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From Cajal's Desk

Santiago Ramon y Cajal, mental functions and neuropsychiatry

Luis Salvador-Carulla

Professor of Mental Health, Deputy Director of the Health Research Institute, University of Canberra, Bruce, ACT, Australia

According to Delgado-Garcia, Santiago Ramon y Cajal's main contributions to Neuroscience were the role of independent neurons as the main functional unit of the brain, the principle of dynamic polarization, brain plasticity as the substrate of memory and learning processes, and the unity of spatial and tonal perception (cognitive need to generate a single and integrated perception corresponding to the whole set of stimuli presenting the external world).[1] As a continuation of his work on histology and physiology, Cajal kept a sustained interest in mental health, psychology and psychiatry, although he repeatedly expressed his frustration on the difficulties in proposing a morphological and dynamic plan of the cerebral cortex able to explain the mental functions.[1]

Cajal was particularly interested in how anatomy and histology might translate into function. He considered pyramidal cells in the cerebral cortex as the morphological substrate of cognition, which led him to labelling these cells as the "psychic neuron" in 1892. Even though he abandoned this expression in his later writings,[1] it was re-taken by the late Patricia Goldman-Rakic,[2] to designate the key role of pyramidal cells of the pre-frontal cortex in working-memory. We now know that disruption, or even a slight slowing of the rate of neuronal production, migration and synaptogenesis in the pre-frontal cortex can lead to cognitive impairment and it is linked to a wide span of mental disorders, as well as the role of genetical and environmental factors in this process.[3]

In 1888, Cajal identified neuronal spines as structures of the neuron and not as artefacts of the stain method as suggested by Golgi and others.[4] He described that spine density was higher in postnatal development than at later stages and proposed that the spines might help to increase and modify synaptic connections.[5] He adopted Berkley's description of the principal central synapse in 1896, and identified the bulbous portion of the spines as substrate of neuronal action potentials.[4] However in 1911 he changed his view and stated that "neurofibrils were the sole conductors of neuronal activity" ("Histologie du Systeme Nerveux de l'Homme et des Vertebrates", 1911 – quoted by Bennet, 2015).[4] Finally, in 1933, he stated that the "exclusive conductive mission" of neurofibrils is "hypothetical" and that the question whether conduction occurred in neuroplasm or in neurofibrils was still unsolved.[6] It is interesting to note that Cajal underscored the importance of learning and environment in shaping neuronal networks (Ramon y Cajal, "Recuerdos de mi vida", 1923 – quoted by Fuster, 2007).[7]

> Functional improvement brought about by exercise (physical education), speaking, writing, playing the piano. . . [is due to] . . . [the] creation of new cellular appendices . . . capable of improving the adjustment and extension of the contacts, and even of organizing absolutely new relationships between primitively unconnected neurons.

Cajal also considered the importance of local and extended networks between pyramidal cells and short axon neurons in a large number of cortical areas. He regarded the relative high number of short-axon neurons in the human brain in comparison to other species "as peculiar stores for the psychic energy, being responsible for higher functions such as memory, ideation, and decision-making."[1] The interaction between Purkinje cells and interneurons in cortical microcircuits and their role in the development of cognitive functions is related to the excitatory/inhibitory function of regular spiking pyramidal neurons and fast spiking interneurons in working memory tasks noted by Goldman-Rakic.[2] Plastic changes in the engagement of inhibitory feedback circuitry enable the dynamic regulation of excitability in these cortical microcircuits. Transient interneuron recruitment could provide enhanced inhibition required to facilitate the temporal synchronization of pyramidal cells and maintain the stability of currently active assemblies while suppressing competing ones.[8]

In spite of his inferences connecting brain morphology to its activity, Cajal was deterred by the limits of the knowledge related to mental functions. As he stated in "La Textura del sistema nervioso del hombre y de los vertebrados" (Ramón y Cajal, 1904, vol. II, p. 1141 – quoted by Ibarz Serrat, 2017)[9]:

> . . . we have already stated that a topo-physiological doctrine of the brain could provide relevant data for the diagnosis and treatment of nervous diseases []; however, it leaves us in the outermost obscurity regarding the knowledge of the inner mechanism of mental acts.

These limitations may explain the gap between his expressed interest on the topic and the dearth of Cajal's publications about mental health. These publications comprise less than 2% of his scientific output.[10] In any case the relationship of Cajal with psychiatry was intense, and it included the mentorship of a whole generation of "organic" psychiatrists such as Lafora, Achúcarro,

E-mail address: Luis.salvador-carulla@canberra.edu.au

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Fig. 1. Cajal and his disciples. Photography published in La Esfera 1915, Number 56, 24 January 2015. From right to left: Gonzalo Rodriguez Lafora; Domingo Sánchez Sánchez; José Miguel Sacristan; Miguel Gayarre Espinel; Nicolas Achucarro Lund; Santiago Ramon y Cajal; Luis Rodriguez Illera; Juan de Dios Sacristan; Tomás Garcia de la Torre (concierge); Jerónimo (lab assistant). https://arhipa.org/fotos/Cajal-y-discipulos-1915.jpg.

Sacristán, Villaverde, Fortún, Prados y Rodríguez Somoza (Fig. 1). These Spanish neuropsychiatrists were part of the so-called "generation of Archivos of Neurobiologia" known by the name of the multidisciplinary scientific journal they founded in 1920 together with neurologists, psychologists, histologists and physiologists with the support of Cajal.[11] The psychiatrists who were part of the editorial board participated in the international training programme promoted by Cajal that granted visiting fellowships with the main leaders in the field such as Emil Kraepelin, Alois Alzheimer or Eugen Bleuler, and shifted the focus of Spanish psychiatry from France to Germany. Unfortunately this group was decimated during the Civil War. Many remained in exile, some of them died and others were ostracized or even banned from practicing psychiatry during Franco's dictatorship (i.e. Sacristán and López-Aydillo).[11]

Cajal's early interest in mental functions was manifested during his time at the University of Valencia (1884–1887), where he organized a "Committee of Psychological Research" and carried out several hypnotic experiments on cataplexy, analgesia, amnesia, and visual, auditory and tactile hallucinations. He also started a clinical practice in Valencia where he treated patients with mental disorders and published the first case study on the use of hypno-analgesia in labour and delivery in 1889.[12] In 1927, he was appointed president of the board of the League of Mental Hygiene in Spain.[11]

Cajal's concern on mental functions had a particular focus on sleep, dreams and hallucinations. In 1895, Cajal advanced the hypothesis of the regulation of sleep/wake cycles based in temporal changes (elasticity) of neuroglial cells in the cortex. According to Cajal, the retraction of these cells would be related to the wake phase and their expansion to sleep by reducing the electrical impulses of the related neurons. Eventually he abandoned this conjecture as he considered that the identification of the neurophysiological and chemical substrate of sleep was still at its very early stages of development ("esta muy verde" as he puts it in one of his letters).[9] The role of astrocytes and neuroglia in the sleep/wake cycle and the contribution of neuroinflammation of microglia to sleep disorders has been pointed out recently.[13]

Until his death in 1934, Cajal conducted a subjective analysis of dreams that was on the antipodes of Freud's interpretation of dreams, whose theories he labelled as collective lies in three letters.[10] His interest in dreams is first noted in a prologue to a book on poetry in 1902.[9] In 1908, he published an introduction to his theory of dreams, "one of the most interesting and fascinating phenomenon of the physiology of the brain".[14] In this paper, he explained his method for the recording of dreams and the analysis of their components: representation, colour, relief, transformation, location and other characteristics of the imagery of dreams and pareidolias. This 1908 paper ended abruptly on a cliffhanger: "to be continued",[14] and so it remained until his death. Cajal registered over 500 of his own dreams, plus an unknown number of dreams of relatives and acquaintances. By 1934, he had two books completed for publication "Dreams and hallucinations" and "Notes of Histological Psychology, hypnotism and suggestion".[9] These two manuscripts were kept at the Cajal Institute with all his notes, documents, drawings and personal effects. Unfortunately these two documents and many others were lost, dispersed or stollen during the Spanish Civil War and the following years. In 1974, a Madrid librarian disclosed 2035 letters by Cajal. The "Epistolario" published by JA Fernandez Santaren estimates that over 12,000 of Cajal's letters are still missing.[15] In a surprising turn of events that probably Cajal would have not liked, the psychoanalyst Jose Rallo Romero found 103 transcriptions of dreams registered by Cajal which he published together with a psychoanalytic interpretation in 2014.[16]

In 2017 a trove of personal objects of Cajal appeared in Madrid's flea market after the sell of his home to build luxury appartments. What remains of Cajal's legacy is now scattered among the "Consejo Superior de Investigaciones Cientificas" (CSIC) where they are kept in storage, the Madrid College of Physicians, and Cajal's family archives. Cajal's legacy gained the UNESCO recognition as a World Heritage treasure in 2017,[17] but this treasure cannot to be seen. In September 2022, the Spanish government announced the year of research "Ramon y Cajal" and the forthcoming establishment of the Cajal Museum by 2025. In his testament Franz Kafka asked Max Brod to burn all his writings but his closed friend decided to preserve and curate every word Kafka wrote. On the contrary, Cajal wanted his legacy to be preserved and he donated it to the Cajal Institute which is a public institution in Spain. Unfortunately there was no Max Brod around to fulfil this promise.

Conflict of interest

None.

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