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At the time when the dispute between Golgi and Cajal over the diffuse nerve net theory versus the neuron theory was most heated, nearly all of the Italian students of the nervous system tended to side with their countryman. Notable exceptions were represented by the two neuropsychiatrists Eugenio Tanzi and his disciple Ernesto Lugaro, who were convinced supporters of the neuron theory and fervent admirers of Cajal's work. Of the two, Tanzi is probably better known in the neuroscience community because he was the first to put forward a synaptic theory of learning and memory already in the nineteenth century (see below), thus acquiring international fame. But Lugaro also made pioneering empirical and theoretical contributions towards the understanding of the nervous system. The most notable of them are briefly reviewed here.

The Lugaro cerebellar cells

Lugaro began his research career in the Laboratory of Normal Histology at the University of Palermo, the city in which he was born in 1870. The Laboratory was headed by Casimiro Mondino, a former pupil of Golgi who, like most of his co-disciples from Pavia, was extraordinarily skilled in neurohistological techniques, particularly with the black reaction. As a medical student, Lugaro quickly learned the craft from Mondino and in 1894, the year in which he graduated in medicine, he was able to produce two remarkable papers on the fine structure of the cerebellum as seen with various versions of the black reaction (Lugaro, 1894a, b). In one of these papers, outstanding for the beauty and precision of its illustrations, he described a new type of cells in the cerebellar cortex that had not been reported in previous studies, including those of Golgi and Cajal. The somata of these cells were usually located in the granular layer, but sometimes they could lie alongside the somata of Purkinje cells or immediately above them. Their characterizing element was a robust axon that, after giving off numerous collaterals in the granular layer, ascended towards the molecular layer and branched profusely in it. In Lugaro's words, "these cells occupy with the extreme ramifications of their nervous processes very extensive territories, more in a longitudinal sense than in a transversal sense, both in the molecular layer and in the granular layer." He termed these cells "cellule intermediarie" (intermediary cells). Cajal (1911) doubted that they existed but subsequent investigators confirmed Lugaro, as detailed by Palay and Chan-Palay (1974), so that the cells have been known as Lugaro cells in neuroscience literature for many years. They are currently the subject of intense morphological and functional investigations (e.g. Laine and Axelrad, 1998; Geurts et al., 2001; Dieudonné, 2001). Recent work indicates that Lugaro cells are inhibitory interneurons using both GABA and glycine as neurotrasmitters, that they are the most important recipients of the serotoninergic input to the cerebellum, and that they project to large numbers of Golgi, basket and stellate cells. Serotonin-induced activation of Lugaro cells is

supposed to cause a synchronization of the activities of Golgi and granule cells over extended longitudinal domains, as well as of the simple-spike activity of Purkinje cells, thus influencing the processing of mossy fiber information by the cerebellar cortex and the modulation thereof of the activities of deep cerebellar nuclei (Dieudonné, 2001).

From neurohistology to psychiatry

Lugaro's name deserves to be remembered for many reasons other than for his discovery of the cerebellar cells that bear his name. While still working in Mondino's laboratory, he had been fascinated by the inaugural lecture of the newly appointed Professor of Psychiatry of the University of Palermo, Eugenio Tanzi (1856-1934), a staunch supporter of the neuron theory of brain functioning and an articulate critic of Golgi's ideas on neural connections (see Boeri et al., 1994; Berlucchi, 2002). In that lecture Tanzi discussed the facts and inferences about the nervous system that he had reviewed in a masterly paper in 1893. Convinced that the existing evidence pointed to the nervous system as an aggregate of neurons separated by tiny distances, Tanzi had proposed that the waves of excitation must normally encounter some difficulties in crossing such distances, and that learning and practice can make the crossing easier by causing small growths of associated neurons, thus reducing the distance between them. This first hypothesis of a synaptic basis for associative memories and practice-dependent motor skills (Tanzi, 1893; see Buchtel and Berlucchi, 1977) was thus proposed before the term synapse was coined by Sherrington (1897). Lugaro was so attracted by Tanzi's personality and ideas that he decided to become his assistant and to follow him to the University of Florence, where Tanzi was appointed Professor of Psychiatry in 1895 (Figures 1, 2). This was the start of Lugaro's career as a psychiatrist, which took place in Florence, Sassari, Messina and Modena. His final position was the chair of Psychiatry in the Medical School of Turin University, which he occupied for thirty years until his death in 1940.

Figure 2: Eugenio Tanzi (left) and Ernesto Lugaro (both seated) with their disciples and collaborators in the garden of the San Salvi Psychiatric Hospital in Florence, *c.*1910.

The clinical duties in the psychiatric wards did not prevent Lugaro from cultivating his interest in the intimate functioning of the nervous system, although his studies became more theoretical than experimental. Tanzi and Lugaro strongly believed in a brain-based psychiatry, and within a few years Lugaro had published several authoritative reviews, in which he provided strong support to the neuron theory and advanced some amazing intuitions about basic neurophysiological mechanisms, including the functional modifiability of the neural connections, the chemical nature of the synapses between neurons of the central nervous system, and the functions of the glia (e.g. Lugaro, 1899, 1904, 1907, 1909). Irritated by these challenges to his diffuse nerve net theory, Golgi took advantage of some half-baked claims in one of Lugaro's early studies on the cerebellum (Lugaro, 1895) in order to accuse him of preferring hypotheses to facts, and even of distorting and suppressing factual evidence for defending the neuron theory (Golgi, 1898; see

Mazzarello, 1999). Lugaro's astute retort began by asserting that science needs both facts and hypotheses, and ended (*in cauda venenum*, the poison in the tail) by pointing out that Golgi himself had put forward some hypotheses, which, though subsequently refuted by new evidence, had nonetheless been beneficial to neurology by stimulating much research work (Lugaro, 1898a).

Lugaro and neural plasticity

I believe that Lugaro was responsible for introducing the term plasticity into the neurosciences (Berlucchi, 2002). Jones (2000) suggested that the Rumanian Ioan Minea was the first to use this term in his 1909 thesis on regeneration in the peripheral nervous system, but Lugaro's priority is documented by the presence of the entries "psychic plasticity; plasticity of the neurons; plasticity of the neurofibrils" in the analytical index of his *Treatise of Psychiatry*, published in Italian in 1906 and in English in 1909. In using these terms, Lugaro expanded on Tanzi's original synaptic hypothesis of learning and memory by proposing that the chemotropic activities responsible for the prenatal organization of the nervous system can continue to some extent throughout life in order to establish fresh anatomo-functional connections between neurons. He maintained that the new connections, based on adaptive chemico-physical and morphological variations in interneuronal relations, can account for nervous and psychic plasticity, as it is manifest in maturation, learning and even functional compensation after brain damage.

Lugaro and chemical synaptic transmission

A firm believer in the neuron theory and in the spatial separation between neurons, Lugaro began very early to make theoretical inquiries about the putative mechanisms that allow neural excitations to move from one neuron to the next, crossing that interneuronal space that Tanzi had called "*malpasso*", difficult passage (Tanzi, 1893). The following quotes from three reviews by Lugaro, which I have already published in the *Journal of the History of the Neurosciences* (Berlucchi, 2002), illustrate the development of an extraordinarily accurate foresight about the process of chemical synaptic transmission between central neurons as it is known today.

"How does an afferent fiber terminal act on the soma or the dendrites of the next neuron with which it is in a relation of contiguity or contact? One can think of two modalities: either the nervous wave, after moving along the fiber as a physical ondulation, remains unchanged in the terminal and as such is transmitted to the second neuron by contact; or, after reaching the terminal, the nervous wave modifies the physico-chemical state first of the terminal itself and then of parts of its surroundings, which in turn acts as a physico-chemical stimulus on portions of other neurons being in a close contiguity relation with the terminal, without needing to be in actual contact with it ... This second hypothesis seems to us the most likely … the fact that the nervous currents are delayed when they cross the gray substance, that is when they move from neuron to neuron, tells us that these passages do not involve a simple transmission by contact, but rather a true energy

"Previously I maintained that the transmission of an impulse from one neuron to another neuron is not to be regarded as a simple physical transmission by contact, such as it occurs with heat or electricity, but rather as a true process of transformation of energy: the nervous impulse is supposed transformation [Lugaro, 1899, p. 495] to induce a chemical modification in the pericellular or peridendritic axon terminal, and this chemical modification should in turn act as a chemical stimulus on the cell or its dendrites, giving rise to a new, quantitatively or qualitatively different impulse" (Lugaro, 1904, p. 431).

"One can distinguish two different processes in the propagation of nervous excitations: a process of conduction, which is essentially intraneuronal, and a process of interneuronal *transmission* … Transmission from one neuron to another presents various phases: the neural excitation which arrives at the axonal terminal causes there a kind of specific secretion; this secretion diffuses in the surroundings and invades the cell bodies or dendrites with which the axon terminal is related; the axonal secretion reacts with specific substances of the cellular or dendritic protoplasm, substances that can be identified with Langley's *receptive substances*; finally, such reaction excites the conductive substance and causes a new neural excitation which propagates

throughout the neuron" (Lugaro, 1909b, pp. 24-25).

The last quote suggests that the present-day terminological distinction between neural conduction and neural transmission was coined by Lugaro, a suggestion confirmed by the following statement by Sir Charles Sherrington: "Lugaro has proposed restricting the term 'conduction' to intracellular propagation of the excited state, and employment of the term 'transmission' for intercellular transference of the excited state" (Sherrington, 1925, p. 520). A further quote shows that Lugaro, most probably borrowing ideas from Schiefferdecker (1906), also clearly saw how different chemical synaptic inputs to the same neuron could interact to allow facilitatory and inhibitory effects:

"When many axonal terminals belonging to neurons of different kinds and endowed with different specific secretions converge onto the same neuron, their actions can reinforce or hinder each other, giving rise to the phenomena of facilitation or inhibition" (Lugaro, 1909b, p. 52).

Lugaro and the glia

Lugaro wrote about the possible functions of the glia at a time when it was still believed that myelin was secreted by the axon (Cajal, 1909). His paper (Lugaro, 1907) accepted previous ideas by Golgi, Cajal and others about the mechanical, nutritive and insulating properties of the glia, but added as possibilities two functional roles for glial cells that have been confirmed by later studies (Somjen, 1988). First, he attributed to the glia a protective, antipoisonous function akin to the glial buffering capacity as it is known today. Second, in broad agreement with modern studies, he hypothesized that glial cells exert secretory chemotactic influences during development to promote axonal growth and the establishment of connections, particularly between neurons with cell bodies separated by large distances. He also postulated that excessive or qualitatively abnormal secretory activities by glial tumors might explain their damaging action on nearby neurons.

Lugaro's theoretical misconceptions and experimental failures

If many of Lugaro's predictions about neural functioning were proven right, several others turned out to be bizarre or blatantly wrong, as it often happens to theoreticians who strive to formulate hypotheses about a multitude of complex biological matters. He believed that the neurofibrils are the main substrate for the conduction of neural impulses, and argued that affective phenomena are based on intracellular mechanisms, whereas intellective phenomena are based on interactions between afferents to the dendrites and somata of cortical pyramidal cells (Lugaro, 1899). He also maintained that analytic and synthetic psychic processes utilize the same cerebral pathways, but with opposite directions of conduction for the two kinds of processes (Lugaro, 1894a).

Although Lugaro had started his career as an experimenter, for most of his life he obviously preferred theory to experimentation. However, after leaving Palermo he did some experiments aimed at testing the idea that synaptic modifiability could be due to changes in the volume of the soma or dendrites of neurons. He tried to demonstrate neuronal modifiability in vivo by killing awake or anesthetized dogs and looking for possible retractions or expansions of dendritic spines of neocortical and archicortical neurons. A counterintuitive finding was that in dogs killed in deep anesthesia dendrites were covered with spines, much less so in dogs killed while awake. He speculated that waking and mental activity may entail the selection of certain inputs to a neuron at the expense of the other inputs, a selection that calls for the retraction of only some dendritic spines. Although the idea of the dendritic spine as a locus for synaptic plasticity anticipated modern concepts, the experiments were so poorly designed and poorly controlled that one tends to discount their findings (Lugaro, 1898b).

Lugaro's many other publications

In addition to the *Treatise* already mentioned (Lugaro, 1906), Lugaro published with Tanzi a textbook of psychiatry, which went through two editions and influenced generations of Italian psychiatrists (Tanzi and Lugaro, 1914/1916; 1924). Lugaro was also one of the editors of the *Rivista di Patologia Nervosa e Mentale*, founded by Tanzi, in which he published several papers on

various psychiatric and neurological topics. He was an elegant and prolific writer and a fiery polemist (Visintini, 1971). During the First World War, he wrote hundreds of pages in the *Rivista* whereby he argued that although the Kaiser and the Austrian Emperor were mentally unfit, the war was to be imputed to a national aberration, that is to an abnormal mental constitution of the entire German people (English translation in Lugaro, 1916). He also claimed that German science was imperialistic, and that it exploited the inventiveness of southern and western European scientists (from Spain, Italy, England, France) by appropriating their ideas and discoveries, as exemplified by the attribution of the neuron theory to Waldeyer rather than Cajal. His elaborate and scholarly view of the development of psychiatric ideas in different European countries, as well as his lucid interpretation of the relations between pure and applied science (Lugaro, 1916/17), are still of some interest for historians of both psychiatry and neuroscience. A complete list of his writings, including essays on neuropathologic, psychiatric, psychoanalytic and philosophical topics, can be found in Visintini (1940).

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Bibliography

Berlucchi, G. (2002) The origin of the term plasticity in the neurosciences: Ernesto Lugaro and chemical synaptic transmission, *J Hist Neurosci*, vol. 11 (in press).

Boeri, R., Peccarisi, C. and Salmaggi, A. (1994): Eugenio Tanzi (1856-1934) and the beginning of European neurology, *J Hist Neurosci*, vol. 3: 177-185.

Buchtel, H. A. and Berlucchi, G. (1977) Learning and memory and the nervous system, in Duncan, R and Weston-Smith, M. (eds.), *The Encyclopaedia of Ignorance*, vol. 2, Oxford: Pergamon, pp. 283-297.

Cajal., R. S. (1909/1911), *Histologie du système nerveux de l'homme et des vertébrés*, 2 vols., Paris: Maloine.

Dieudonné, S. (2001) Serotonergic modulation in the cerebellar cortex: Cellular, synaptic and molecular bases, *Neuroscientist*, 7: 207-219.

Geurts, F. J., Timmermans, J., Shigemoto, R., De Schutter, E. (2001) Morphological and neurochemical differentiation of large granular layer interneurons in the adult rat cerebellum, *Neuroscience*, 104: 499-512.

Golgi, C. (1898) Intorno alla struttura della cellula nervosa, *Boll Soc Med-Chir Pavia*, 13: 3-16.

Jones, E. G. (2000) Plasticity and neuroplasticity, *J Hist Neurosci*, 9: 37-39.

Laine, J. and Axelrad, H. (1998) Lugaro cells target basket and stellate cells in the cerebellar cortex, *NeuroReport*, 9: 2399-2403.

Lugaro, E. (1894a) Sulle connessioni tra gli elementi nervosi della corteccia cerebellare con considerazioni generali sul significato fisiologico dei rapporti tra gli elementi nervosi, *Riv Sper Fren Med Leg*, 20: 297-331.

Lugaro, E. (1894b) Ueber die Histogenese der Körner der Kleinhirnrinde, *Anat Anz*, 9: 710-713.

Lugaro, E. (1895) Sulla struttura del nucleo dentato del cervelletto nell'uomo, *Mon Zool Ital*, 6: 5-12.

Lugaro, E. (1898a) A proposito di un presunto rivestimento isolatore della cellula nervosa. Risposta al prof. C. Golgi, *Riv Patol Nerv Ment*, 3: 265-271.

Lugaro, E. (1898b) Sulle modificazioni morfologiche funzionali dei dendriti delle cellule nervose, *Riv Patol Nerv Ment*, 3: 337-359.

Lugaro, E. (1899) I recenti progressi dell'anatomia del sistema nervoso in rapporto alla psicologia ed alla psichiatria, *Riv Patol Nerv Ment*, 4: 481-514, 537-547.

Lugaro, E. (1904) Sullo stato attuale della teoria del neurone, *Arch Ital Anat Embriol*, 3: 412-437.

Lugaro, E. (1906) *I Problemi Odierni della Psichiatria*, Milan: Sandron.

Lugaro, E. (1907) Sulle funzioni della nevroglia, *Riv Patol Nerv Ment*, 12: 225-233.

Lugaro, E. (1909a) *Modern Problems in Psychiatry*, trans. D. Orr and R. G. Rows, Manchester: The University Press.

Lugaro, E. (1909b) La fonction de la cellule nerveuse, XVIe Congrès International de Médecine, 11e Session, Budapest, pp.5-57.

Lugaro, E. (1916) *An Emperor's Madness or National Aberration?* London: Routledge & Sons; New York: Dutton & Co.

Lugaro, E. (1916/1917) La psichiatria tedesca nella storia e nell'attualità, *Riv Patol Nerv Ment*, 21: 241-283, 337-386, 449-501, 577-617; 22: 65-104, 185-239, 249-302.

Mazzarello, P. (1999) *The Hidden Structure: A Scientific Biography of Camillo Golgi*, trans./eds. H. Buchtel and A. Badiani, Oxford: Oxford University Press.

Palay, S. L. and Chan-Palay, V. (1974) *Cerebellar Cortex: Cyrology and Organization*, Berlin: Springer.

Schiefferdecker, P. (1906) *Neurone und Neuronenbahnen*, Leipzig: J. A. Barth.

Sherrington, C. S. (1897) The central nervous system, in M. Foster, *Text-Book of Physiology*, vol. 3, London: Macmillan.

Sherrington, C. S. (1925) Remarks on some aspects of reflex inhibition, *Proc Roy Soc B*, 97: 519-545.

Somjen, G. G. (1988) Nervenkitt: notes on the history of the concept of neuroglia, *Glia*, 1: 2-9.

Tanzi, E. (1893) I fatti e le induzioni dell'odierna istologia del sistema nervoso, *Riv Sper Fren Med Leg*, 19: 419-472.

Tanzi, E., and Lugaro, E. (1914/1916) *Trattato delle Malattie mentali*, 2 vols., 2nd edn., Milan: Società Editrice Libraria.

Tanzi, E. and Lugaro, E. (1923) *Trattato delle Malattie mentali*, 2 vols., 3rd edn., Milan: Società Editrice Libraria.

Visintini, F. (1940) Ernesto Lugaro, *G R Acad Med Torino*, 18: 19-33.

Visintini, F. (1971) Ernesto Lugaro nel centenario della nascita, *Minerva Med*, 62: 1-4.