





CENTRO INTEGRAL EN NEUROCIENCIAS A.C. HM CINAC

Part of Hospital Universitario HM Puerta del Sur in Móstoles, Madrid, this Centre specialises in the treatment of neurodegenerative, neurofunctional and psychiatric disorders.

This pioneering and world-leading integrated care project takes a multidisciplinary clinical and experimental approach, aimed at identifying the origin of neurodegenerative and neuropsychiatric disorders, optimising their diagnosis, and making advances in the treatment of patients with such conditions.

➤ Vision and objectives

HM CINAC is primarily dedicated to translational research. It is made up of a clinical care department, a clinical and experimental research department, and a teaching department.

HM CINAC's aim is to become the number-one clinical neuroscience centre.

One line of research pursues the ambitious but possible goal of halting the progression of Parkinson's disease, while providing optimal healthcare to patients with neurological conditions, focusing in particular on neurodegenerative diseases

(Parkinson's disease, Alzheimer's, etc.) and neuropsychiatric disorders.

The main objectives are as follows:

➤ **1. Research in clinical neuroscience**, which focuses on neurodegenerative diseases such as Parkinson's disease, cognitive decline and behaviour disorders. Advanced neuroimaging (PET-integrated functional magnetic resonance imaging) and neurophysiology techniques (non-invasive transcranial stimulation, movement studies and the recording of oscillations), neurocognitive techniques (behavioural laboratory) and neurosurgical techniques (deep brain stimulation, focused ultrasound) are used to advance clinical and pathophysiological research and develop new treatment options for Parkinson's disease and

other neurodegenerative conditions, and other movement and behaviour disorders (dystonia, myoclonus, impulse control disorder, Tourette's syndrome, etc.).

➤ **2. Development of basic knowledge** through experimental neuroscience, with a pre-clinical research centre working on the neurobiological mechanisms of neurological disorders, where use is made of neuroimaging techniques (PET and MRI), neurophysiological techniques that enable integrated studies of single and multiple neuron activity and field potentials, behavioural laboratories, and the usual histopathological techniques.

➤ **3. National and international collaborative ties**, giving rise to a working network with the shared goal of making progress in the fight against neurodegenerative diseases and neurofunctional disorders.

HM CINAC also provides teaching and continuous professional development, with a focus in this case on neurodegenerative diseases and neuropsychiatric conditions.



THE TEAM

staff

The team at **HM CINAC** has been put together with the main objective of ensuring a high degree of multidisciplinary collaboration and synergy, and consequently excellence in clinical care and research. The working group consists of professionals from a range of different disciplines, including neurologists, neurosurgeons, engineers, neuropsychologists, basic neuroscientists, specialist nurses and clinical research nurses, under the direction of Dr José A. Obeso, together with the executive secretary and a technician. What's more, the Centre combines professionals with extensive experience in the study of neurodegenerative diseases with a group of young experts, most of whom have returned from periods training abroad, who bring enthusiasm, a modern approach and cutting-edge technical knowledge to the projects they work on. This group and combination of people has resulted in a highly motivated and



driven team with an understanding of and shared ambition to achieve high-level translational research, the primary objective being to have a decisive impact on the neurodegenerative process of Parkinson's disease. Ultimately, the goal is to halt the progression of the disease, thus offering a new treatment approach that changes the way it develops.



> Dr José A. Obeso - Director of HM CINAC



Neurologist and Professor of Neurology at the Faculty of Medicine of CEU San Pablo University. Dr Obeso graduated from the University of Navarra in 1976, specialising in neurology and neurophysiology in San Sebastián and Pamplona. Between the years 1980 and 1982, he specialised in Parkinson's disease and movement disorders with Professor C. David Marsden at King's College

Hospital, Institute of Psychiatry in London, an exciting and defining period in his career.

Dr Obeso has dedicated himself to caring for patients with Parkinson's disease and other movement disorders, and to both clinical and laboratory-based research. Together with Tom Chase and Fabriccio Stochi, he pioneered the development of the concept of "continuous dopaminergic stimulation" for Parkinson's disease, and played an important role in the recent

revival of surgical treatments for the disease. He has published more than 350 original research articles and 90 reviews in journals, edited 18 books and special-topic supplements in medical journals and in 98 book chapters, and contributed to the latest edition of *Harrison's Principles of Medicine*.

His current Hirsch index is 70 – the highest in Spain in the field of neurology. He has also been Editor-in-Chief of the journal *Movement Disorders* since 2010.

healthcare



>> HEALTHCARE Services at HM CINAC

- 12 consulting rooms for all specialties in the branch of neuroscience (neurology, neurosurgery, psychiatry, neurophysiology, etc.).
- Nuclear Medicine Department, equipped with:
 - Simultaneous acquisition PET-MR scanner, the only one in Spain with very-high-field 3-Tesla NMR.
 - State-of-the-art gamma camera.
- Psychophysical and motor control laboratories, a special room for monitoring and carrying out pharmacological tests and treatment.
- Clinical neurophysiology laboratories dedicated especially to the areas of functional neuroscience, with a particular focus on magneceutical therapy (transcranial magnetic stimulation), and functional neuropsychology.
- Sleep unit with the full range of services corresponding to this branch of clinical neurophysiology (video-EEG, multiple latency tests, etc.).
- Personalised patient care (NeuroCare).

On top of providing patients with excellent healthcare, **HM CINAC** has made a special effort to equip this Integrated Centre with a state-of-the-art research structure, for both basic and clinical research. For that purpose, the Centre has established lines of work aimed at improving the care of patients with neurological and psychiatric conditions:

> Neurofunctional treatment program

At **HM CINAC**, patients have access to the latest technology and first-rate staff, whose aim it is to offer those with neurological and psychiatric conditions the best treatments available.

The lines of development are as follows:

Deep brain stimulation: a technique involving the insertion of intracerebral electrodes that can help to improve quality of life and prognosis for a broad spectrum of patients, and that can be used for Parkinson's disease, essential tremor, tics and Tourette's syndrome, obsessive compulsive disorder and other neurological and psychiatric conditions.

HIFU (High-Intensity Focused Ultrasound): **HM CINAC** has equipped itself with a system that uses focused ultrasound to provide intracranial treatment without the need for surgery, which was the standard treatment until now. Conditions covered by this treatment include essential tremor, Parkinson's disease and trigeminal neuralgia, among others. **HM CINAC** is also a leader in using this technology to develop new targets for the treatment of neuropsychiatric diseases.

Transcranial magnetic stimulation and magneceutical therapy, which makes it possible to activate or inhibit areas of the brain so as to arrive at the most accurate diagnosis, and even to modulate brain activity by applying fixed electromagnetic fields to certain areas of the brain.

capacity

PSYCHIATRY DEPARTMENT



The Psychiatry and Clinical Psychology Department of HM Puerta del Sur, directed by Dr Luis Caballero Martínez, provides personalised and patient-oriented clinical care using the very best diagnostic and treatment means, while working in close collaboration with the Centro Integral de Neurociencias AC (HM CINAC) and with the professionals, institutions or groups that entrust it with the psychiatric care and mental health of their patients.

The Department is run by psychiatrists, clinical psychologists and highly qualified nursing staff who coordinate with one another to develop **personalised treatment plans** in accordance with the highest professional and ethical standards, and to build caring relationships with patients and their family members.



For diagnostic purposes, the Department draws on an extensive selection of clinical, laboratory, psychometric and neuroimaging resources, among others (genetics). For treatment purposes, it uses a wide range of psychotherapeutic procedures (including integrative therapy, cognitive behavioural therapy, psychodynamic therapy, couples and group therapy and rehabilitation techniques) and biological procedures (including psychopharmacotherapy, electroconvulsive therapy, magnet therapy and psychosurgery) associated with contemporary psychiatry and clinical psychology.

In addition to providing healthcare, the Department carries out regular teaching activities (continuing education for the team, university education on undergraduate degrees in medicine and psychology and Masters at CEU San Pablo University and others); research tasks (its own clinical research, and integrated research at **HM CINAC**); and activities associated with technological innovation.



technology:

Eager to be able to offer its patients the best possible treatment, **HM CINAC** has acquired the most sophisticated technology for diagnosing and treating neurological diseases, making it a global leader when it comes to healthcare equipment.



➤ PET-MR Biograph mMR, by Siemens Healthcare

This is the first system in the world capable of integrating whole-body molecular magnetic resonance with data-acquisition technology. **HM CINAC** is the first health centre in the whole of Spain to have this revolutionary device, which

marks a before and after in diagnostic procedures.

The new hybrid 3-Tesla system enables the simultaneous acquisition of magnetic resonance (MR) and positron emission tomography (PET) data.



This innovative system has the potential to be an especially valuable tool for identifying neurological, oncological and heart conditions in patients, and for facilitating the planning of suitable treatments. Since MR does not emit ionising radiation, Biograph mMR has the advantage of being able to produce images at a low radiation dose. It also opens up new research opportunities, such as the development of new biomarkers or new treatment approaches.

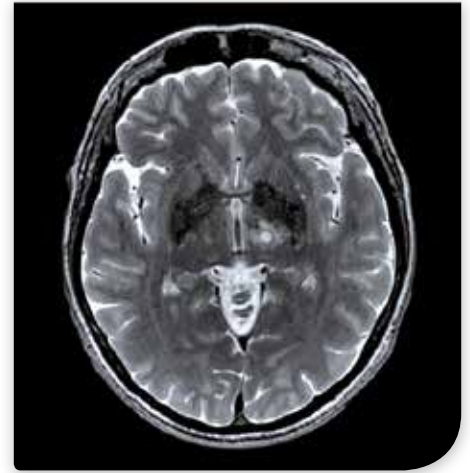
a closer look

➤ HIFU (High-Intensity Focused Ultrasound)

This is the first system in Spain designed to treat neurofunctional disorders. Through an ultrasound technique and diagnostic imaging using magnetic resonance (compatible only with a 3T MRI machine, which **HM CINAC** also has), this process consists in applying an ultrasound treatment to a target measuring a few millimetres, which leads to localised hyperthermia and finally ablation of the target zone. By acquiring this device, **HM CINAC** has become one of the few centres in Europe that's able to offer the treatment. In fact, Spain is the second country in Europe, together with Switzerland, to have HIFU technology.

The HIFU equipment acquired by HM Hospitales and ERESA is indicated for patients with essential tremor and other tremors that can be treated with thalamus surgery, although in the near future it will be used mainly for Parkinson's disease and possibly brain tumours, chronic pain, trigeminal neuralgia, some neuropsychiatric disorders, and so on. Currently, when these types of patient don't respond to medical treatment, they are treated with deep brain stimulation, i.e. brain surgery in which electrodes are inserted into the brain and connected to a generator. This has the effect of stimulating an area of the brain and overriding the tremor. It's an invasive procedure and costly in terms of healthcare.

The main advantage of HIFU is that it doesn't require any intracranial treatment to be carried out. During the treatment, the medical professional can check that the correct area is being targeted and the procedure is having the desired effect, and make adjustments to improve effectiveness and reduce adverse effects before focal tissue ablation takes place.



research on parkinson's



➤ Parkinson's disease

➤ When does the disease develop?

To date, all the treatments with a curative purpose have failed, and one of the suggested reasons for this is the delay in diagnosis with respect to the onset of the degenerative process. For that reason, **at HM CINAC we're conducting a study in patients using magnetic stimulation or neuroimaging techniques focused on identifying the onset of the disease.**

➤ Loss of dopaminergic neurons: why are they produced?

Parkinson's disease is primarily characterised by the **progressive degeneration of the dopaminergic neurons of the substantia nigra pars compacta (SNpc)**, which at the same time are key during learning and habit acquisition.

At HM CINAC, we're studying the role that education and the continuous and simultaneous performance of routine tasks play in the onset of the neurodegenerative process. To that end, we're conducting experiments using **highly innovative techniques** such as in vivo calcium visualisation of neuronal activity and optogenetics, as well as conventional electrophysiology.

➤ How is this loss compensated for?

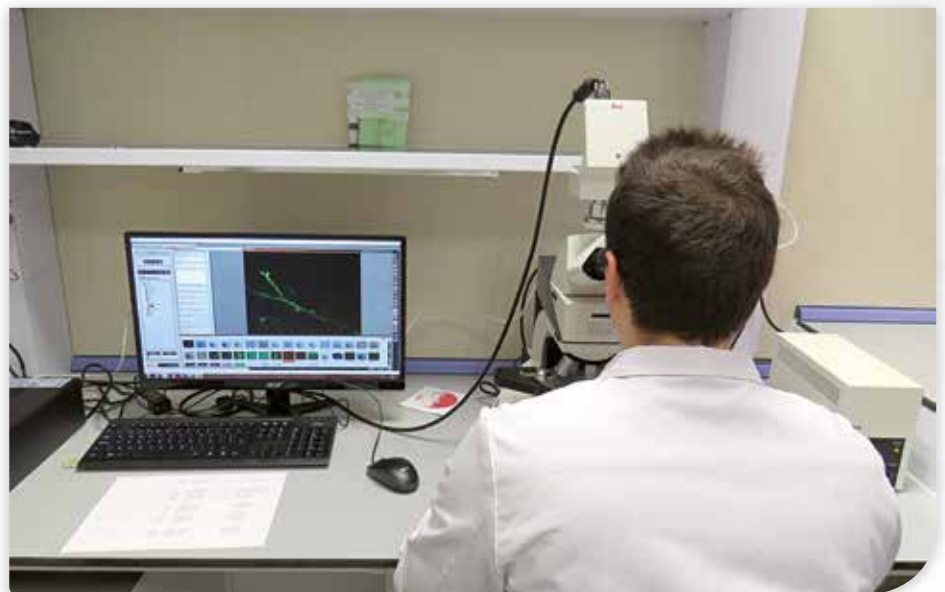
Dopaminergic depletion already exists in the patient's brain before the disease is diagnosed. It is therefore assumed that during this phase a series of compensatory mechanisms occur which hinder the emergence of motor signs.

At HM CINAC, we're conducting studies

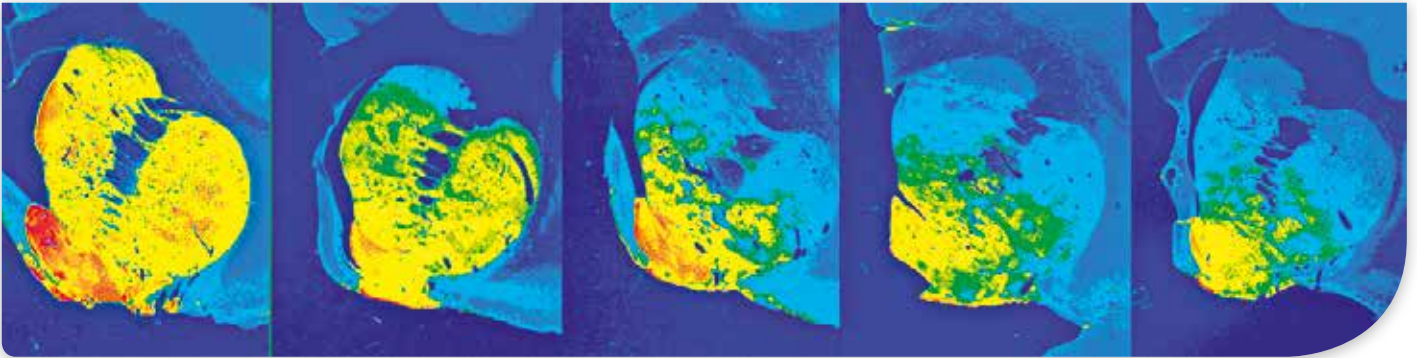
aimed at identifying these mechanisms with the help of animal models of Parkinson's disease, and using techniques for recording neuronal activity.

➤ The origin and mechanisms of levodopa-induced dyskinesia

Dopamine replacement therapy with levodopa (L-DOPA) is a very effective treatment against the main symptoms of Parkinson's disease. However, this therapy is linked to motor complications if used for an extended period of time, and can cause involuntary movements, or dyskinesia. **At HM CINAC, we're studying the molecular bases and pathophysiological mechanisms involved in the generation of these movements.**



disease



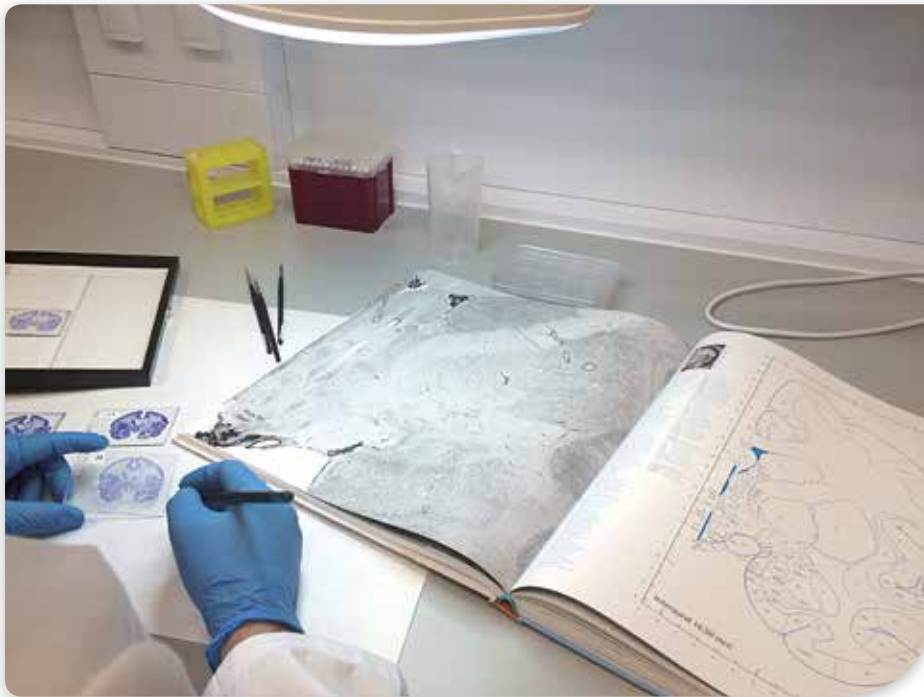
➤ HIFU: a new treatment strategy for Parkinson's disease

Thanks to the recent development of **High-Intensity Focused Ultrasound (HIFU)**, **focal lesions can be made in the brain in a controlled, non-surgical manner**, thus considerably reducing morbidity, mortality and costs compared to existing treatments. This treatment has been shown to be effective and safe for performing thalamotomy to manage essential tremor and Parkinson's disease. At HM CINAC, our aim is to carry out experimental studies first and then studies in patients second, not only to improve the symptoms of the disease but also to act on its medium- and long-term progression and development.

➤ Cortex treatments for the disease

There are various lines of research into nigrostriatal degeneration, the origin of which is unknown. At HM CINAC, we're working on a very novel hypothesis, which postulates that nigrostriatal neurodegeneration is the result of changes in the cerebral cortex. This hypothesis would be **revolutionary from a treatment point of view**, because it would mean cortex surgery could be performed not only to treat the symptoms, but also to interfere with the disease's progression.

research on parkinson's disease

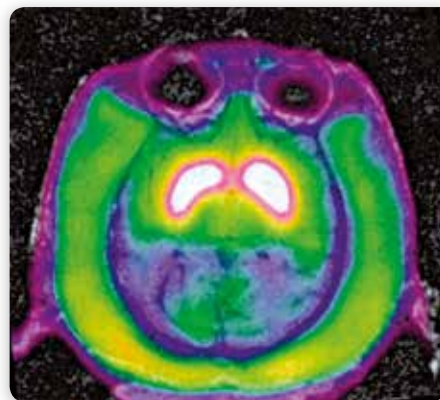


➤ Treatment of cognitive impairment caused by Parkinson's disease

Identifying the risk factors and mechanisms involved in cognitive decline in Parkinson's disease is important not only from a clinical and prognostic point of view, but also at the start of non-pharmacological treatments (transcranial magnetic stimulation and cognitive rehabilitation).

At HM CINAC, we're carrying out studies aimed at identifying early mechanisms associated with cognitive impairment and treatments to prevent or halt its progression.

➤ Neuroimaging studies: positron emission tomography (PET) and magnetic resonance (MR)



The objective of this line of research is to identify markers for the diagnosis and development of Parkinson's disease (PD). HM CINAC's state-of-the-art equipment allows us to use image-processing techniques to characterise the neurodegeneration process in PD and the relevance of specific genes in its development, and to identify the trace that early symptoms of the disease leave in neuroimaging.

Scientific activity



In 2015 (HM CINAC's first year active) we published 20 scientific articles, attaining a cumulative impact factor of 149.897 and an average impact factor of 7.49.

➤ Most notable publications (in the last 5 years)

➤ Originals:

Blesa et al. Progression of dopaminergic depletion in a model of MPTP-induced Parkinsonism in non-human primates. An (18)F-DOPA and (11)C-DTBZ PET study. *Neurobiol Dis.* 2010;38; 456-63.

Rodríguez-Oroz et al. Involvement of the subthalamic nucleus in impulse control disorders associated with Parkinson's disease. *Brain.* 2011;134(Pt 1):36-49.

González-Redondo et al. Grey matter hypometabolism and atrophy in Parkinson's disease with cognitive impairment: a two-step process. *Brain.* 2014;137(Pt 8):2356-67.

Obeso I et al. The subthalamic nucleus and inhibitory control: impact of subthalamotomy in Parkinson's disease. *Brain.* 2014;137(Pt 5):1470-80.

Recasens et al. Lewy body extracts from Parkinson disease brains trigger α -synuclein pathology and neurodegeneration in mice and monkeys. *Ann Neurol.* 2014;75(3):351-62.

➤ Reviews:

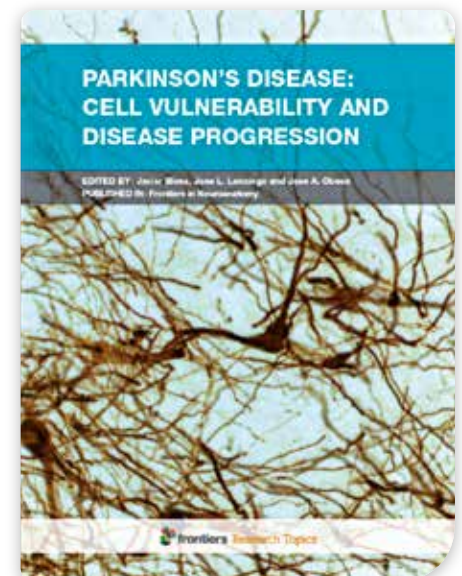
Obeso et al. Missing pieces in the Parkinson's disease puzzle. *Nat Med.* 2010;16(6):653-61.

Schapira et al. Priorities in Parkinson's disease research. *Nat Rev Drug Discov.* 2011;10(5):377-93.

Lang & Obeso. Stem cell therapy for Parkinson's disease. *Ann Neurol.* 2012;71(2):283.

Obeso et al. The expanding universe of disorders of the basal ganglia. *Lancet.* 2014;384(9942):523-31.

Jahanshahi et al. A fronto-striato-subthalamic-pallidal network for goal-directed and habitual inhibition. *Nat Rev Neurosci.* 2015;16(12):719-32



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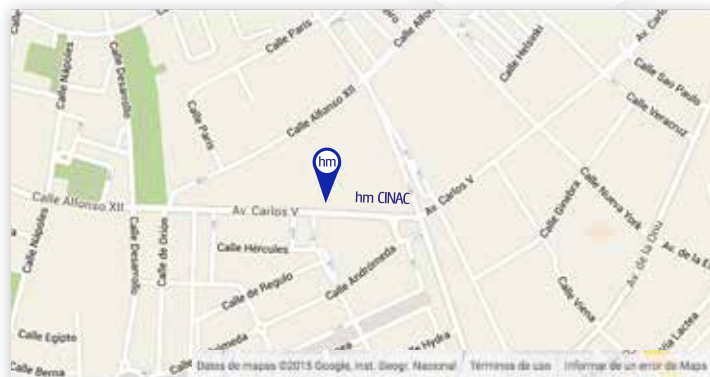
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