

18. Changeux, J. P. Cajal on neurons, molecules, and consciousness. *Ann. NY Acad. Sci.* **929**, 147–151 (2001).
19. Sherrington, C. S. Double (antidromic) conduction in the central nervous system. *Proc. Roy. Soc. Lond. B* **61**, 243–246 (1897).
20. Ramón y Cajal, S. Significación probable de las células de axon corto. *Trab. Lab. Invest. Biol. Univ. Madrid* **1**, 151–157 (1901).
21. Piccolino, M. Cajal and the retina: a 100-year retrospective. *Trends Neurosci.* **11**, 521–525 (1988).
22. Ramón y Cajal, S. Les problèmes histophysiologiques de la rétine. *XIV Concilium. Ophthalmologicum Hispaniae* **11**, 11–19 (1933).
23. Gallego, A. Reflejo de la obra de Cajal en la neurofisiología moderna. *An. Ins. Farm. Esp.* **11–12**, 25–50 (1963).
24. Ramón y Cajal, S. *Recuerdos de Mi Vida: Historia de Mi Labor Científica* 3rd edn (Juan Pueyo, Madrid, 1923).
25. Droz, B. in *The Nervous System* (ed. Tower, D. B.) 115–127 (Raven, New York, 1975).
26. Ramón y Cajal, S. *Cajal's Degeneration & Regeneration of the Nervous System* (eds DeFelipe, J. & Jones, E. G) (Oxford Univ. Press, New York, 1991).
27. Sotelo, C. & Alvarado-Mallart, R. M. The reconstruction of cerebellar circuits. *Trends Neurosci.* **14**, 350–355 (1991).

Acknowledgements

I thank J. Lerma and H. Korn for useful discussions.

Online links

DATABASES

The following terms in this article are linked online to OMIM: <http://www.ncbi.nlm.nih.gov/Omim/> Kallmann syndrome

FURTHER INFORMATION

Encyclopedia of Life Sciences: <http://www.els.net/>

Ramón y Cajal, Santiago

MIT Encyclopedia of Cognitive Sciences:

<http://cognet.mit.edu/MITECS/>

Cajal, Santiago Ramón y | Golgi, Camillo

Access to this interactive links box is free online.

OPINION

The contribution of Santiago Ramón y Cajal to functional neuroscience

Rodolfo R. Llinás

Santiago Ramón y Cajal — arguably the most accomplished anatomist in the history of neuroscience — became recognized as such not only because of his incredible anatomical skills and his indefatigable working habits, but also because of his uncanny sense of the functional implications of his work, a sense that made him a true genius in the field of biology.

Everyone who has had the pleasure of reading Ramón y Cajal's work knows that his splendid neuroanatomical studies were always presented in a functional context. Indeed, beyond the shape of neurons, their synaptic connectivity and the network they weave, three themes run through all his writings.

The first theme was his realization that understanding brain function must be more

than a piecemeal endeavour. To him, such understanding came about only with reference to 'the big picture'. Ramón y Cajal used schematic drawings as working hypotheses and, regardless of how primitive such hypotheses were, he considered such a depiction to be better than no attempt at all. This attitude has clear merit in the sense that science, from a positivist point of view, must generate possible conjectures that are unambiguous enough so that they can be falsifiable on empirical or theoretical grounds¹.

Second, he believed that the presence of strictly organized neuronal circuits is a fundamental characteristic of all brains. Ramón y Cajal was the first to understand that the common denominator for all brains was the presence of neurons, and that all brains are cellular societies, the common goal of which is to orchestrate the behavioural interaction of the organism with the external milieu.

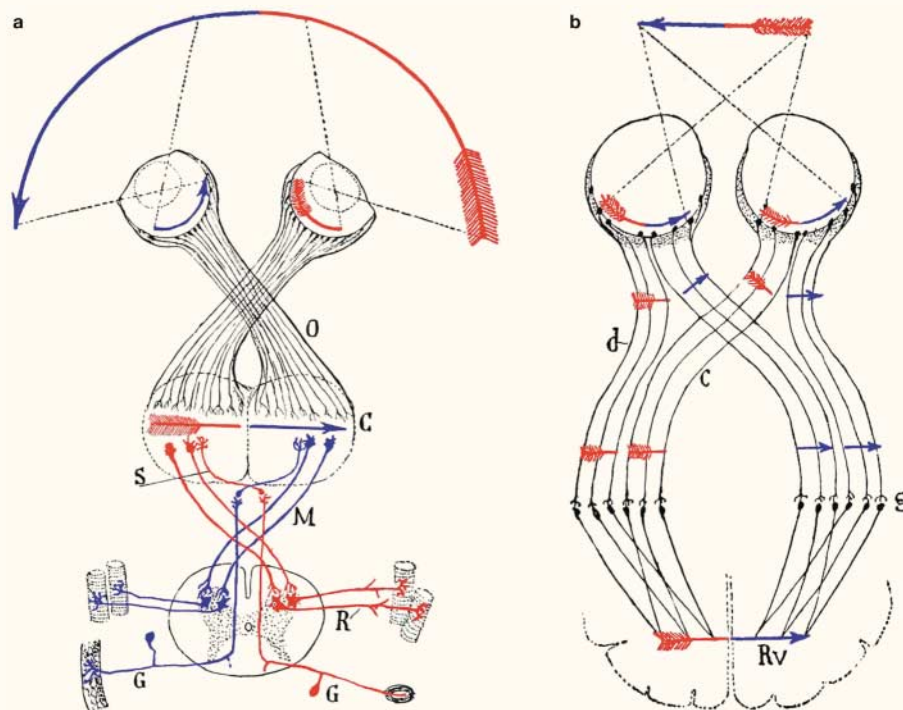


Figure 1 | The organization of the central visual pathways. a | The visual system of a lower vertebrate. The lateral location of the eyes in the head is such that the visual field overlap is small. The image must be continuous over the left/right axis of the animal in spite of the inversion generated by the optical properties of the eye. This inversion of the image is corrected, Cajal noted, by the total crossing of the optic nerve (O) and its orderly termination on the optic tectum (C). Both sensory (G and S) and motor (M and R) pathways from each side — red and blue — are also crossed such that all sensory inputs may be congruous in the generation of a global sensory image used for the activation of the motor system of each side. **b** | The visual system in humans. The frontal location of the eyes results in a large overlap of the visual image in both eyes. In this case, the crossing of the optic nerve occurs only for the nasal half of each retina (c) whereas the temporal half projects directly to the same side (d). The thalamocortical organization is such that corresponding points in each retina must terminate near each other at the visual cortex (Rv). This internal congruence in visual space is essential for the exquisite eye–hand coordination that is found in humans. g, neurons of the lateral geniculate nucleus. Modified, with permission, from the Instituto de Neurobiología “Ramón y Cajal”, Madrid, Spain.

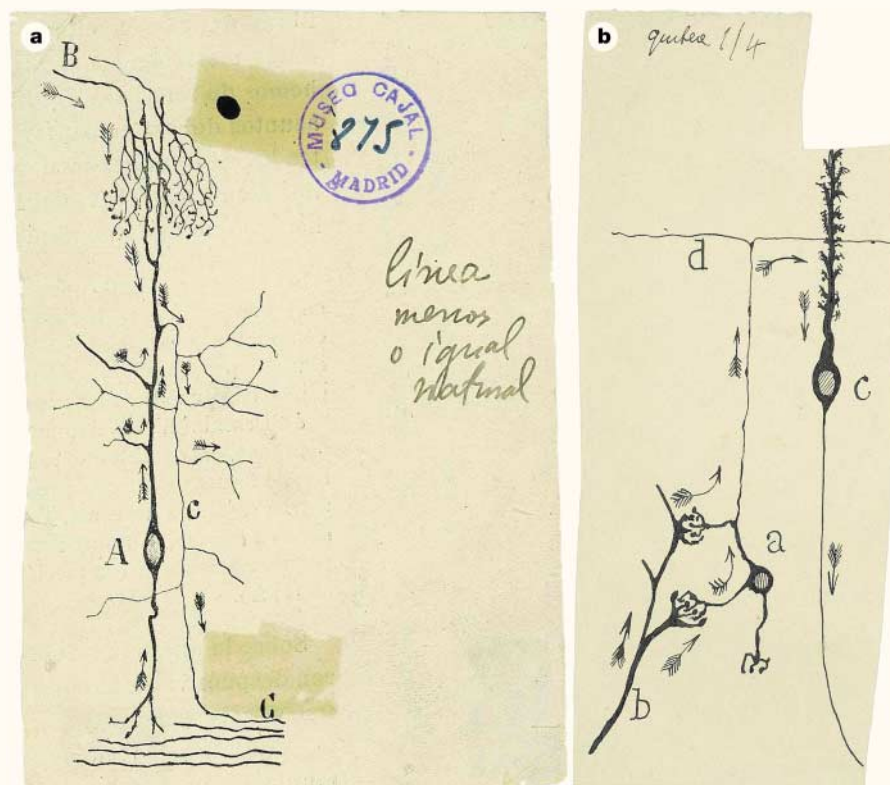


Figure 2 | **The directionality of the 'nervous current'**. Cajal named the organized direction of neuronal current flow from the dendrites to axon "Dynamic Polarization". As controversy arose concerning the 'somatopetal' as opposed to the 'axopetal' direction of such flow, he illustrated several cases in which the axon arose from a dendrite. **a** | A neuron from an avian optic lobe. **b** | A neuron from a rodent cerebellum. In both cases, Cajal correctly inferred that in order for the incoming nervous impulse to proceed to the next neuron it had to be conducted towards the axon (c in part **a**, and d in part **b**). So, some dendrites and the soma itself would have to conduct activity in a retrograde direction. Arrows indicate the direction of current flow. Reproduced, with permission, from the Instituto de Neurobiología "Ramón y Cajal", Madrid, Spain.

Last, as a corollary to the previous two themes, Ramón y Cajal considered that brain function must be understood in the context of the evolutionary and ethological niche in which it has developed and survived². Today, we all agree that a true understanding of biological systems comes from direct experimental inquiry, which is often aided by the building of models as heuristic tools.

The trend towards the integration of specific data into a global framework is particularly evident in Ramón y Cajal's *opus magnum*, *Textura del Sistema Nervioso del Hombre y de los Vertebrados*³. In this work, he begins his discussion with a view of the general organization of the brain from a phylogenetic perspective. Each chapter is followed by a description of the corresponding structures in lower vertebrates and of a possible functional organization.

His drive towards finding a functional explanation of his anatomical findings is clearly evident at other levels. A good example is his diagram comparing the organization of the general connectivity of the visual system in

lower vertebrates (FIG. 1a) with that of humans (FIG. 1b). He explains, quite beautifully, the need for a commissural crossing of retinotectal fibres in life forms that do not have a high degree of overlap in their visual fields, owing to the fact that their eyes are laterally placed. He reasoned that, if a congruent and homomorphic internal image of the visual world is to be formed in the brain, then it must correct the image inversion that results from the optical properties of the retina. This correction requires the fibres from the two eyes to cross at the midline and to be distributed in such a way that the nasal retina projects to the lateral extremes of each tectum, whereas the temporal projections abut each other at the inner edges of the tectum (that is, next to each other in visual space).

This diagram also explains why the connectivity from the visual centres to the spinal cord must be crossed (FIG. 1b). Each eye observes the environment that corresponds to the ipsilateral side but, given the crossed visual representation, the motor fibre must cross over to activate the correct limb. Likewise,

tactile representation of the limb must cross to be congruent with visual space. In this way, we can begin to understand how the brain forms a spatially contiguous cognitive whole. This arrangement is contrasted with that of the partial crossing of retinotectal fibres at the optic chiasm (FIG. 1b) in species such as humans. In this case, our visual space overlaps; the nasal and temporal halves of each eye must therefore project to the same side with only the nasal components crossing the midline.

An even more daring step was taken by Ramón y Cajal when he proposed that the organization of the central nervous system (CNS) was constrained by three well-defined 'laws' of optimization⁴. First, space optimization ('el ahorro del espacio') — packing compactness. Second, matter optimization ('el ahorro del material') — each element must be of the right size. And third, time optimization ('el ahorro del tiempo') — conduction time must be optimal. In our technically oriented world, the importance of optimization is so much second nature that little else needs to be said, other than the fact that many aspects of neuronal and circuit morphology clearly derive from these evolutionary advantageous biological traits.

But perhaps the most significant insight into single cell function was Ramón y Cajal's realization that the conduction of the 'nervous current' — the element that ultimately forges functional dynamics — had a direction: from the terminals of the presynaptic neuron to the dendritic tree, towards the somata and out through the axons of the postsynaptic neurons. Moreover, he understood that in neurons where the axon arose from a dendrite, such as in the case of the avian optic lobe (FIG. 2a), the currents had to be conducted somatopetally from the dendrite, through the soma, and up the opposite dendrite onto the axon, in an axofugal direction. Implicit here is Ramón y Cajal's early realization⁵ that the nervous system was made of individual separate elements, as reviewed by Sotelo in the accompanying paper⁶. This directionality of neuronal conduction, which he named the 'dynamic polarization of nerve cells', was proposed and defended on the basis of pure deductive reasoning. This idea emerged from his studies of the organization of circuits such as the cerebellar cortex⁷ (FIG. 2b), the olfactory pathways from the olfactory epithelium through the olfactory bulb and onto the pyriform cortex, the retinal input through the thalamus into the visual cortex, and the organization of reflexes in the spinal cord, to name a few. And he came to these conclusions without the benefit of our present understanding of cable properties or ion

channels. This insight drove him to depict the direction of nervous currents in neuronal networks, with arrows in his drawings (FIG. 2a,b). The implication of his vision was that he could tell the functional organization of circuits by looking at the anatomical arrangements of the constituting network — it was a bold step indeed.

In a similar functional vein, he further proposed that this dynamic polarization was the basis of the fundamentally unidirectional nature of neuronal circuit organization, from the sensory to the motor domains. Indeed, Charles Bell had shown, in 1811, that the ventral spinal roots had an exclusively motor function⁸, whereas Francois Magendie, in 1822, provided proof of the exclusively sensory nature of the dorsal roots and the unidirectionality of dorsal to ventral root conduction (REFS 9, 10; and see Fulton's discussion in REF 11). Ramón y Cajal stopped short of proposing that the unidirectionality of network conduction was a fundamental property that was derived from the one-way conduction of synapses. This crucial step was not finally taken until Hagiwara and Tasaki¹² made simultaneous recordings from the presynaptic and postsynaptic fibres at the squid giant synapse and showed that postsynaptic spikes did not activate the adjoining presynaptic

fibre, whereas the opposite effect was easily observed. A final understanding of this fundamental concept required the acceptance of chemical synaptic transmission and the demonstration of the ultrastructural asymmetry between the presynaptic and postsynaptic terminals¹³. Today, we know that some feedback modulation does exist and that a certain degree of presynaptic self-modulation is present, but even the most recalcitrant scientists among us know that neuronal networks cannot really run backwards.

Concerning the functional organization of neuronal networks, given their divergent nature Ramón y Cajal proposed that the anatomical organization favoured what he termed 'avalanche conduction'³, in which a small, well-defined stimulus could result in the activation of a large number of neurons. He considered this to be important in light of our ability to detect even the smallest of sensory stimuli, which would require the initial signal to be amplified to attain cognitive threshold.

The idea of inhibition as a neuronal property was missing in Ramón y Cajal's description of network function. But he was aware that inhibition existed and referred to it in his writings³. Indeed, he was aware of the crossed inhibitory reflex in the spinal cord and the fact that cortical input to the spinal cord was,

under certain conditions, accompanied by the inhibition of segmental reflexes. Not being aware of inhibition as a specialized neuronal function, he proposed that such inhibition was a form of saturation that would occur with very large incoming messages³. Our present understanding of inhibition had to await the demonstration of chemical synaptic transmission by John Eccles (REF 14).

One of the most exciting aspects of Ramón y Cajal's thinking emerged from his study of comparative neuroscience. He marvelled at the issue of network size versus functional complexity. In comparing the nervous system of a large vertebrate with that of invertebrates such as the squid or small insects, Ramón y Cajal was amazed that all three can solve equally complex problems such as eating, swimming, flying, fighting and reproducing, despite the extraordinary differences in brain size. Indeed, he compared the differences between large and small nervous systems to the contrast between large clocks such as Big Ben and wristwatches¹⁵. Although the differences in size are enormous, both timepieces tell the time with similar accuracy.

Concerning the retina (FIG. 3), Ramón y Cajal wrote that "...the complexity of the insect retina is stupendous, indeed disconcerting, and with no precedent in other

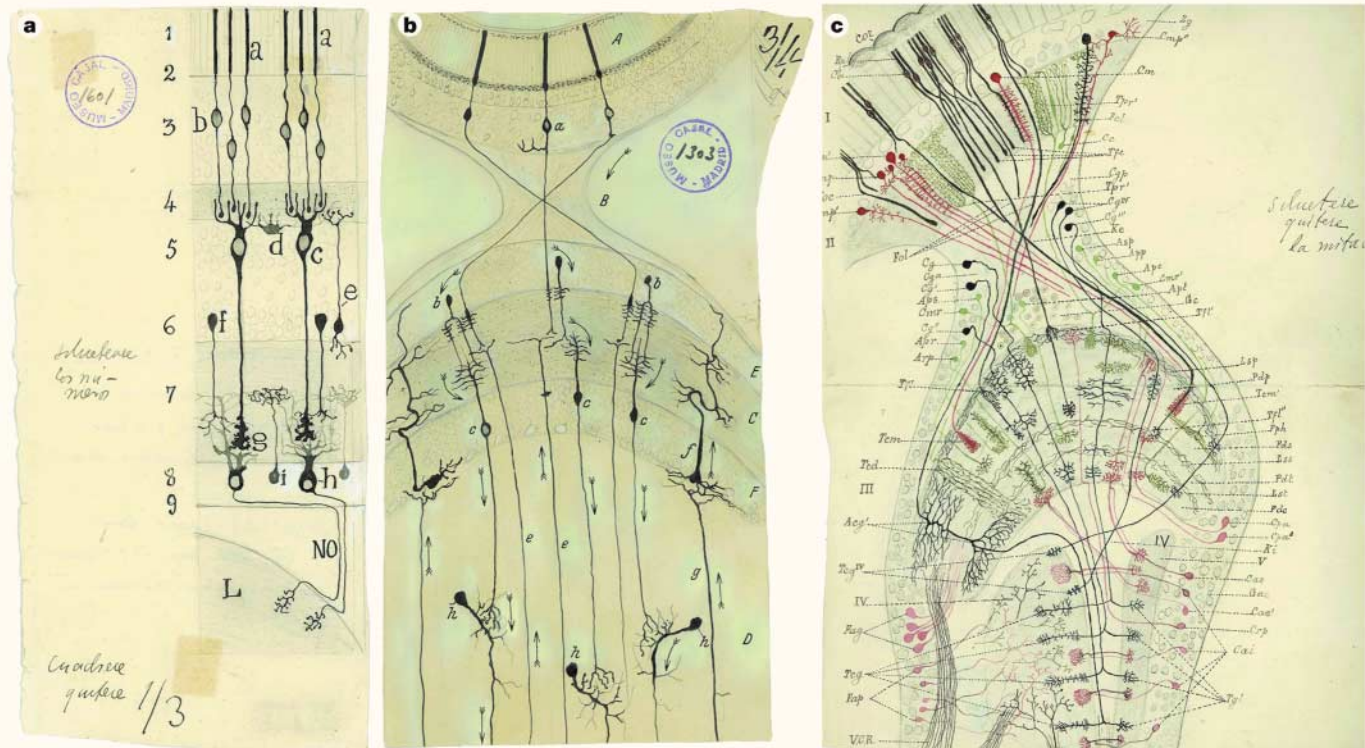


Figure 3 | Physical dimensions of the neuronal circuits of a mammal, a cephalopod and an insect. In a the organization and size of the mammalian visual system comprising the retina (1–9), optic nerve (NO) and the central nervous system (L) is more than one order of magnitude larger than that of a cephalopod (*Sepia*) in b. The cephalopod system is more than one order of magnitude larger than that of a housefly in c. However, all three do a good job imaging and detecting movement, given the requirements of each animal. Reproduced, with permission, from the Instituto de Neurobiología "Ramón y Cajal", Madrid, Spain.

animals ... indeed, the retina of vertebrates seems by contrast gross and deplorably simple...” (REF 15, pages 389–390). We now know that this is not really the case, as the complexity of the vertebrate retina easily rivals that of any other in the phylogenetic scale. But if we compare the neuronal size and complexity of, say, the early stages of the visual system in mammals (FIG. 3a), cephalopods (FIG. 3b) and insects (FIG. 3c) it is clear that the most amazing miniaturization of network architecture is found in insects. Consider, for example, that the thinnest neurites in the CNS of insects might be as thin as 50 nm (REF. 16); that is, of the same order of magnitude as a synaptic vesicle. The biophysical problems that are introduced by such a degree of size optimization are worth serious consideration. Issues such as the input resistance of a neuronal process with an internal diameter of 35 nm, or the integrative properties of dendrites in neurons where the gating of a single ion channel could drive transmembrane voltages to amplitudes that rival action potentials, are not every day fare. If we consider insects such as the tiny Costa Rican wasp *Dicopomorpha echmepterygis*, which has a total body length of 135 μm and a head diameter of 40 μm , we can only wonder at the degree of miniaturization that is ultimately achievable by biological neuronal networks.

To many of us, Ramón y Cajal personifies, above all, the belief that we actually can understand the nervous system, which represents, more than anything else, the very nature of what we are. The image that comes to mind relates to the account by Wilder Penfield of his visit to the old master shortly before his death, which appears as an appreciation of Ramón y Cajal in the English translation of his scientific testament *Neuron Theory or Reticular Theory*²¹⁷. Penfield describes him, relegated to his bed, drawing a pyramidal dendritic spine, nervously placing his quill into ink and, before guiding it to the paper, shaking yet another drop on to the large ink stain on the wall to the right side of his bed. Yet another drawing of his beloved brain studies, the stated reason for his own existence.

**Rodolfo R. Llinás is at the Department of Physiology and Neuroscience, New York University Medical School, New York, New York 10016, USA.
e-mail: llinar01@popmail.med.nyu.edu**

doi:10.1038/nrn1011

1. Popper, K. *Logik der Forschung* (Springer, Vienna, 1934).
2. Ramón y Cajal, S. The Croonian Lecture. La fine structure des centres nerveux. *Proc. Roy. Soc. Lond. B* **55**, 444–468 (1894).
3. Ramón y Cajal, S. *Textura del Sistema Nervioso del Hombre y de los Vertebrados* (Moya, Madrid, 1899).
4. Ramón y Cajal, S. Leyes de la morfología y dinamismo de las células nerviosas. *Rev. Trim. Micrográfica* **2**, 1–12 (1897).
5. Ramón y Cajal, S. Sobre las fibras nerviosas de la capa molecular del cerebelo. *Rev. Trim. Histol. Normal Patol.* **1**, 33–49 (1888).
6. Sotelo, C. Viewing the brain through the master hand of Ramón y Cajal. *Nature Rev. Neurosci.* **4**, 71–77 (2003).
7. Ramón y Cajal, S. Estructura del kiasma óptico y teoría general de los entrecruzamientos de las vías nerviosas. *Rev. Trim. Micrográfica* **3** (1898).
8. Bell, C. *An Idea of a New Anatomy of the Brain: Submitted for the Observations of his Friends* (Strahan & Preston, London, 1811).
9. Magendie, F. Expériences sur les fonctions des racines des nerfs rachidiens. *J. Physiol. Exp. Pathol.* **2**, 276–279 (1822).
10. Magendie, F. Expériences sur les fonctions des racines des nerfs qui nascent de la moëlle épinière. *J. Physiol. Exp. Pathol.* **2**, 366–371 (1822).
11. Fulton, J. F. *Physiology of the Nervous System* (Oxford Univ. Press, New York, 1938).
12. Hagiwara, S. & Tasaki, I. A study on the mechanism of impulse transmission across the giant synapse of the squid. *J. Physiol. (Lond.)* **143**, 114–137 (1958).
13. Couteaux, R. Motor endplate structure in *Structure and Function of Muscle* (Bourne, G.) 337 (Academic, New York, 1960).
14. Eccles, J. C. The nature of central inhibition. *Proc. R. Soc. Lond. B* **153**, 445–476 (1961).
15. Ramón y Cajal, S. *Recuerdos de Mi Vida: Historia de Mi Labor Científica* 3rd edn (Juan Pueyo, Madrid, 1923).
16. Meinertzhagen, I. A. and O’Neil, S. D. Synaptic organization of columnar elements in the lamina of the wild type in *Drosophila melanogaster*. *J. Comp. Neurol.* **305**, 232–263 (1991).
17. Ramón y Cajal, S. *Neuron Theory or Reticular Theory?* (Consejo Superior de Investigaciones Científicas, Madrid, 1954).

Acknowledgement

I thank I. Meinertzhagen for conversations on neuronal size in insects.

Online Links

FURTHER INFORMATION

Encyclopedia of Life Sciences: <http://www.els.net/>
neural information processing | Ramón y Cajal, Santiago
MIT Encyclopedia of Cognitive Sciences:
<http://cognet.mit.edu/MITECS/>
Cajal, Santiago Ramón y | neural networks
Access to this interactive links box is free online.