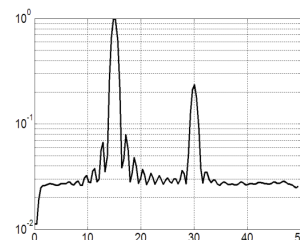
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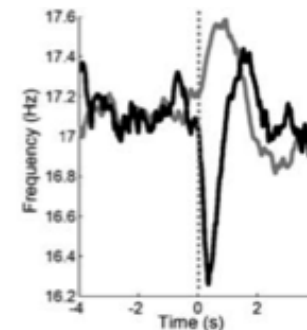
ANALISI DELLE
OSCILLAZIONI

Attività sincrona
presinaptica e
postsinaptica di ampie
popolazioni di neuroni →
EEG di profondità - local
field potentials (LFPs)

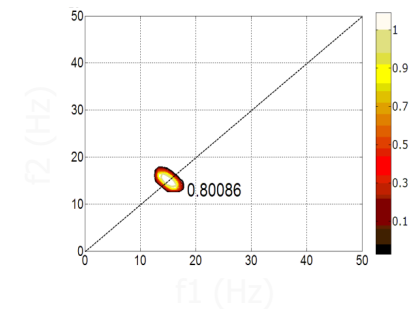
Modulazioni
di ampiezza



Modulazioni
di frequenza

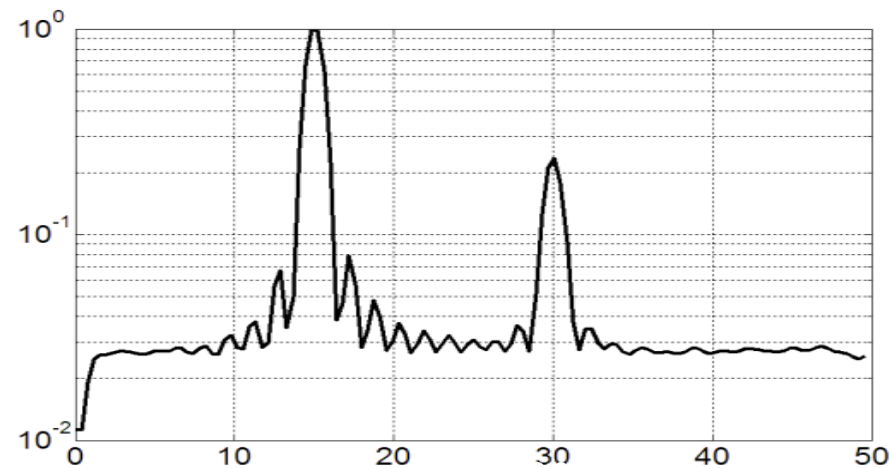


Relazioni tra
oscillazioni

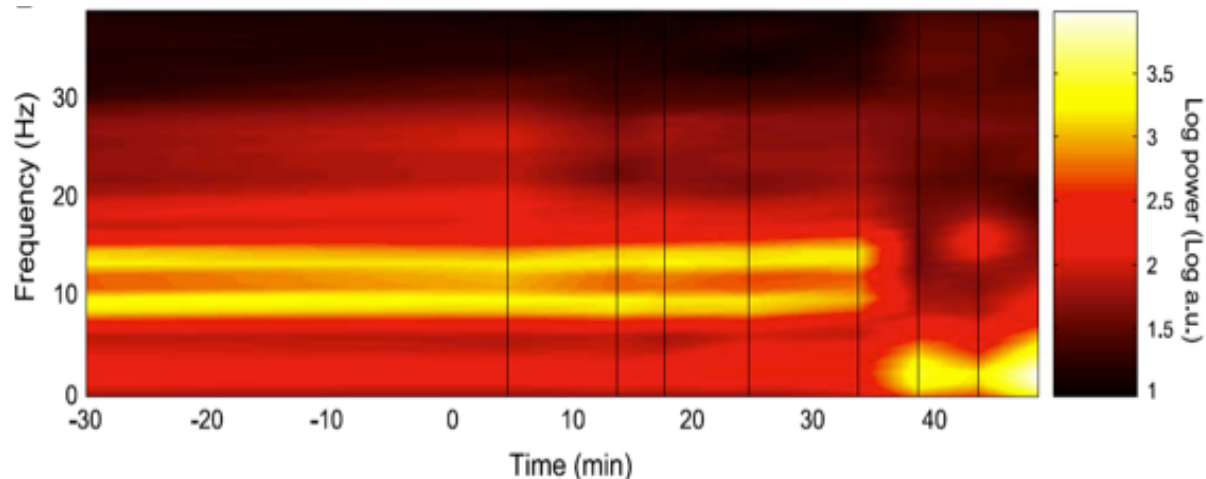


ANALISI DEI LFP

- Studio della attività oscillatoria a riposo → spettro di potenza

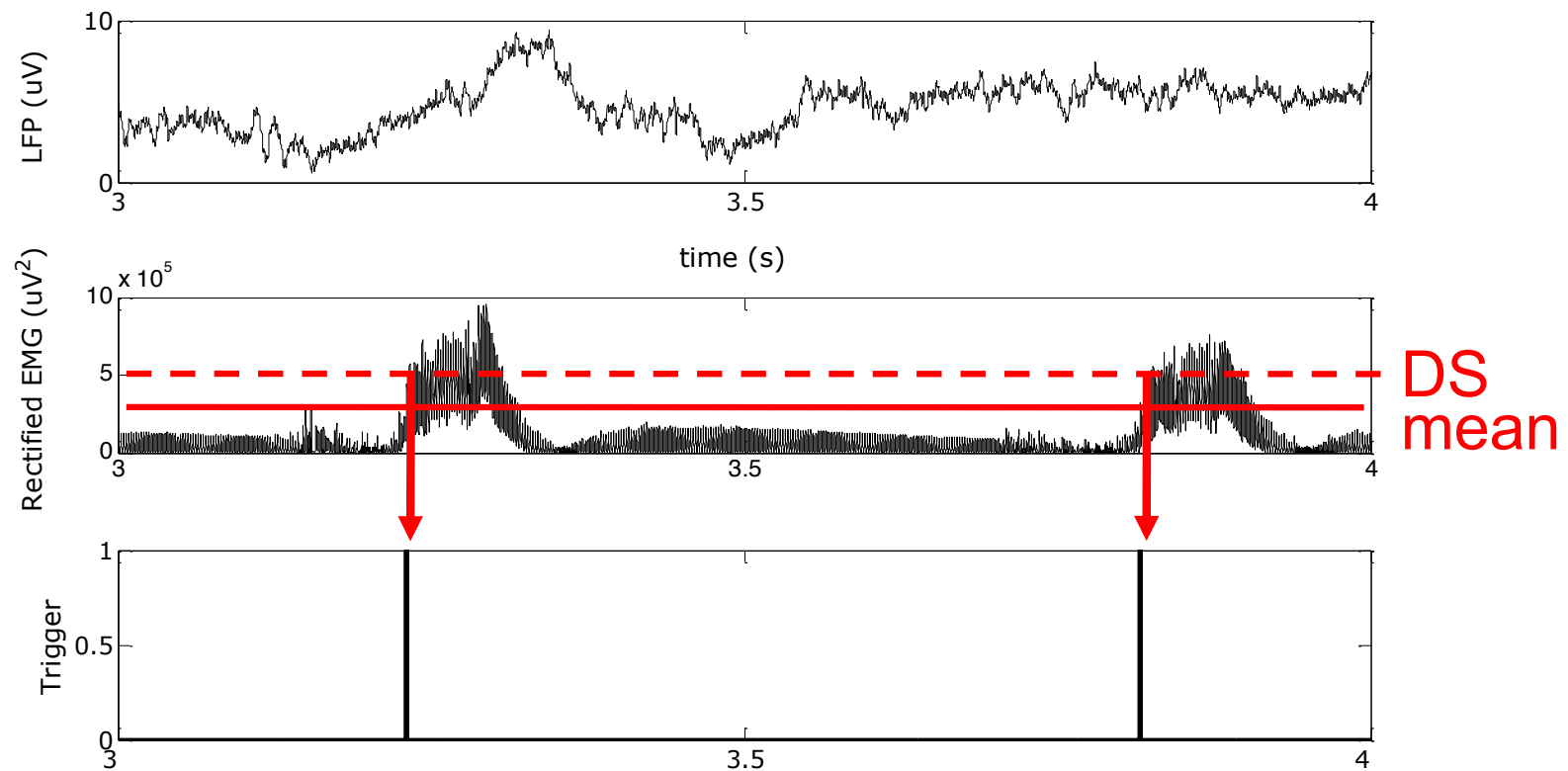


- Studio della dinamica delle diverse oscillazioni durante l'esecuzione/immaginazione di movimenti → analisi tempo-frequenza



ANALISI DEI LFP

Il segnale EMG viene utilizzato come trigger per l'analisi movimento correlata



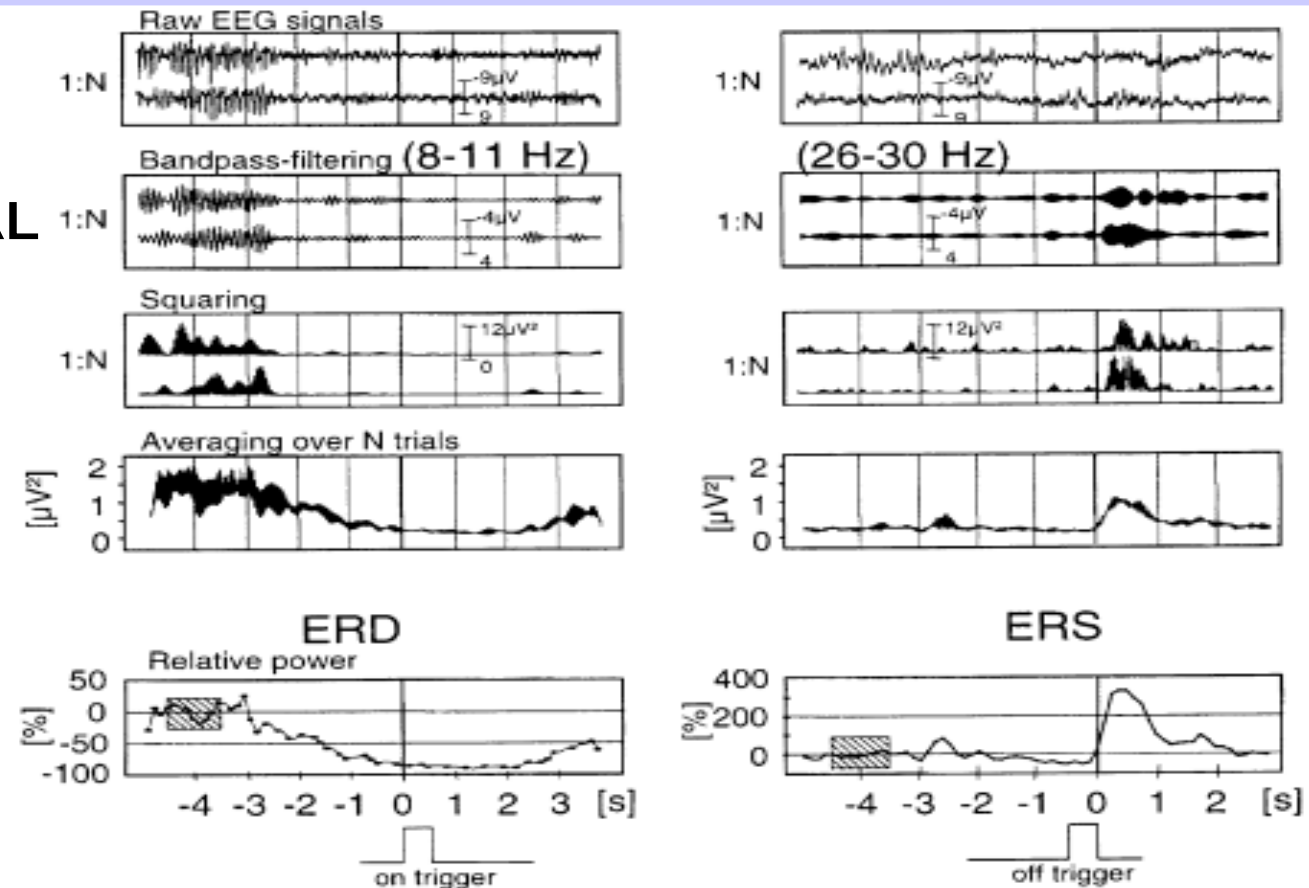
ERD E ERS

RAW SIGNAL

FILTERED SIGNAL

POWER

AVERAGE



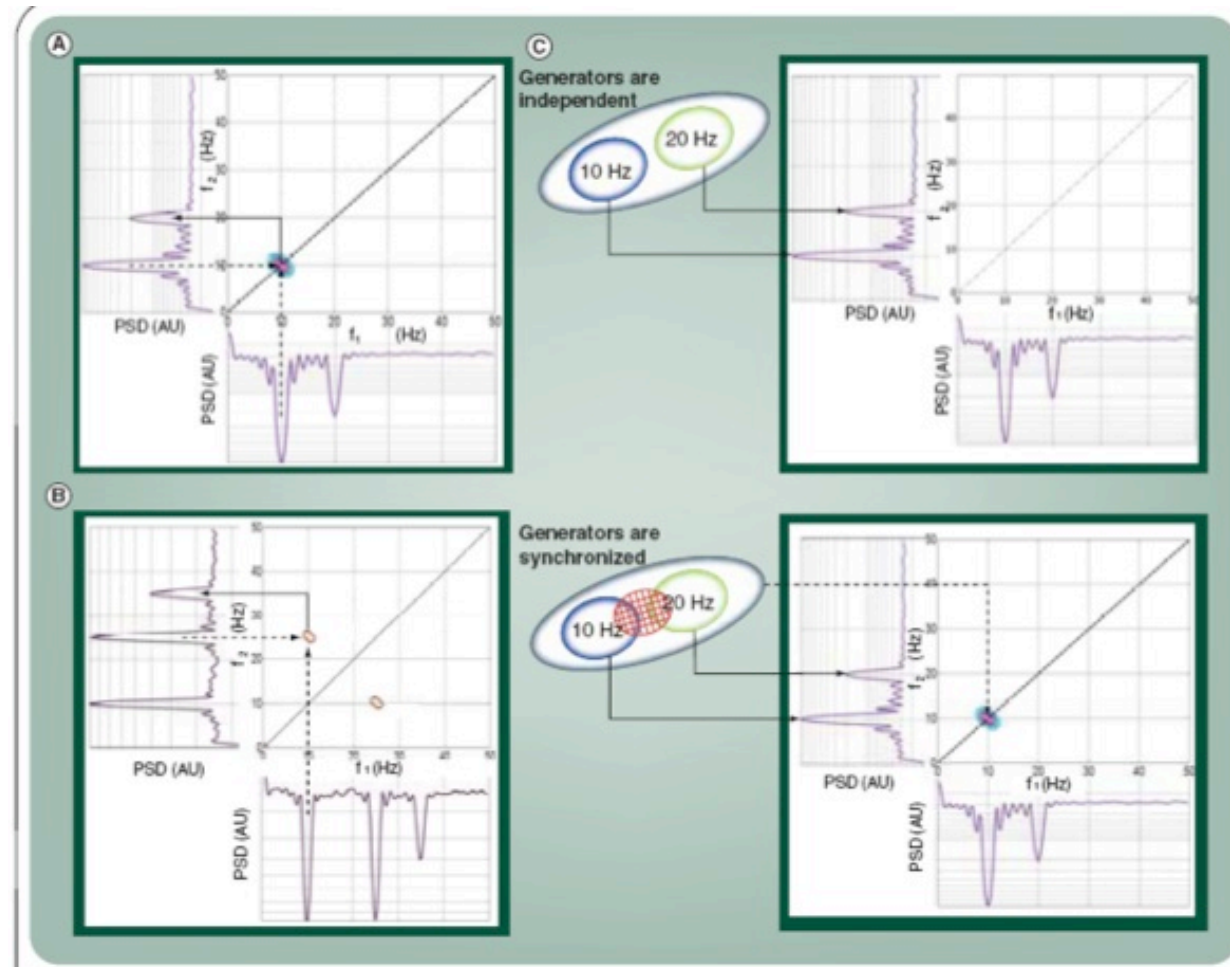
LA EVENT RELATED SYNCHRONIZATION E DESYNCHRONIZATION CONSISTONO NELLA VALUTAZIONE DELLA VARIAZIONE (AUMENTO O DIMINUZIONE) DI POTENZA DI UN CERTO RITMO, IN CONCOMITANZA CON UN DATO EVENTO (ES: MOVIMENTO)

SINCRONIZZAZIONE TRA OSCILLAZIONI



ANALISI SPETTRALE DI ORDINE SUPERIORE (terzo ordine) → BISPETTRO

- Trasformata di Fourier del momento terzo
- Il bispettro rappresenta le relazioni di fase costanti in un dominio bidimensionale.
- Se due ritmi a frequenza f_1 e f_2 sono in relazione di fase costante tra di loro e generano un ritmo a frequenza f_1+f_2 , allora il bispettro avrà un picco in corrispondenza della coppia (f_1, f_2)



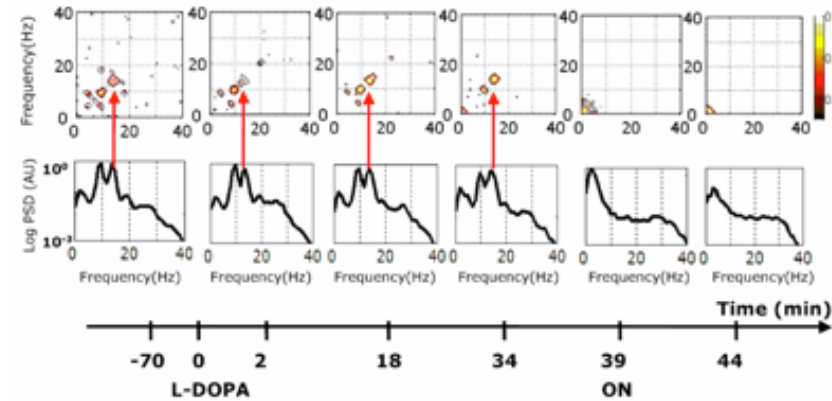
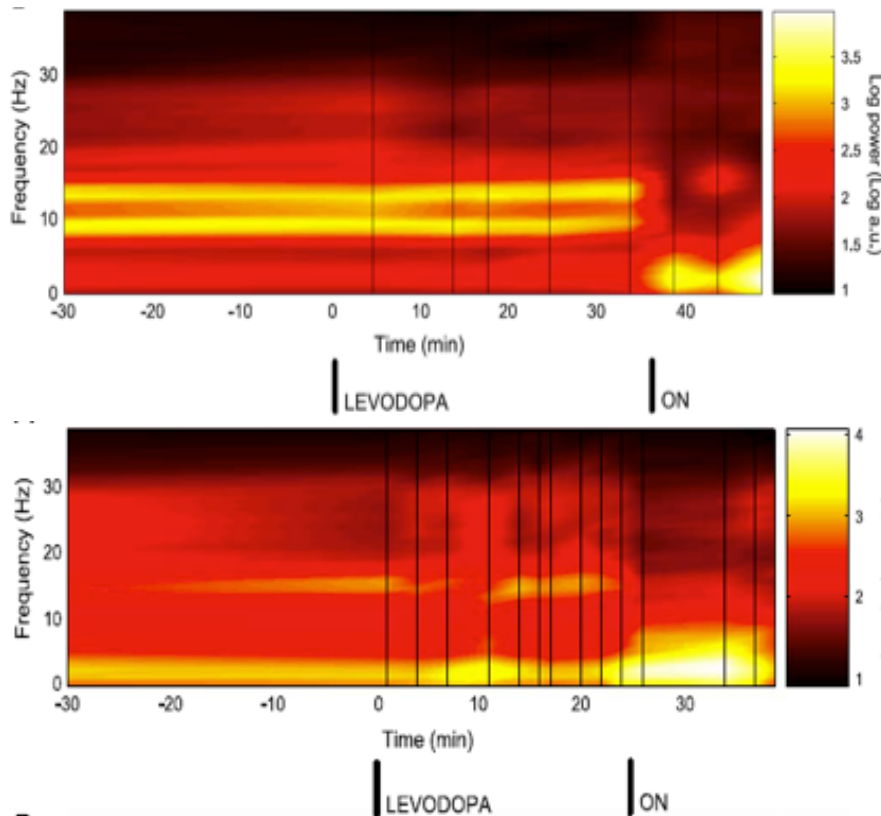
Basal ganglia local field potentials:
applications in the development of
new deep brain stimulation devices
for movement disorders

Sara Marceglia, Lorenzo Rossi, Guglielmo Foffani, AnnaMaria Bianchi,
Sergio Cerutti and Alberto Priori¹

CORRELATO CLINICO DEL LFP



Risposta alla terapia dopaminergica



Modulazione ritmo-specifica e delle correlazioni tra ritmi a seguito della somministrazione di levodopa

Rhythm-specific pharmacological modulation of subthalamic activity in Parkinson's disease

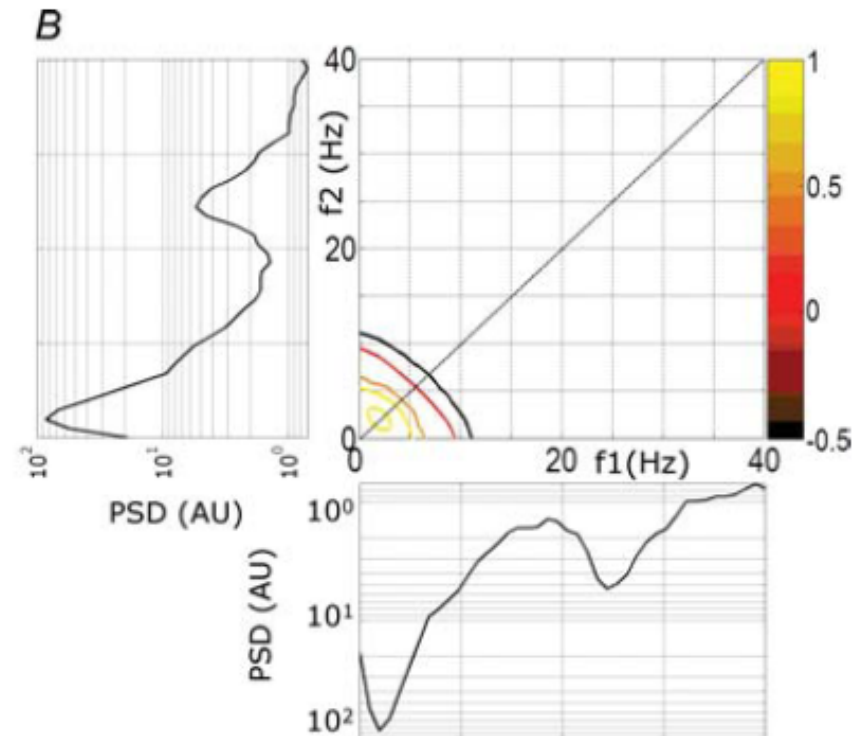
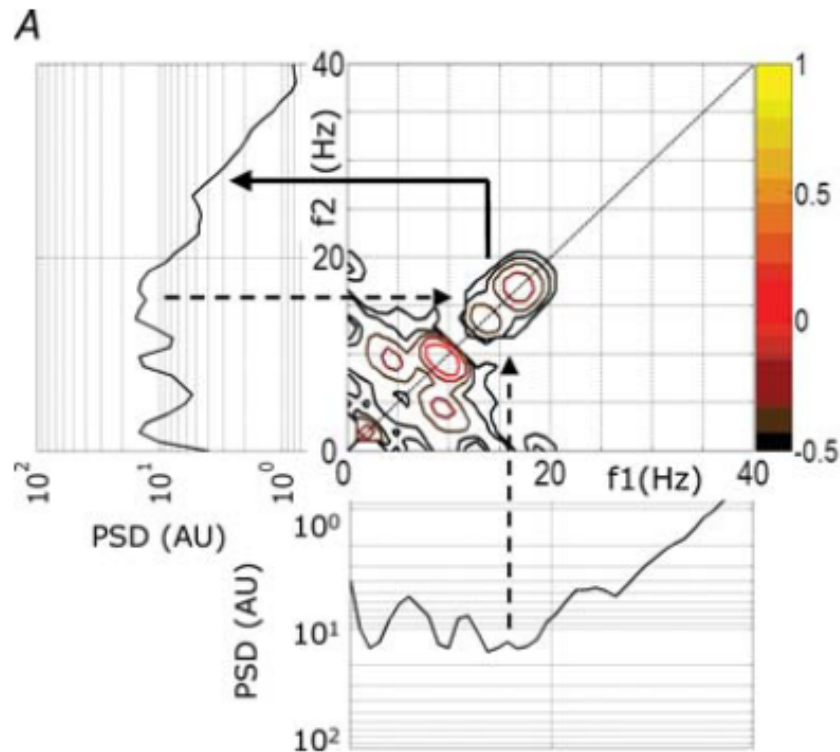
A. Priori^{a,*-1}, G. Foffani^{b,c,1}, A. Pesenti^a, F. Tamma^d, A.M. Bianchi^b,
M. Pellegrini^b, M. Locatelli^a, K.A. Moxon^e, R.M. Villani^a

J. Physiol 571.3 (2006) pp 579-591

Dopamine-dependent non-linear correlation between subthalamic rhythms in Parkinson's disease

S. Marceglia¹, G. Foffani^{1,2,3}, A. M. Bianchi⁴, G. Baselli⁴, F. Tamma⁵, M. Egidio¹ and A. Priori¹

CORRELATO CLINICO DEL LFP

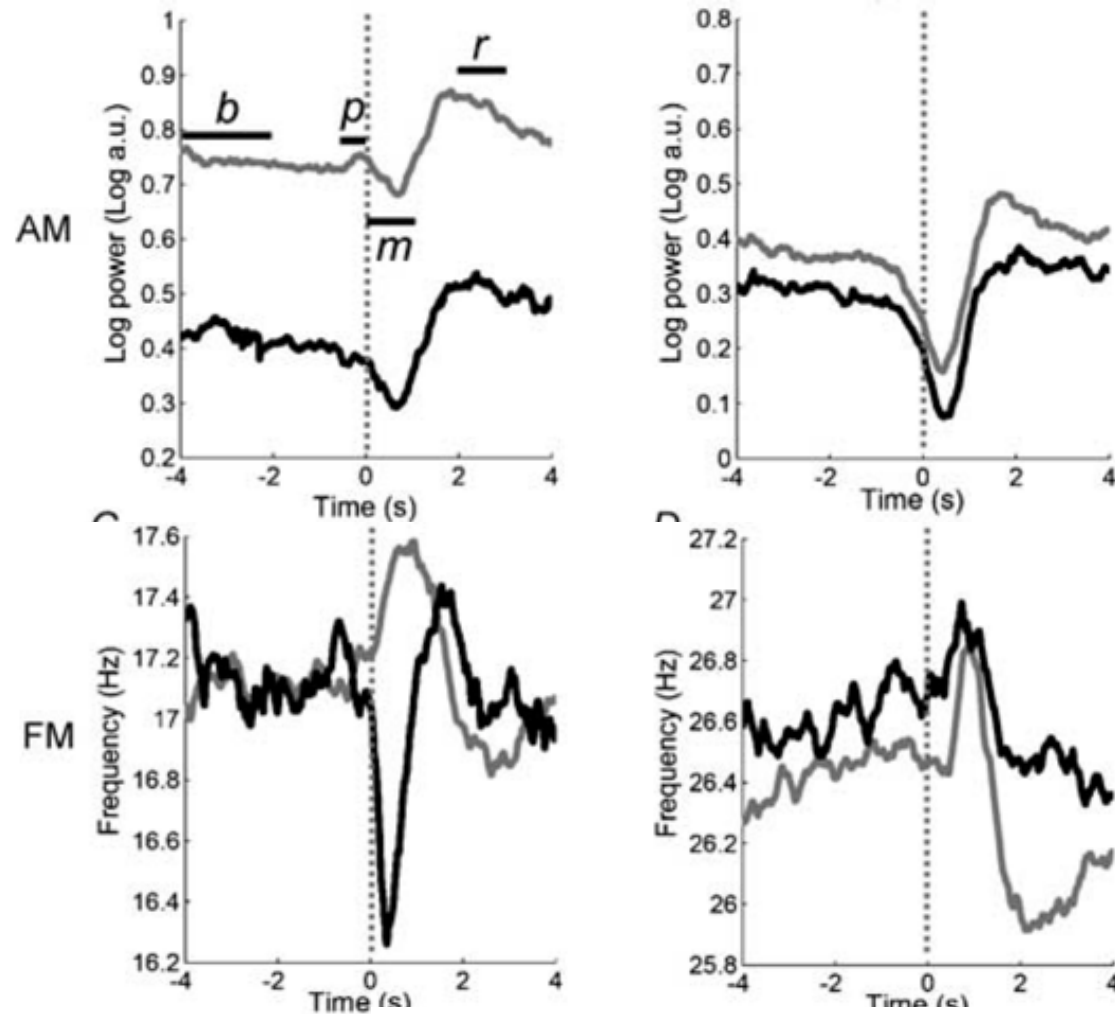


Dopamine-dependent non-linear correlation between subthalamic rhythms in Parkinson's disease

S. Marceglia¹, G. Foffani^{1,2,3}, A. M. Bianchi⁴, G. Baselli⁴, F. Tamma⁵, M. Egidi¹ and A. Priori¹

CORRELATO CLINICO DEL LFP

Modulazione
durante
l'esecuzione di
movimenti



J. Physiol 568.2 (2005) pp 699-711

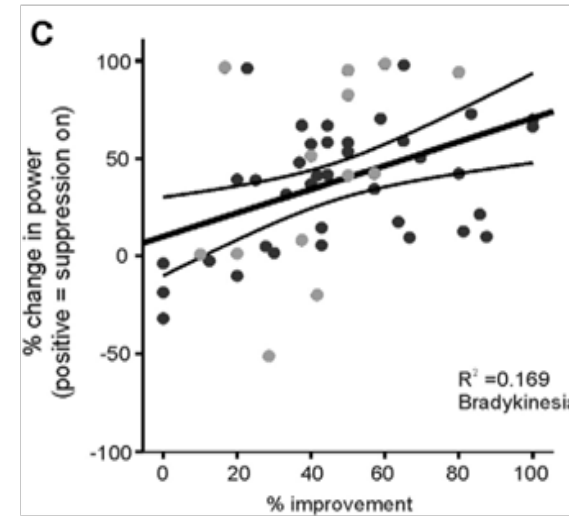
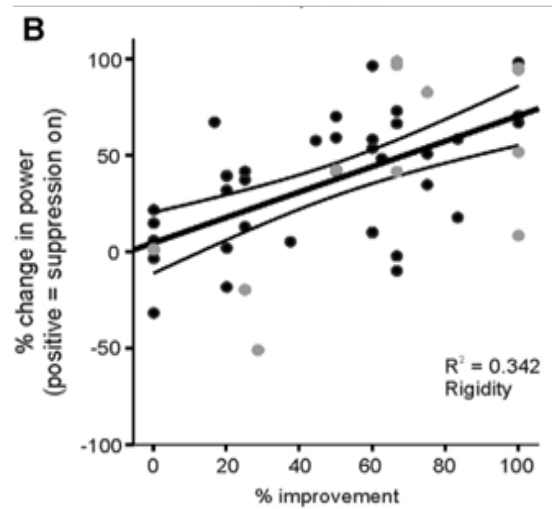
699

Movement-related frequency modulation of beta oscillatory activity in the human subthalamic nucleus

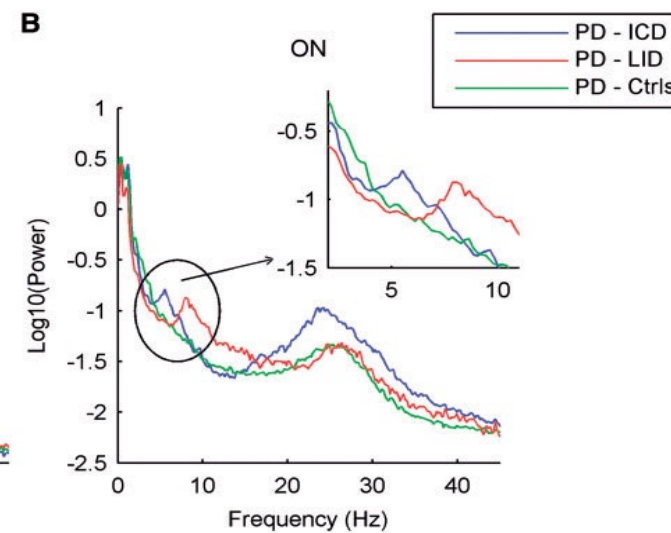
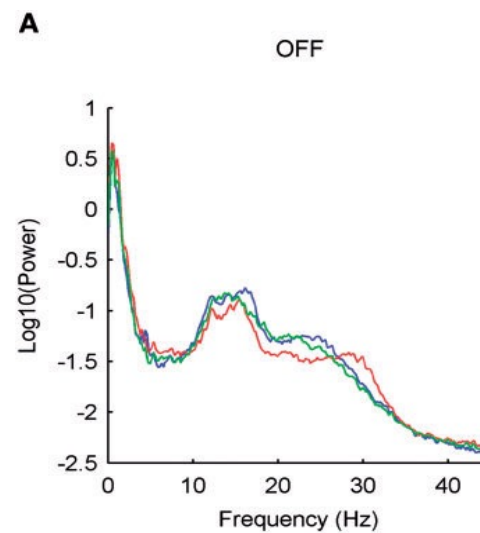
G. Foffani^{1,2}, A. M. Bianchi³, G. Baselli³ and A. Priori¹

LFP E STATO CLINICO

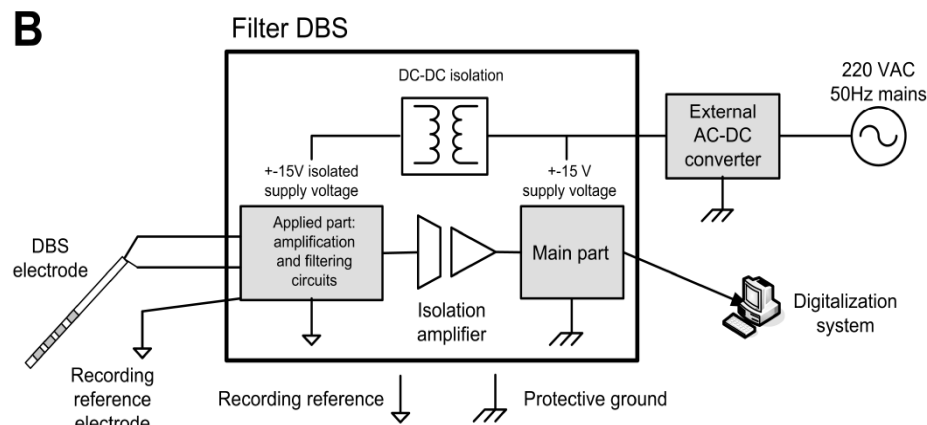
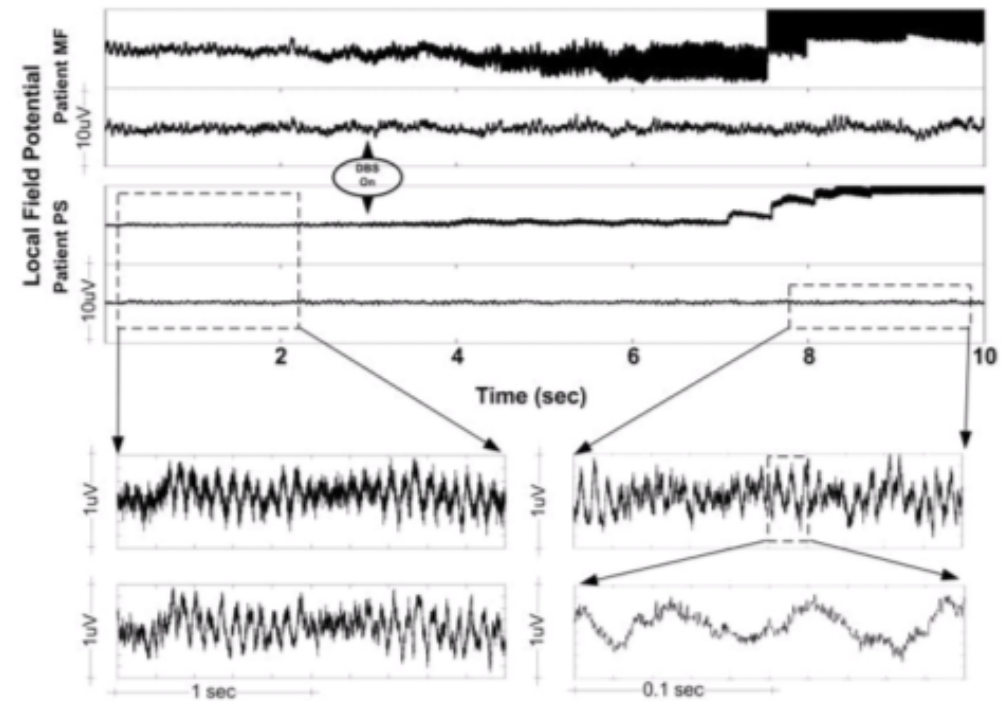
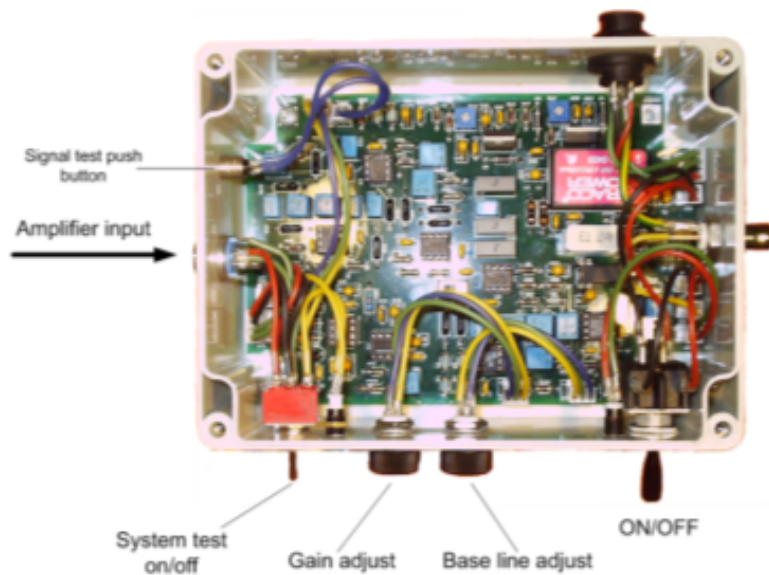
La potenza in banda beta correla con bradicinesia e rigidità



Lo spettro di potenza durante discinesie presenta un pattern tipico



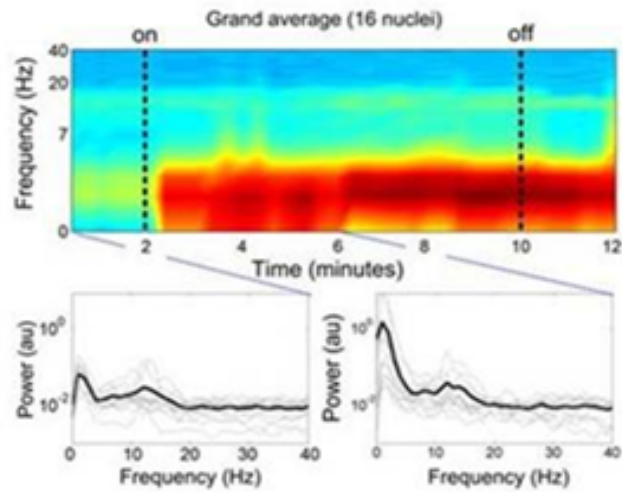
LFP DURANTE DBS



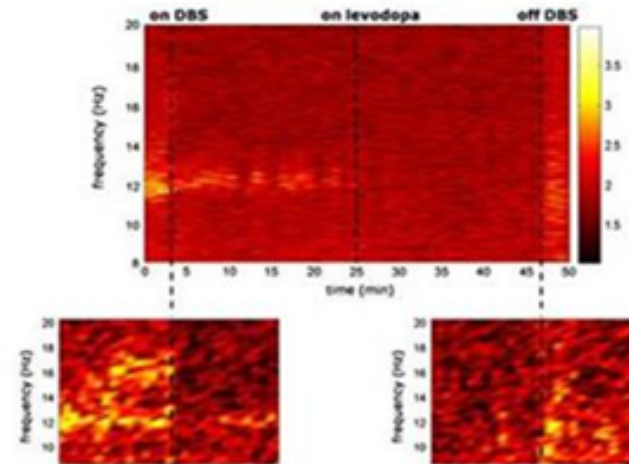
I LFPs possono essere registrati durante la stimolazione dallo stesso elettrodo stimolante.

LFP DURANTE DBS

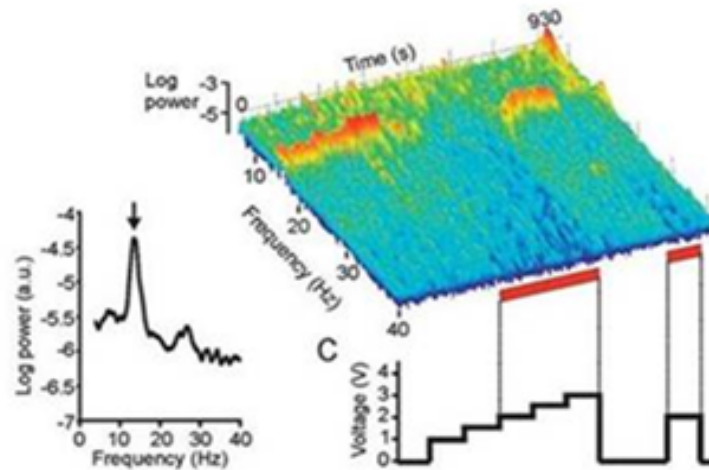
A MODULAZIONE IN BASSA FREQUENZA



B

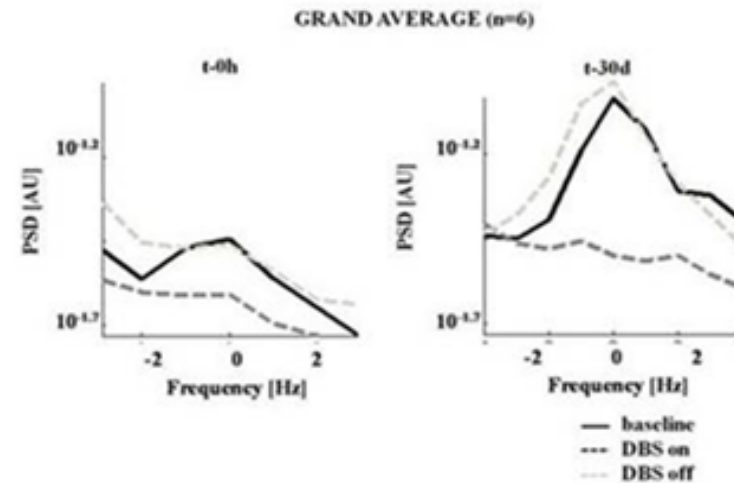


C

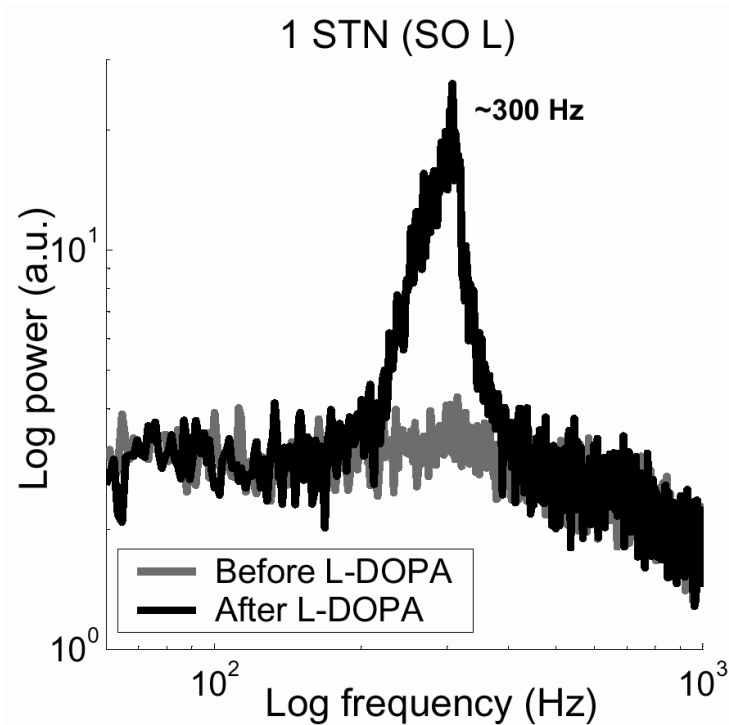


D

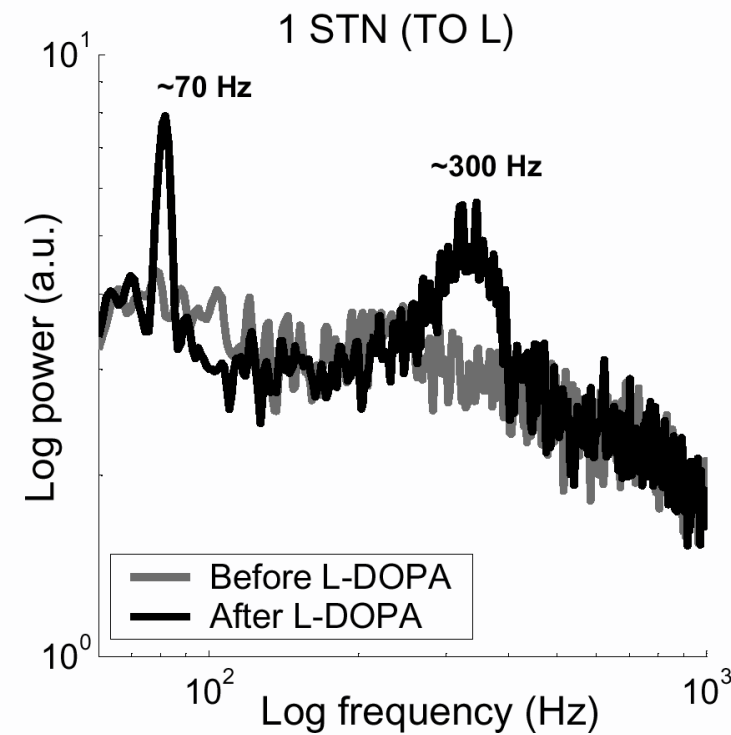
MODULAZIONE IN BANDA BETA



ALTISSIME FREQUENZE LFP (300Hz)

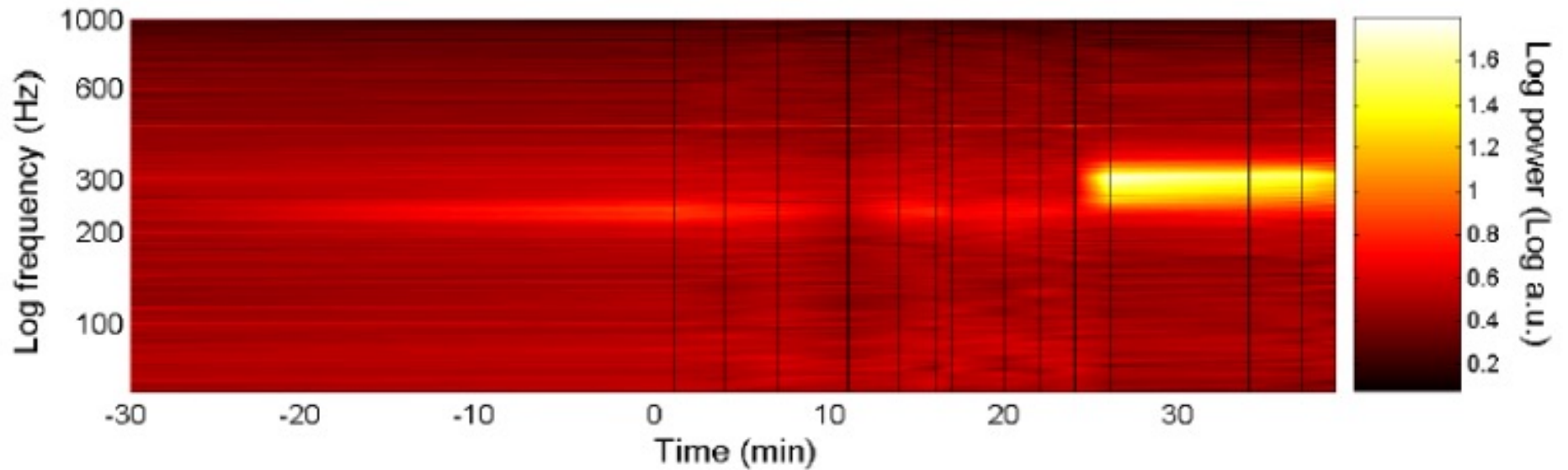


Oscillazione a 300 Hz
dopo l'assunzione di
levodopa



Coesistenza di una
oscillazione a 70 Hz e
di una a 300 Hz dopo
l'assunzione di
levodopa

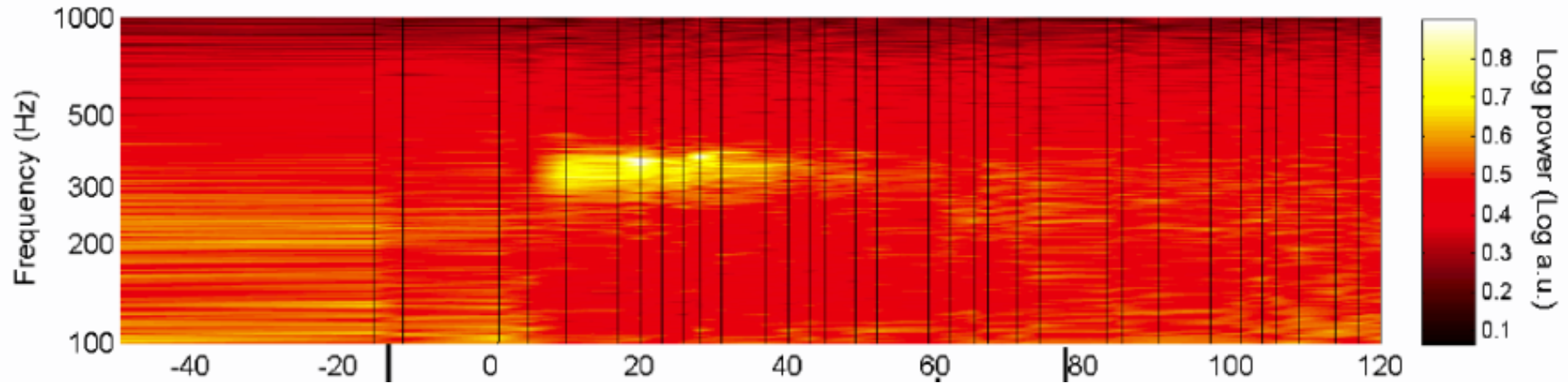
ALTISSIME FREQUENZE LFP (300Hz)



L-DOPA



ON

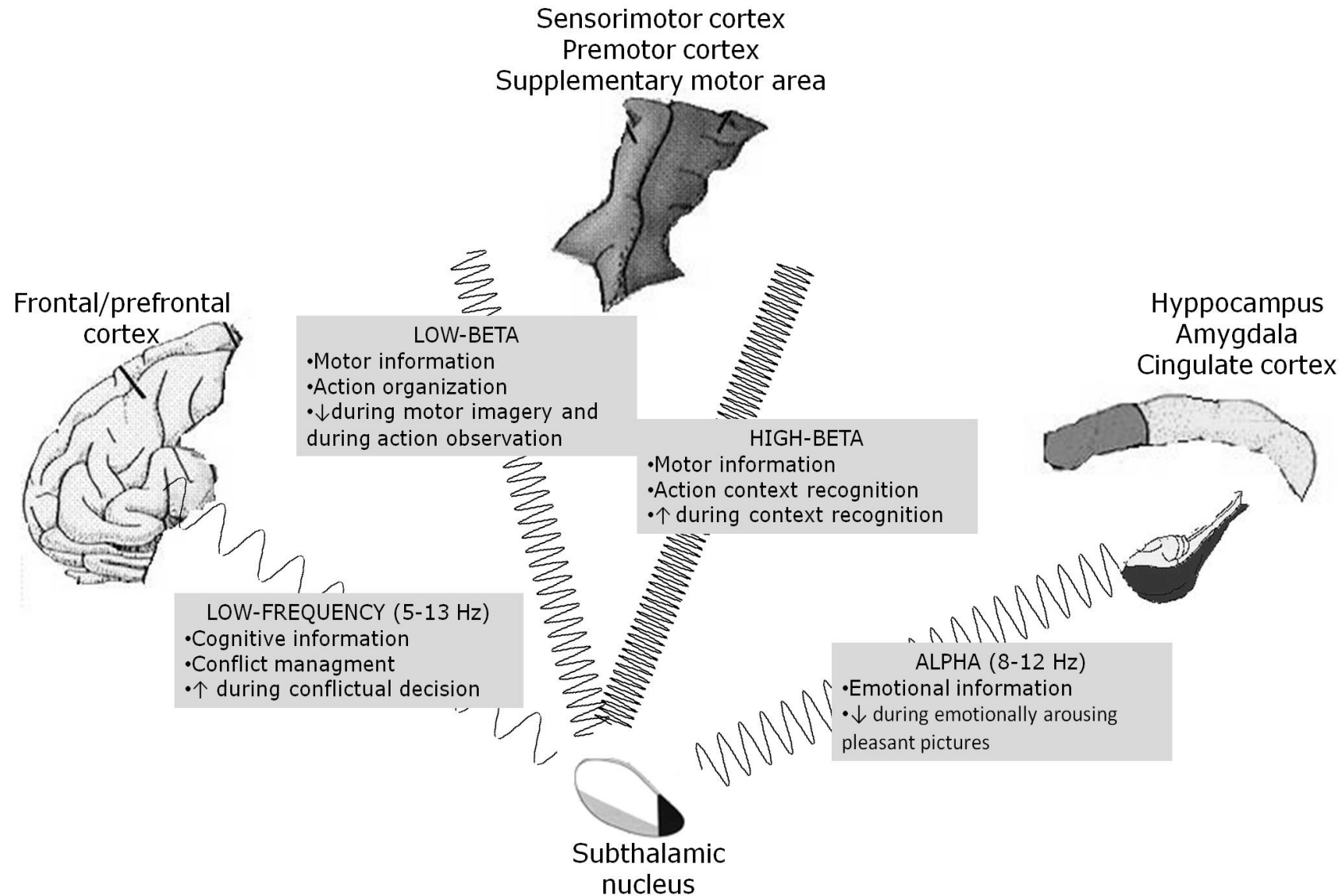


APO

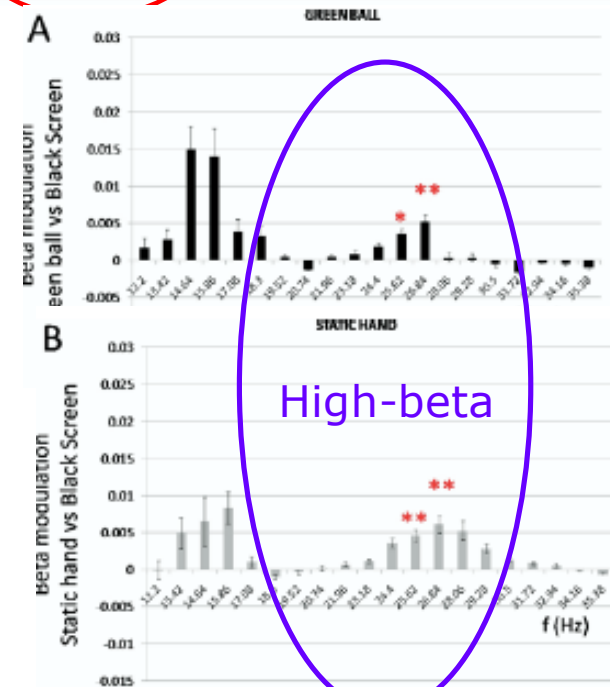
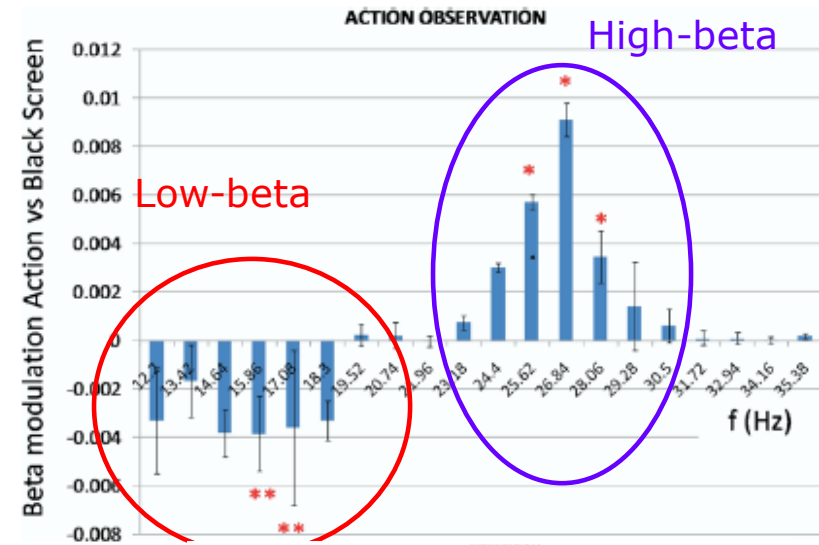
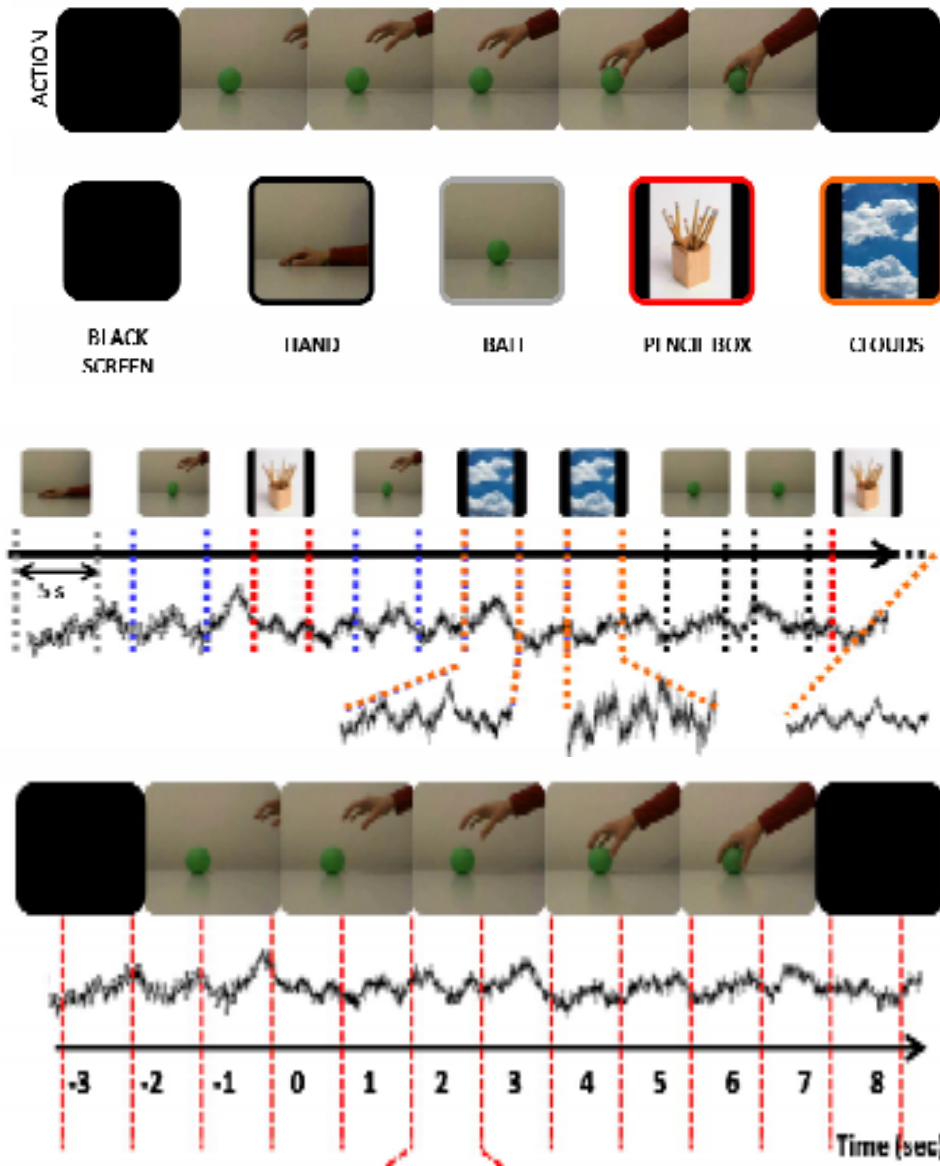


ON

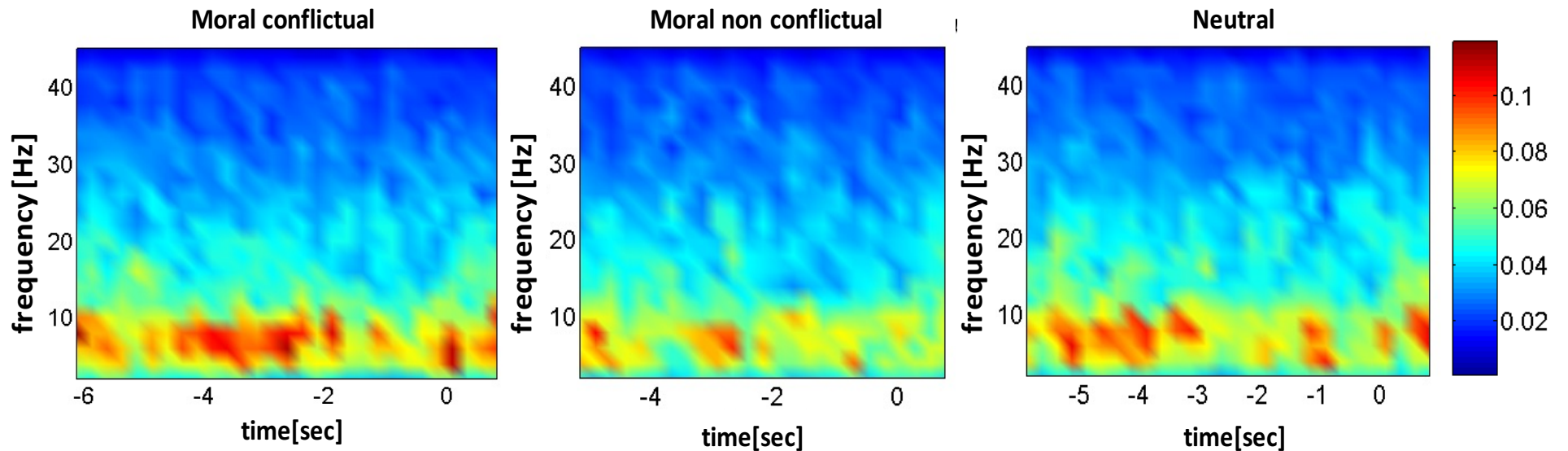
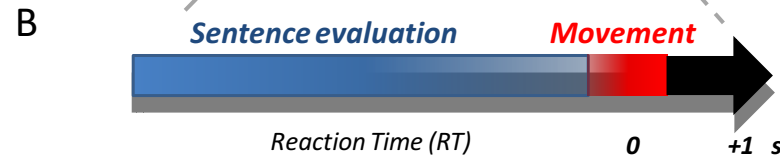
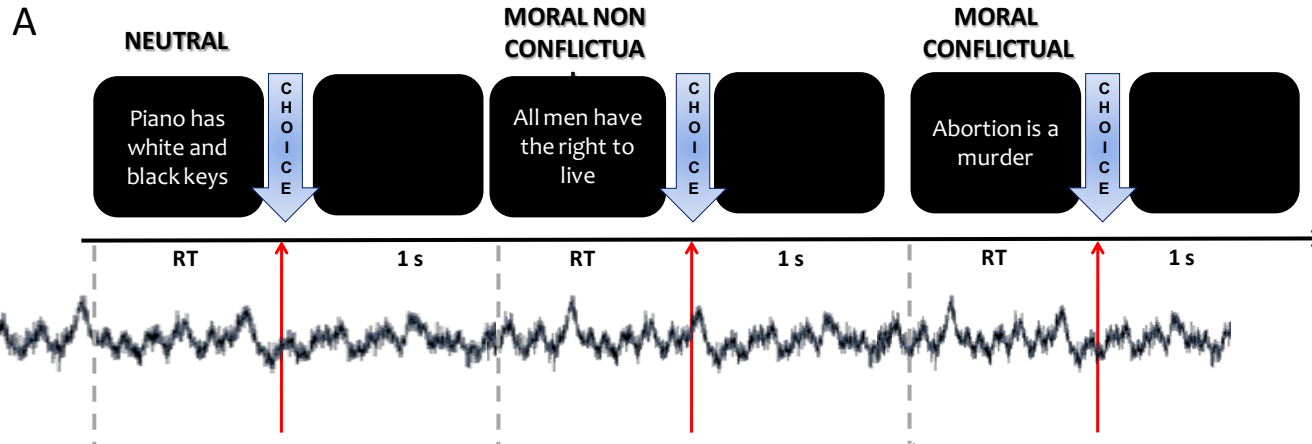
CORRELATI NON MOTORI



ESEMPIO: LFP DURANTE L'OSSERVAZIONE DI MOVIMENTI



ESEMPIO: LFP E DECISIONI MORALI





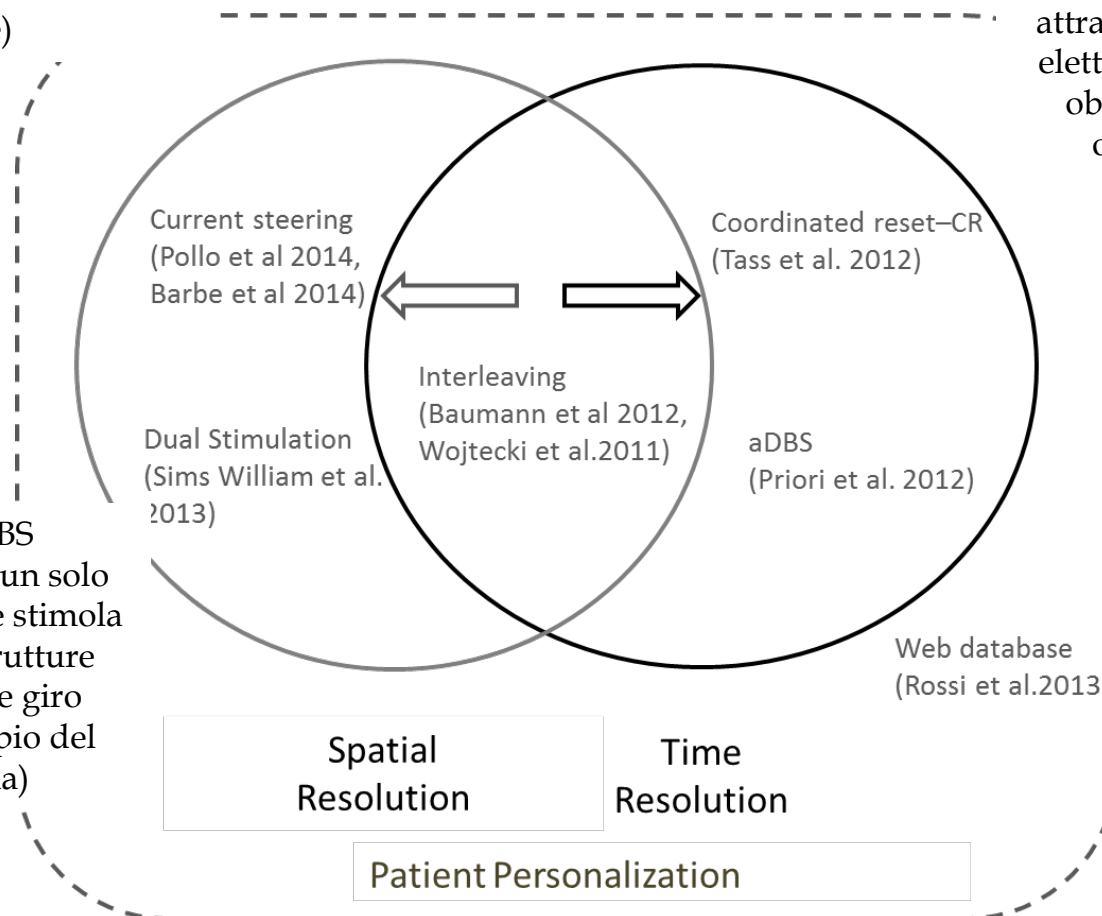
INNOVAZIONI TECNOLOGICHE

Current steering → DBS basata su elettrodi di nuova generazione che consentono di direzionare la corrente sia lungo l'asse dell'elettrodo stesso sia intorno all'asse dell'elettrodo (orizzontalmente)

Interleaving stimulation → stimolazione in cui due elettrodi forniscono una diversa quantità di carica (ampiezza e lunghezza dell'impulso), ma con la stessa frequenza

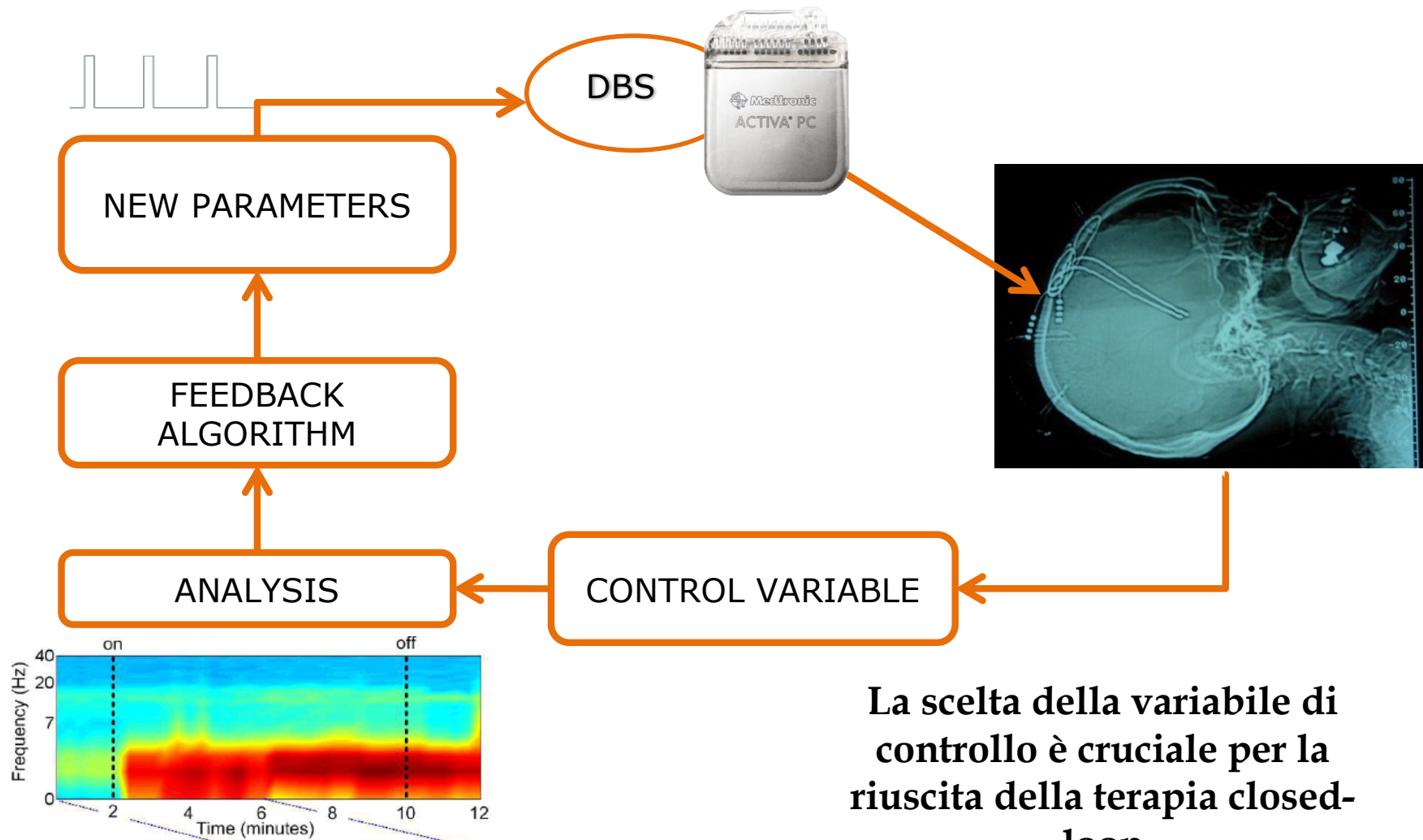
Coordinated-reset DBS → Strategia di stimolazione basata su treni di impulsi ad alta frequenza attraverso i diversi contatti degli elettrodi impiantati che ha come obiettivo il reset della fase di oscillazione delle diverse sottopopolazioni

Dual stimulation → DBS somministrata utilizzando un solo elettrodo, con 16 contatti, che stimola indipendentemente due strutture profonde diverse (talamo e giro periventricolare, nell'esempio del dolore da arto fantasma)



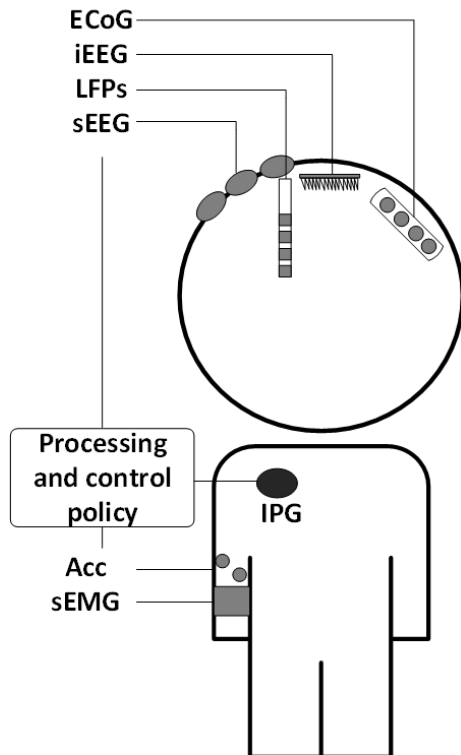
(Priori 2015)

ADAPTIVE DBS o CLOSED LOOP DBS



La scelta della variabile di controllo è cruciale per la riuscita della terapia closed-loop

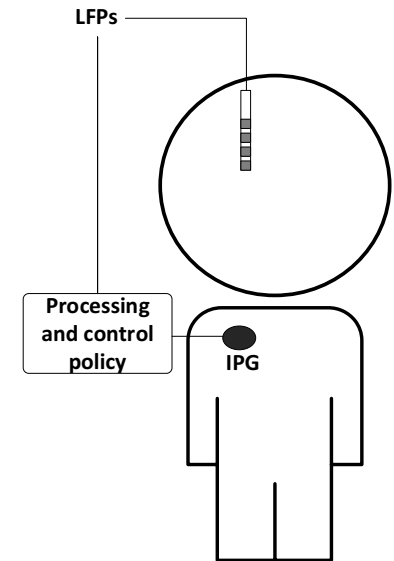
VARIABILI DI CONTROLLO



(Arlotti 2016)

	sEMG and accelerometers	Cortical neurosignals	Basal ganglia LFPs	Neurotransmitters
Additional implant/equipment	YES – external sensors required	YES – implanted cortical electrodes required	NO – LFPs are recorded from the implanted DBS electrode	YES – at least 4 additional CFM
Changes in the surgical procedures	NO – the additional implant is external and does not affect the surgical procedure	YES – the surgery needs to include the implant of cortical electrodes	NO – no additional implant during surgery	YES – the additional CFMs need to be implanted during surgery
Patient's management/acceptability	NO – it may be difficult to manage the recording sensors and the external equipment may be uncomfortable	YES – all the equipment is implanted	YES – the patient perceives the same system as for traditional DBS	NO - CFMs have a time life of only a few months and have to be replaced
Correlation with the clinical state	YES/NO – optimal correlation with tremor, but no correlations with rigidity and bradikinesia	YES – EcoG phase amplitude coupling and M1 action potentials correlate with main PD symptoms and can be used to drive aDBS	YES – multiple LFP oscillations are modulated by levodopa administration, DBS, movements, and non-motor tasks even years after electrode implant	YES - the time duration of tremor-free period is comparable to the duration of increased levels of stimulation-induced dopamine release after DBS pulse trains
Personalization and adaptability	NO – cannot be used if patients do not show tremor	YES/NO – it may encode patient specific information	YES – the presence of multiple rhythms correlating with different patient's characteristics may account for inter-subject variability	NOT YET TESTED
Low battery consumption	YES/NO – the processing can be done externally, but triggers should be sent via telemetry links	YES/NO – the IPG needs to include the sensing circuit and the feedback algorithm	YES/NO – the IPG needs to include the sensing circuit and the feedback algorithm	NO – the IPG needs to include the sensing circuit and the feedback algorithm
Proof of concept	YES in humans (ET) [Yamamoto et al., 2013]	YES in animals [Rosin et al., 2011]	YES in humans (PD) [Little et al., 2013; Rosa et al., 2015; Little et al., 2015]	NO

PERCHÈ I LOCAL FIELD POTENTIALS



1. Acquisibili direttamente dall'elettrodo impiantato, anche durante la stimolazione
2. Correlano con lo stato clinico
3. Elaborazione tramite algoritmi già implementati
4. Sono stabili in cronico
5. Sono modulati dalla DBS

aDBS NELL'UOMO

