Brief History of Neurology and Research in Alzheimer's Disease and Parkinson’s Disease in Spain

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1817

Parkinson’s disease

1850: A Carlsson, dopamine
1967-1968: First trial with levodopa

1919: Konstatin Tretiakoff, 1938: Rolf Hassler, substantia nigra main cerebral area affected
World, chronology of the 19th Century

**Europe:** collapse of the Spanish, Portuguese, Chinese, Holy Roman and Mughal (Persian) Empires. Grow of British Empire, German Empire and United States of America. **Significant developments in the fields of mathematics, physics, chemistry, biology, electricity, and metallurgy that lay the groundwork for the technological advances of the 20th century; Industrial Revolution**

**China:** Opium wars occupied all the century

**India:** Burmese and Sikh wars; British domination

**Africa, America, Europe:** Trade slavery abolished

**United States:** war with Mexico; major settlement of the western territories by migrants from the states in the east, largely through the Oregon trail and the California Gold Rush; civil war (1861-185); war with Spain

**Australia:** convicts transported to Tasmania and Australia

**Japan:** Bunsei era; Meiji restoration; war with China

**South America:** Independence: Paraguay (1911); Mexico (1813); Argentina (1816); Chile (1818); Gran Colombia and Venezuela (1819); Brazil (1822); Bolivia (1825); Gran Colombia splits into three countries: Colombia, Venezuela and Ecuador; United Provinces of Central America breaks into five republics: Guatemala, El Salvador, Honduras, Nicaragua, and Costa Rica (1838); war of the triple alliance between Paraguay, Brazil, Argentina, and Uruguay; war of the Pacific involves Chile, Peru, Bolivia; Spanish-Cuban-American war

**Central Africa:** Liberia is formed by ex-slaves; Congress of Berlin (1855) partitions Africa among the European powers; Belgium’s king Leopold II starts his brutal colonial project in central Africa

**South Africa:** Afrikaner rebellion against British; Zulu wars; diamonds discovered in Orange Free State and Kimberley; Anglo-Boer wars

**North Africa:** decline of Ottoman Empire; colonization of Algeria and protectorate in Tunisia by France
The Ship of Fools: 1490-1500
Narrenschiff, Hieronymus Bosch

The extraction of the stone of foolish, Hieronymus Bosch

Madness
Don Quijote, the sublime creation of Miguel de Cervantes (1547-1616). The stereotype of Spanish genius and madness

Frail evidences of familial dementia in the Castilian court

Portrait by Juan de Flandes, ~1500

Demencia de Doña Isabel
Pelegrin Clavé (1811-1880)

Demencia de Doña Juana
Lorenzo Vallés (1830-1910)

Doña Isabel (1428-1496) second wife of Juan II de Castilla and mother of Isabel I de Castilla (Isabel la Católica) (1451-1504), mother of Doña Juana de Castilla (1479-1555)
Francisco de Goya (1746-1828). Madness and dementia at the beginning of the 19th Century

*Casa de locos*  
*Corral de locos*

*Viejos comiendo sopas*
Spain, chronology of the 19th Century

1808-1814: Independence War (1)
1812: Cortes de Cadiz: Liberal Constitution (1812)
1814-1833: Fernando VII: Absolutism excepting the liberal triennia
1833-1868: Isabel II; Constitution 1837, Constitution 1845
1868-1870: Provisional Government: Constitution 1869
1870-1873: Amadeo de Saboya
1873: First Republic (2)
1874: Coup d'état, General Pavía (3)
1875-1885: Alfonso XII; Restauration (A Cánovas del Castillo) (4); Constitution 1876
1885-1902: Alfonso XIII, Maria Cristina Regency; 1898 end of Cuba’s war (5), intervention of the U S A: loss of Cuba, Filipinas and Puerto Rico
Narcis Monturiol

The first submarine: Ictineo, 1859

Neurology in Spain, Translation of “Diseases of the Nervous System” 6 volumes, 1886

The obscure Century (with exceptions)
The vertigo years (1900-1914)
Philipp Blom
Weidenfeld & Nicholson
London 2008

Ford T, 1908

Zeppelin, 1900-1937

Titanic, 1912

Dreadnought, 1906
Psychoanalysis
Sigmund Freud (1856-1939)

Physicists and Chemists
Henri Beckerel (1852-1908)
Wilhelm Conrad Röntgen (1845-1923)
Pierre Curie (1859-1906)
Marie Curie (1867-1934)
Ernest Rutherford (1871-1937)
Albert Einstein (1979-1955)

Evolution, theory
Gregor Mendel (1802-1884)
Charles Darwin (1809-1882)
Friedreich Leopold August Weismann (1834-1914)
Thomas Hunt Morgan (1866-1945)

Eugenics: nature versus nurture
Francis Galton (1822-1911) Hereditary genius (1869)
First International Congress of Eugenesis, 1912

Psychiatry
Emil Kraepelin (1856-1926)
Mental diseases at the end of the 19th and beginning 20th centuries

Progressive general paresis (paretic dementia)

Clinical symptoms

Progressive dementia, tremor, and speech disturbances; muscular weakness; and ultimately generalized paralysis. It is often accompanied by periods of exultation and delusions of grandeur. May be accompanied by other alterations of tertiary syphilis.

Neuropathology

Meningoencephalitis with activated microglia in the form of rod cells
Neuron loss and reactive astrogliosis

Neuron loss, encephalitis, and rod cells
Neurasthenia is a mental disorder triggered by stress or anxiety. Symptoms may include:
• weakness or fatigue, which may be accompanied by chest pain
• rapid intense heartbeat that may be irregular (palpitations, tachycardia)
• cold, clammy hands and feet
• abnormally rapid breathing (hyperventilating)
• dizziness or faintness
• periodic sighing
• sweating for no apparent reason

Diagnostic criteria for neurasthenia include:
• Persistent and distressing symptoms of exhaustion after minor mental or physical effort including general feeling of malaise, combined with a mixed state of excitement and depression.
• Accompanied by one or more of these symptoms: muscular aches and pains, dizziness, tension headache, sleep disturbance, inability to relax and irritability.
• Inability to recover through rest, relaxation or enjoyment.
• Disturbed and restless, un-refreshing sleep, often troubled with dreams.
• Duration of over three months.
• Does not occur in the presence of organic mental disorders, affective disorder, panic or generalized anxiety disorder.
Female hysteria was a once-common medical diagnosis, made exclusively in women, which is today no longer recognized by modern medical authorities as a medical disorder. Its diagnosis and treatment were routine for many hundreds of years in Western Europe. Hysteria was widely discussed in the medical literature of the Victorian era.

Clinical symptoms included:
• faintness
• nervousness
• insomnia
• fluid retention
• heaviness in abdomen
• muscle spasm
• shortness of breath
• irritability and loss of appetite for food or sex

Treatments:
• hydrotherapy
• pelvic massage: difficult for a physician to master and could take hours to achieve "hysterical paroxysm" (orgasm)
• massage devices. By 1870, a clockwork-driven vibrator was available for physicians. In 1873, the first electromedical vibrator was used at an asylum in France for the treatment of hysteria. A 1918 Sears, Roebuck and Co as included several models of vibrators
Spain, crossing the Century

Ramón Casas. *Baton charge*, 1899-1900 (dated 1903)
Ramon Casas. *Fresh air* (1892)

Ramón Casas. *Ladies portrait* (1896)
The Institucion Libre de Enseñanza (ILE): Free Educational Institution: Krausism

The "Decree Orovio" proposed by Canovas in 1875 suspended academic freedom in Spain to strengthen a fundamentalist principle that made the nation a project held in the divine will.

ILE was a famous educational effort inspired by the philosophy of Karl Christian Friedrich Krause who had an exceptional impact on the intellectual life of the nation, in which she played a key role renewal. ILE was founded in 1876 by a group of professors: Francisco Giner de los Ríos (1), Gumersindo de Azcarate (2), Teodoro Sainz Rueda and Nicolás Salmerón (3), separated from the Central University of Madrid to defend academic freedom. Consequently, they had to continue their educational work outside the State by creating a secular private educational institution, which began in the first place by the university and later extended to primary and secondary education.

Outstanding figures contributed to the classes and seminars: Bertrand Russell, Henri Bergson, Charles Darwin, John Dewey, Santiago Ramón y Cajal, Miguel de Unamuno, Maria Montesori, Leo Tolstoy, HG Wells, Rabindanath Tagore, Juan Ramón Jiménez, Gabriela Mistral, Benito Pérez Galdós, Emilia Pardo Bazán, Azorín, Eugenio d’Ors, Ramón Pérez de Ayala, Julián Sanz del Rio, Antonio Machado, Manuel Machado, Julio Rey Pastor, Luis Simarro and Nicolás Achúcarro among others.
Pablo Ruiz Picasso. *Science and Charity* (1897)
**Santiago Ramon y Cajal (1852-1934)**

1889
Meeting of the German Society of Anatomy in Berlin in October: International success of Santiago Ramón y Cajal. **Theory of the Functional Unity of the Neuron**

1890, 1891
Several studies of the development of the nervous system: neurogenesis, discovery of the growth cones
**Theory of the tropism of the neuron**: axonal growth, arrival and targeting
Ontogenic study of the cerebellum
Studies of the structure of the cerebral cortex
Studies of the neuroglia
Structure of the olfactory pathways
Alzheimer’s disease  Alois Alzheimer (1864-1915)

Alzheimer A. A unique illness involving the cerebral cortex: a case report from the mental institution in Frankfurt am Main. Allg Z Psychiatr-Geric Med 1907: 64146-148

Alois Alzheimer

Auguste D: 51 y

Neurofibrillary tangles and senile plaques
From left to right: Gonzalo Rodríguez Lafora, Domingo Sánchez, Jose María Sacristán, Manuel Gayarre, Nicolás Achúcarro, Santiago Ramón y Cajal, Luis Rodríguez Illera, Juan de Dios Sacristán, the technician and the caretaker. Published by “La Esfera”, 1915
Spanish neuroscience before the Spanish Civil war. The Golden Age of Neuroscience

Gonzalo Rodríguez Lafora       Fernando de Castro       Pío del Río Hortega       Nicolás Achucarro       Rafael Lorente de No

Pedro Tello, Felipe Jiménez de Asúa, José Miguel Sacristán, Luis Calandre, Miguel Gayarre, Luis Simarro, and others

Luis Simarro

Other branches of science  F. Durán I Reynals  Ramon Turro  August Pi I Sunyer
The Spanish Civil War was the Spanish share in the tragic European breakdown of the twentieth century, in which the liberal heritage of the nineteenth century, and the sense of optimism which had lasted since the renaissance, were shattered. Hugh Thomas “The Spanish Civil War”
After World War II, Franco and Spain had been forcibly isolated as a consequence of supporting Germany. The Allied Forces imposed sanctions and on Spain resulting in a significant negative economic impact. However this changed in the early 1950s when Spain was seen as a strategically important geographical location in the Cold War era. Franco entered into trade and military agreements with the US and in 1955 became a member of the United Nations. This paved the way for Spain’s economic growth in the 1960s. Throughout his reign Franco decreed that all political opposition and non-sanctioned trade unions were suppressed. This repression extended to ensuring a constant visible presence of armed military police (la Guardia Civil) in all towns and cities. In this way General Franco imposed his dictatorship.
Francisco Franco  (1892-1975). General and leader of the Nationalist forces that overthrew the Spanish democratic republic in the Spanish Civil War (1936–39); thereafter he was the head of the government of Spain (Generalísimo y Caudillo de España) until 1973 and head of state until his death in 1975.

In July 1974, the aged Franco fell ill from various health problems but soon recovered. One year later he fell ill once again from more health problems including a long battle with Parkinson’s disease. Franco died on 20 November 1975, just two weeks before his 83rd birthday, the same day of the year as the death of José Antonio Primo de Rivera, founder of the Falange.
**Adolfo Suarez** (1932-). Spain's first democratically elected prime minister after the dictatorship of Francisco Franco, and the key figure in the country's transition to democracy. On 31 May 2005, Suárez's son announced on Spanish television that his father was suffering from Alzheimer's disease.

23F 1982 Spanish coup d’état attempt

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**Jordi Solé Tura** (1930-2009)
Politician and jurist, one of the Fathers of the Spanish Constitution of 1978


Alzheimer’s disease
José Luis García Berlanga (1921-2010)

Bienvenido Mister Marshall (1952)

Eduardo Chillida (1924-2002)

El peine del viento, San Sebastián

Carmen Conde Abellán (1907-1996)

Teacher, poetess, storyteller, academic

Alzheimer’s disease
Gala died on June 10, 1982. After Gala's death, Dalí lost much of his will to live. He was afflicted by tremor which made difficult his painting. Yet several pieces were created at that time. There is no fair diagnosis of the neurological impairment. Apathy, gastrointestinal disorders, abnormal sleep behavior and inexpressive face, together with altered gait prompted the diagnosis of parkinsonism, may be toxic or degenerative. On January 23, 1989, while his favorite record of *Tristan and Isolde* played, he died of heart failure at Figueres at the age of 84.

Salvador Dalí (1904-1989). A master of surrealism. Did he suffer from PD?

*Leda atomica*, 1949

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*Leda atomica*, 1949
Modern Spanish neuroscientists

Lluis Barraquer I Roviralta (1855-1928), founder of the Spanish neurology

B. Rodríguez Arias
Lluis Barraquer Farré
Antonio Subirana Oller
Lluis Barraquer I Bordás

Neurohistologists

Miguel Marín Padilla (1)
Constantino Sotelo (2)
Facundo Valverde (3)

Neuropathologists

Roman Alberca Lorente
Eduardo Pons Tortella
Carlos Olivera de la Riva
Luis Valenciano Gaya
Wenceslao Calvo
Jordi Cervós Navarro (4)
Parkinson disease

Incidence: 4.5-16 (16-19) per 100,000 per year
Prevalence: 18-328 (150-200) per 100,000
Total affected around 100,000 persons in 2005

Dementia

Incidence: 1,000 per 100,000 inhabitants per year
Prevalence: 6% older than 65 years; 22% men and 30% women older than 85 years
Total affected around 500,000 in 2005

<table>
<thead>
<tr>
<th></th>
<th>Total population</th>
<th>Older than 65 years</th>
<th>Patients with dementia</th>
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<tbody>
<tr>
<td>2001</td>
<td>41 116 842</td>
<td>6 796 936</td>
<td>407 816</td>
</tr>
<tr>
<td>2004</td>
<td>43 197 684</td>
<td>7 184 921</td>
<td>431 000</td>
</tr>
<tr>
<td>2030*</td>
<td>50 878 142</td>
<td>9 900 000</td>
<td>594 460</td>
</tr>
<tr>
<td>2050*</td>
<td>53 159 991</td>
<td>16 387 874</td>
<td>983 272</td>
</tr>
</tbody>
</table>

Data from Spanish Foundation of Neurological Diseases (FEEN) with the support of the Spanish Society of Neurology, February 2010
A south-north gradient, with large geographical areas suggesting clustered towns with high mortality, was seen in Asturias, the Basque Country, Balearic Islands and, particularly, in the Lower Ebro valley around Tarragona. Similarly, there was a suggestion that lowest mortality was clustered in the south-east and south-west. We identified some isolated or clustered municipalities with high mortality that were situated near industrial plants reported to be associated with environmental xenobiotic emissions. However, the same pattern was also observed for some cities with low mortality.
ADPD at present: Strong institutional support and social cohesion

Instituto de Salud Carlos III
Centro de Investigación de Enfermedades Neurodegenerativas (CIEN)
CIBERNED (Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas)
Consejo Superior de Investigaciones Científicas
Instituto Cajal

Spanish Society of Neurology (created in 1949)
Spanish Club of Neuropathology (created in 1978)
Spanish Society of Neurosciences (created in 1985)
Sociedad Española de Medicina de Familia y Comunitaria
Sociedad Española de Psiquiatría
Sociedad Española de Geriatría y Gerontología
Colegios Oficiales de Médicos
Colegios Oficiales de Farmacéuticos
Colegios Oficiales de Psicólogos
Colegios oficiales de Enfermería
Asociacion de Terapeutas Ocupacionales

Fundación Cien (Centro de Investigación Enfermedades Neurológicas)
Fundación Reina Sofía
Fundación Pascual Maragall

Fundación Española de Enfermedades Neurológicas
Fundacion Alzheimer España
Asociaciones de Familiares de Enfermedad de Alzheimer
Federación Española de Párkinson-FEP- groups 40 associations in Spain

The Silver Age of science in Spain, 1990-2008
In 2008, the Spanish government promised a new Silver Age of science that would comprise the creation of a new Ministry of Science together with major, long-awaited investments in research and development. Unfortunately, those expectations have not translated into reality. The recently tabled 2010 national budget proposes that funding for the Ministry of Science should be cut by more than 15%, thus returning to 2006 levels. In fact, the situation will be even more serious given that the new Ministry also comprises the Health Institutes, which were previously the oversight of the Ministry of Health.

Spain's science budget could be slashed

Amid rumours of cuts, Spanish researchers face a tense wait before the next budget announcement.
Michele Catanzaro

In April 2009, governance of universities was switched from the science ministry to the education ministry. When the new budget for 2010 was announced, the cuts to science effectively amounted to 15%, as an analysis by Confederation of Spanish Scientific Societies (COSCE) showed in February 2010. Spanish science is already feeling the blow. Research institutions depending on the ministry have suffered up to a 30% reduction in government contributions since 2008.