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Review

The butterfly and the loom

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ABSTRACT

The relationship between structure and function in the brain has an interesting counterpart in the scientific relationship of Santiago Ramon y Cajal and Charles Sherrington. In their search for the principles of organization of the nervous system, both men met at the synapse. For Sherrington, who coined the word 'synapse', the neuron was the functional unit that integrated excitatory and inhibitory input. For Cajal, the synapse was the explanation for how neurons could be individual elements, yet connected to form circuits. Both men were primarily concerned with local circuits in spinal cord and brain, but imaginatively extrapolated their discoveries on simple circuits to higher cognitive functions. Both men wrote poetically about their discoveries and so provided neuroscience with a rich vocabulary, vivid and memorable images, and concepts that remain part of the currency of 21st century neuroscience.

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1. A close encounter

> 'Cajals rich voice compelled attention to whatever he said. The memory of that voice reminds me I have a privilege regarding him which, owing to lapse of time, must become rare. My mind's eye recalls him as he walked and talked and indeed as his outward appearance was, just at that time of his career when he had recently become, in his own line of science, an international figure. I see him a man perhaps a little below medium height – at least in London – broad-shouldered, spare and strongly built. Of dark complexion, his olive-skinned face lit by brilliant eyes deep brown in colour and of steady gaze. His hair almost black and closely cropped, trespassed low on a wide forehead. The strong face, completely shaven, had mobile, muscular lips. His hands as he sat and talked seemed to ask to be doing something.' (Sherrington, In: Cannon, 1949).

These words of Charles Scott Sherrington are his recollections of his first encounter with Santiago Ramon y Cajal in London in 1894 on the occasion of the Croonian lecture, which was to Cajal deliver to the Royal Society. After a gap of 55 years, Sherrington can be forgiven for misremembering Cajal as clean-shaven: every one of the many self-portraits Cajal made through his lifetime shows him to be sporting a beard and moustache. The invitation to give the Croonian Lecture was accompanied by letters from Michael Foster (then Secretary of the Royal Society) and from Sherrington (then Foreign Secretary of the Royal Society). They must have been persuasive for, despite a critically ill daughter, Cajal arrived in London and stayed for 2 weeks with the Sherringtons' in their home in Battersea, London. Cajal initially thought England decadent, because of its apparent lack of factories and business, but he had enormous respect for its scientists and institutions: 'The grey matter grows well under grey skies' (Sherrington, 1935).

It is remarkable to think that at the time of their meeting, the word 'synapsis' did not yet exist. Its coinage by Sherrington lay 3 years in the future when he used it for the first time in his chapter in the 7th edition of Foster's '*A Text Book of Physiology*' (Sherrington, 1897). But, before their meeting in 1894, both Sherrington and Cajal were already working on the implications of the synapse-to-be. For Cajal, the synapse explained how neurons could communicate without there being a reticulum. For Sherrington synapses provided an explanation of what Foster called the 'busy time' of the spinal cord: the latencies for reflexes that could not be accounted for by conduction delays. Both Cajal and Sherrington provided complementary evidence, one from structure, the other from function, for the existence of an individual entity called the neuron, and their means of connection, the synapse.

2. Joined at the shoulder: structure and function

In 1906, with the neuron theory well-established, Santiago Ramon y Cajal and Camillo Golgi shared the Nobel Prize for Medicine and Physiology for 'two mutually exclusive discoveries' as an eye witness at the event, Robert Tigerstedt (then professor at the Royal Caroline Institute) mischievously described it (Granit, 1966). The prize was awarded, 'in recognition of their work on the structure of the nervous system.' In his acceptance speech, Camillo Golgi, whose serendipitous discovery had provided the fuel to propel Cajal onto the world stage, made his defiant last stand as Reticularist, while Cajal in his turn made an overwhelming case for the neuron as the fundamental unit of the nervous system. Yet, their respective drawings of the cerebellum almost seem to have been made by a common hand, so alike are they. While their eyes saw the same thing, in their mind's eye they saw something quite different (Fig. 1).

For neurophysiologists, 1906 was also a special year, for it was the year that Sherrington published his book, '*The Integrative Action of the Nervous System*' (Sherrington, 1906). Sherrington, only 5 years younger than Cajal, had paralleled his advances in anatomy to demonstrate reflex functions of the spinal circuits. In fact, Sherrington had begun his scientific life as a histologist and had studied bacteriology for a year with Robert Koch in Berlin. Back in England he was encouraged by W.H. Gaskell to work on the spinal cord and so launched into a lifetime's research on how anatomical organization expresses itself in function. Some 30 years after the publication of '*Integrative Action*' our own mentor and colleague, David Whitteridge, watched 'The Old Man' (Sherrington) cutting his own sections of the spinal cord in the University Laboratory of Physiology in Oxford. As late as 1940 Sherrington published a paper with Sybil Cooper on the border cells in the spinal cord (Cooper and Sherrington, 1940). He was certainly confident of his knowledge of comparative anatomy, as shown by his own account of helping Cajal set up demonstrations for his 1894 Croonian lecture: 'I was helping him to choose some microscopic preparations from among those he had brought with him for the illustration of his Croonian Lecture at the Royal Society. He handed me a preparation showing nerve fibers descending to, and ending in, the spinal cord, and, as he did so, said, 'Pyramidal tract.' 'But,' said I, after a hesitation, 'isn't this from the chick? Birds have not any pyramidal tract.' All he answered was, 'Bien; c'est la même chose.' My remark, though correct, touched a

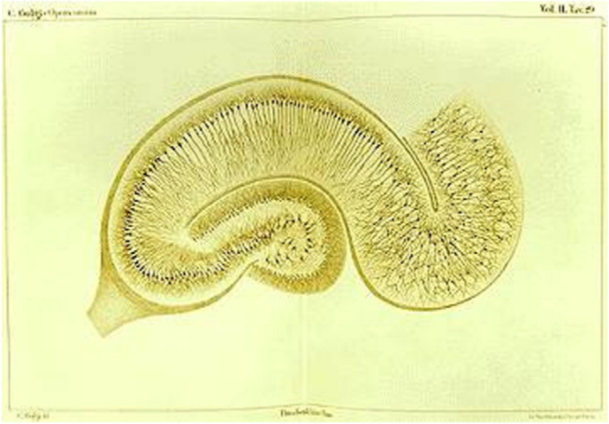

Fig. 1 – Drawing by Camillo Golgi of a hippocampal section stained by the silver nitrate method (Golgi, 1880).

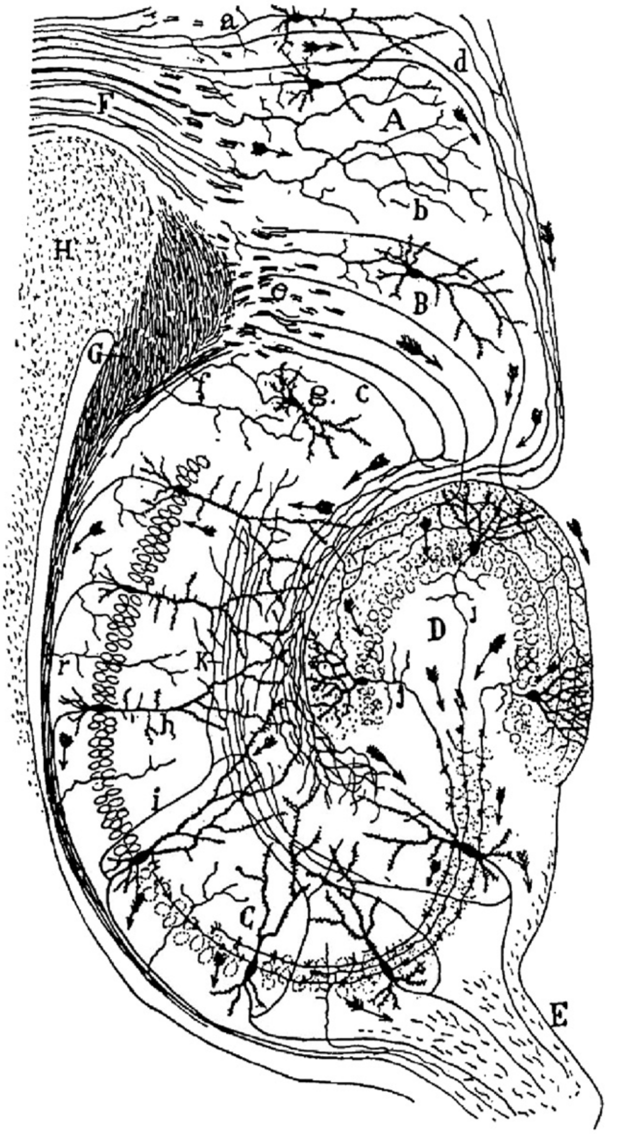

Fig. 2 – Drawing of the neural circuitry of the rodent hippocampus (Cajal, 1911).

detail too trivial for him to regard' (Sherrington, In: Cannon, 1949). As a pupil of Sherrington, Whitteridge needed no convincing about the importance of anatomy for understanding function, but he expressed his own view of the relationship between the two disciplines in a characteristically sharp aphorism, 'physiology equals anatomy plus thought' (Fig. 2)!

3. Integration seen through two eyes

'Integration by the nervous system is *sui generis*' wrote Sherrington (1941). His experiments as described in '*Integrative Action*' led him to the idea of a functional unit, the neuron, which could be excited or inhibited by synapses. The integrative action of the nervous system was best summed up in his concept of a 'final common path', which he conceived of as the final neuron in a reflex arc formed of multiple neurons whose final link ended on a muscle. The integrated action of the neuronal arcs thus led to a co-ordinated action. In his poetic style of expression, which equalled Cajal's own, he said: 'To move things is all mankind can do… whether whispering a syllable, or felling a forest, the motor system is the only available external output channel of the brain…' (Sherrington, 1924). ED Adrian, with whom Sherrington shared his Nobel prize in 1932, said it in a more Anglo-Saxon dialect: 'The chief function of the central nervous system is to send messages to the muscles which will make the body move effectively as a whole' (Adrian, 1932). Sherrington probably demurred about Adrian's use of the word *messages* since, 'we have to bear in mind that they are not messages in the sense of organized symbols. To call them *signals* presupposes an interpreter, but there is nothing to read *signals* any more than *messages*' (Sherrington, 1941).

As Sherrington saw it, movement, not sensation, gave rise to mind. Again and again in *Man* he returns to this same simple point: 'The motor act as conative would seem to have been the earliest nurse of the infant mind' (Sherrington, 1941, p. 193).

While he developed his concept of final common path and applied it the co-ordination of the motor reflex, Sherrington also explored whether there was any comparable principle underlying the synthesis that occurs in sense perception. Here again he converged with Cajal, for he took as his example binocular vision. Cajal had noticed that the size of the ispilateral projection from the eyes in different species correlated positively with their degree of binocular overlap. Cajal's question in 1898 was then, what is the purpose of the partial decussation at the optic chiasm? His solution was to suppose that centrally there must be a unified retinotopic representation of binocular space, which Cajal called the 'mental image'. In animals with panoramic vision and no overlap in the visual fields of left and right eye, this unified representation could be achieved by complete decussation. In the case of animals with binocular overlap, however, the unified representation of binocular visual space could only be obtained by a partial decussation. Although the linkage of the two hemifields was not discussed, the diagrams presented by Cajal seem to assume that the two hemifields are stitched together down the vertical meridian. This conjecture was only established through a very difficult experiment executed by Choudhury et al. (1965), in which they split the optic chiasm and recorded from the hemisphere contralateral to the stimulated eye to show that cortical units activated across the corpus callosum had receptive fields located on the vertical meridian. Their finding was soon confirmed by Berlucchi et al. (1967), and by Hubel and Wiesel (1967), who chose the rather simpler expedient of recording directly from axons in the corpus callosum.

It is remarkable that Cajal assumed that the arrangements of the projections from the retina to the thalamus and on to the visual cortex, were retinotopic. Although diagrams from at least as early as Descartes' show a retinotopic projection of the retina to the brain, this was far from being an established experimental fact. The first convincing evidence came from experimental studies late in the 19th century (Dean and Usher, 1896; Pick, 1896), and the debate about topography in the optic pathways continued late into the 20th century (Aebersold et al., 1981; Horton et al., 1979; see review by Horder and Martin, 1978). Despite his own mapping studies, Sherrington was never wholly convinced about topographic representations in the cortex, but as late as 1960, his erstwhile pupil, David Whitteridge was involved in a debate with Robert Doty as to whether there was a retinotopic map on the primary visual cortex of the cat. Whitteridge, following Talbot (1942), insisted on there being a localized response, while on the other side Doty reported that cortical response to a localized visual stimulus was not localized. Immediately following the congress where they first aired their disagreements, they agreed to resolve their differences by joint experiments in Whitteridge's Edinburgh laboratory. The results were apparently clear-cut and Doty was magnanimous in defeat: 'I think Dr. Whitteridge definitely scored the best in our argument' (Doty, 1961). They agreed that the early response was highly localized, but that the longer latency response, arising presumably from intercortical connections, was less localized. If only all scientific debates were so directly resolved, it would certainly lessen the load on referees for Nature and Science.

4. Temporal fusion of monocular images

Sherrington's approach to binocular fusion, as described in *Integrative Action*, was typically thorough. He designed an experiment to test whether single vision through two eyes is achieved by direct confluence of the left and right eye images. Through an apparatus of his own devising, he presented separately to conjugate points on each retina flickering spots and examined how different combinations of frequencies were perceived for brightness and fusion when binocularly viewed images were compared to monocularly viewed stimuli. His conclusions from an extensive series of experiments were much as that supposed by Cajal: the monocular images were independently processed and then combined to form the binocular image. Sherrington, however, was agnostic on where this combination actually took place, but he raised the novel and now very contemporary idea of binding by temporal coincidence rather than by spatial convergence: 'pure conjunction in time, without necessarily cerebral conjunction in space lies at the root of the solution of the problem of the unity of mind' (Sherrington, 1941, p. 381). Later work of Hubel and Wiesel, and of Pettigrew and colleagues, showed that, on the contrary, binocular cells exist already in the primary visual cortex. Nevertheless, the idea of temporal contiguity is important, for example, when discussing the spontaneous activity of the cerebral cortex. Sherrington pointed to the similarities between the rhythmic 'self-firing' of the respiratory neurons and neurons in the cortex, which 'hold hands and groups of them self-fire together'. The step to Moshe Abeles' modern concept of the 'synfire chain' (Abeles, 1991) is a small one.

5. A Rosetta stone for circuits

Given that conceptually Cajal had so much in common with Sherrington, it is curious that he did not use the term synapse in his Nobel lecture of 1906, nor does the word appear in the English translation of Cajal's autobiography. Nevertheless, the connection between nerve cells was critical to both in developing the idea of an arc, or circuit of neurons. By reformulation of the 'law of forward conduction' of William James, which described the fact that conduction proceeds on one direction only, Cajal brilliantly found the means to solve circuits. He proposed that dendrites conduct towards the cell body while the axon conducts away from the cell body: i.e., that neurons themselves were polarized. Sherrington was quite clear about this insight:

> 'He solved at a stroke the great question of the direction of the nerve-currents in their travel through brain and spinal cord. He showed, for instance, that each nerve-path is always a line of one-way traffic only, and that the direction of that traffic is at all times irreversibly the same. The so-called nerve-networks with unfixed direction of travel he swept away. The nerve-circuits are valved, he said, and he was able to point out where the valves lie-namely, where one nerve-cell meets the next one'.

By relentlessly applying his 'law of dynamic polarization', he was able to trace chains of nerve cells and so provide us with many of the textbook diagrams we still use today.

One diagram we do not find in textbooks is that for the neocortex. The reason for this is given in Cajal's autobiography

> 'Devotion to the cerebral hemispheres, enigma of enigmas, was old in me…the supreme cunning of the structure of the grey matter is so intricate that it defies and will continue to defy for many centuries the obstinate curiosity of investigators. That apparent disorder of the cerebral jungle, so different from the regularity and symmetry of the spinal cord and of the cerebellum, conceals a profound organization of the utmost subtlety which is at present inaccessible.'

His frustration is quite palpable, although, with characteristic competitive zeal, he 'launched himself into that dark thicket, where so many explorers had lost themselves' and of course, made many fundamental observations of the different cell types of neocortex. His quest, 'to determine so far as possible its fundamental plan or at least complete an enquiry similar to that carried out some years earlier in the cerebellum' was the search for the fundamental cortical circuit that has continued through the 20th Century. There is no general agreement that this grail has yet been found.

Following on from the early cortical anatomists like Betz, Edinger, Flechsig, Forel, Golgi, Koelliker, Martinotti, Meynert, Retzius and of course Cajal himself, a new wave or anatomists led by Brodmann, Campbell, and the Vogts, set out to study the structure of the neocortex. Their interest was not in solving the basic circuit of the neocortex, but much more in the cytoarchitectonic parcellation of the neocortex into different areas. Thus the next major step in defining the fundamental cortical circuit waited for Lorente de No in his much-cited 15th chapter in Fulton's *Physiology of the Nervous System* published in 1949. (In the introduction to his chapter he apologizes for being so late in producing it. One can imagine Fulton, a disciple of Sherrington, grinding his teeth). Lorente de No of course had benefited by the advances made by Erlanger and Gasser who introduced the cathode ray oscillograph in 1922 and by the developments of the microelectrode, which allowed recordings to be made from single units. Electrophysiology had entered the modern age. He thus benefited from a much richer conceptual framework. Sherrington, however, never took this leap technically and all his significant experimental work was done in the pre-electronic age. His main instrument of measurement was the torsion wire myograph, which he used to record the muscle contractions. Once he wanted to record the movements of the tiny eye muscles and went to AG Dew-Smith, co-founder with Sir Horace Darwin of the Cambridge Scientific Instrument Company (apparently Dew-Smith was always dressed in a velvet jacket) and asked him for some light aluminum levers. 'Have you ever thought of a straw?' Dew-Smith asked him (Granit, 1966). Light levers had featured in his work before, most notably in his work with Charles Roy 'on the regulation of the blood-supply of the brain'. This paper, which was published in the *Journal of Physiology* in 1890 (Roy and Sherrington, 1890), has spiked in citations (raising suspicions that many are tralatitious) since the discovery of blood oxygen level derived (BOLD) signal and other intrinsic optically recorded signals of brain activity. Their measurements of changes in the brain volume in response to various nerve stimulations and drugs were made with an ingenious apparatus of Roy's devising, which involved a craniotomy sealed with a closed chamber connected with rigid wall tubing to a piston that moved a recording lever.

6. Columns, modules, and the Yin–Yang

In contrast to the fundamental circuits developed by S. Ramon y Cajal, Lorente de No's cortical circuits are modest in their use of arrows to indicate the flow of current through the circuits (Fig. 3). He excused this by pointing out that his arrows were only there to indicate the synapses of common origin whose convergence would favor transmission. He was interested in the same solution as Cajal, but now addressed specifically the notion of a cortical column: 'all the elements of the cortex are presented in it, and therefore it may be called an elementary unit, in which, theoretically the whole process of transmission of impulses from the afferent fiber to the efferent axon may be accomplished' (Lorente de Nó, 1949). This notion was echoed years later by Hubel and Wiesel:

> 'the machinery may be roughly uniform over the whole striate cortex, the difference being in the inputs. A given region of cortex simply digests what is brought to it, and the process is the same everywhere…. It may be that there is a great developmental advantage in designing such machinery once only, and repeating it over and over monotonously, like a crystal' (Hubel and Wiesel, 1974).

Lorente de No's major advance was not in describing more cell types or their likely connections: in that he did not go beyond Cajal. Indeed, neither Lorente de No nor Cajal had taken on board the fundamental discoveries of Sherrington of

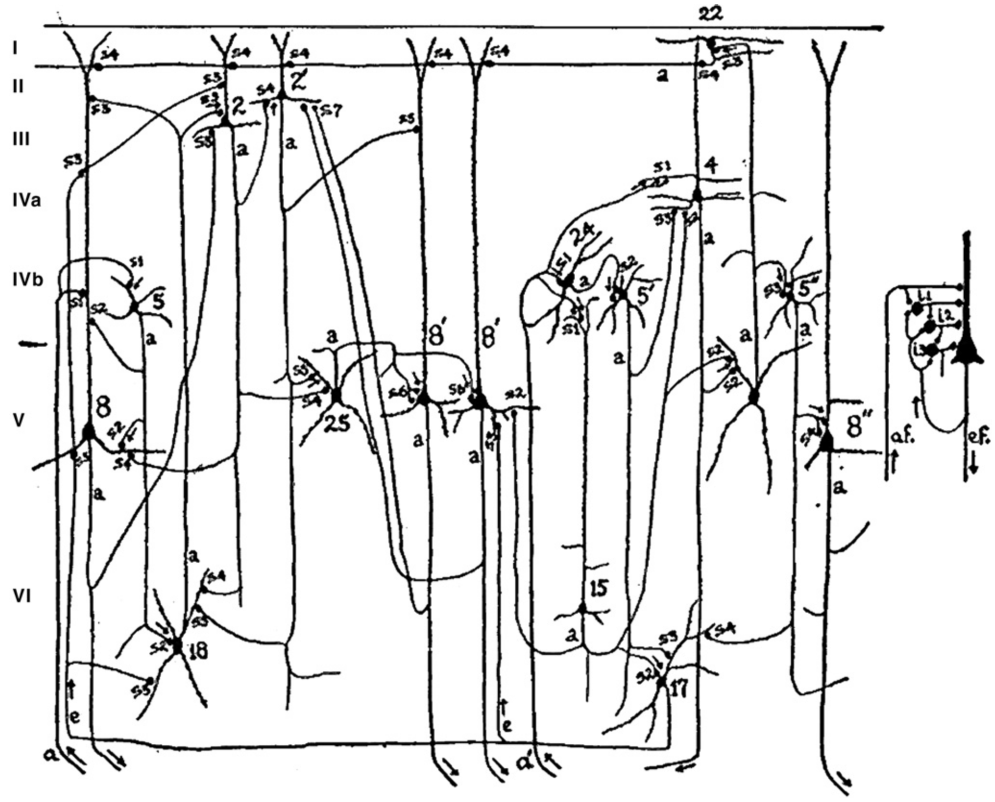

Fig. 3 – Lorente de Nó proposed that, functionally, the cortex is composed of vertical processing chains of neurons, rather than of layers (Lorente de Nó, 1949). In his view, neurons in all layers except I and II receive input from the thalamus. The processed input is then propagated vertically to the most superficial layers.

spinal inhibition and of reciprocal innervation. Neither attempted to differentiate the class of excitatory neurons from the inhibitory neurons, as the neo-Golgi anatomists like Jones, Lund, Peters, Szentagothai, and Valverde, were to do 30 years later. Yet the evidence for the reciprocal action of inhibition and excitation was evident in the heyday of Cajal. Denny-Brown's edited *Selected writings of Sir Charles Sherrington* (1939) begins with a quote (in French) from a speech made by the President of the Ninth International Congress of Physiology, H.J. Hamburger, in which he describes a demonstration made by Sherrington at the Fourth International Congress of Physiology, held in Cambridge in 1898: 'Those who, in Cambridge, witnessed the experiment of Sherrington, showing the relaxing effect that accompanies the excitation of the antagonist muscle, have enriched their knowledge forever. I still feel the triceps of the monkey melting, so to say, between the fingers, at the moment when the biceps contracts.' For Sherrington, excitation and inhibition provided the algebra of the nervous system: 'the net change which results there when the two areas are stimulated concurrently is an algebraic sum of the plus and minus effects producible separately by stimulating singly the two antagonistic nerves' (Sherrington, 1908).

Sherrington established beyond doubt that inhibition is an active process, as Foster had anticipated, and not simply a withdrawal of excitation, and he had established that inhibition and excitation go hand in hand. Even today, this Yin–Yang of the central nervous system is not properly understood. For Sherrington at least, it was a fundamental principle of the nervous system. Granit recalls telling him in 1932: 'I am sure that there must be inhibition in the retina…. But I cannot see how one shall ever be able to prove it.' Sherrington replied: 'don't worry. After a couple of years you will prove it yourself' (Granit, 1966). The result of Granit's studies was another Nobel prize for Physiology and Medicine, for which the citation read in part: 'These [discoveries] show the importance of inhibition in the integrative action of the retina and the principles for spectral discrimination by retinal elements.'

Granit shared his prize with George Wald, the chemist who, with Ruth Hubbard, discovered the visual pigments; and with Keffer Hartline, who demonstrated lateral inhibition in the horseshoe crab. Hartline's classic work is now in every textbook. It showed quantitatively the dynamics of lateral inhibition and disinhibition. His discoveries were seminal for the work later carried out by Horace Barlow, Steve Kuffler, and David Hubel and Torsten Wiesel. Horace Barlow was supervised by ED Adrian and took as his thesis project a study of summation and inhibition in the frog's retina. Adrian had strongly advised him against the project because Keffer Hartline had already recorded from the frog retina. 'I wouldn't do that', Adrian warned him, 'Hartline's a very clever chap you know' (Barlow, 1990). However, the graduate student's persistence was rewarded and he was able to demonstrate that the receptive fields of the vertebrate ganglion cells possess an inhibitory surround. In the same year, Kuffler independently demonstrated the inhibitory surround in cat ganglion cells. Barlow reflected on his results in a way that not only synthesized key aspects of the thinking of Cajal, Sherrington, and Adrian, but gave birth to the idea that single neurons code for perceptually significant events:

> 'an optic nerve fibre is the final common path for activity aroused in a considerable region of the retina, and if some purposive integration has taken place, it should be possible to relate this to the behaviour of the frog…. it is difficult to avoid the conclusion that the 'on–off' units are matched to this stimulus and act as fly detectors' (Barlow, 1953)

It was this embryonic idea that was going to have an enormous impact on the conceptual underpinnings of much of modern cortical physiology.

7. Reverberations through the cortex

In writing the definitive account of the architecture, intracortical connections and motor projections of the cerebral cortex for Fulton's book, Lorente de No's most important contribution was synthetic and conceptual. Using his physiological knowledge he was able to extrapolate beyond what he saw down the microscope to develop a hypothetical vertical chain of neurons that could, in theory, maintain a state of self-excitation in the cortex and even produce synchronous volleys of activity. Activity arising in the afferent fibers was thus subject to modification according to the existing state of cortical activity. In this idea he was providing a more detailed instantiation of the rhythmic self-excitation that Sherrington thought was a *sine qua non* of the 'roof-brain' (neocortex). Sherrington's descriptions of the activity in these recurrent cortical circuits rival in color and vividness anything that Cajal wrote. In his best known passage he imagined a brain changing from a state of sleep to a state of wakefulness thus:

> 'The great topmost sheet of the mass, that where hardly a light had twinkled or moved, becomes nor a sparkling field of rhythmic flashing points with trains of travelling sparks hurrying hither and thither. The brain is waking and with it the mind is returning. It is as if the Milky Way entered upon some cosmic dance. Swiftly the head-mass becomes and enchanted loom where millions of flashing shuttles weave a dissolving pattern, always a meaningful pattern though never an abiding one; a shifting harmony of subpatterns.'

It may seem a bit rash to compare a brain of 1.5 l with our galaxy, but the dimensions that astrophysicists and astronomers talk about have their parallel in the numbers that anatomists deal with. In the neocortex we have ten thousand million nerve cells, which is the same order of number as the stars in our galaxy. The number of connections they make are the same order as a thousand galaxies. But the really astronomic figure emerges from the cardinal property of brains — their connectivity. Astrophysicists, like Archimedes, have calculated the number of atoms in the universe to be about 10^{80}. If we ask how many nerve cells you would need to create 10^{80} different patterns of connections, then the number is 17. One, seven! Seventeen nerve cells can be connected in over 10^{80} different ways. It will therefore come as no surprise to learn that despite the large number of genes that are involved in setting up and maintaining our brain that our genes cannot specify the individual connections in the brain.

The idea of self-excitation in the neocortex was central to Sherrington's development of the idea of mind. Like Lorente de No, he supposed that this ongoing cortical activity was modified by the activity arising from outside, by light, or sound, or touch, for example. Sherrington, who had mapped the motor cortex in anthropoid apes (chimpanzee, gorilla, orangutan; Leyton and Sherrington, 1917) had been impressed by the work of Philip Bard and Wade Marshall at Johns Hopkins University, who were able to record evoked potentials from the somatosensory cortex in response to light touch and who had demonstrated the existence of a somatotopic map (Woolsey et al., 1942). This mapping work was developed further by Clinton Woolsey and brought to a fine grain by Vernon Mountcastle, who provide the first convincing evidence for functional columns (Mountcastle, 1957; Powell and Mountcastle, 1959; Fig. 4), which were the physiological expression of Lorente de No's vertical circuits. Bard introduced Mountcastle to a visitor from Oxford, Tom Powell, who helped Mouncastle consolidate the physiological observations and also provided the important anatomical link to the cytoarchitecture of the somatosensory cortex (Jones, 1999).

While Bard and collaborators had mapped large areas of cortex, Mountcastle and Powell confined themselves to much smaller regions of the cortex and used single unit recordings rather than evoked potentials. They were able to demonstrate the segregated representation of different receptor types. Mountcastle also suggested that the existence of pericolumnar inhibition provided the mechanism for maintaining the columnar specificity. Mountcastle and Powell worked in the controlled conditions of the anesthetized animal. Only later, following Jasper and Evarts, did Mountcastle use alert monkeys, where he was able to study the dynamic activity in the somatosensory cortex of monkeys as the monkey executed sensory tasks. The conundrum pointed to by Sherrington was how two successive touches ever felt alike since the peripheral activity was entering a cortical network whose state was continually varying. Since subjectively successive touches can feel alike, his conclusion was that there is a mystery still to be solved in sense perception. Despite the extraordinary technical advances in recordings from awake humans and non-human primates, this stability of perception remains a mystery.

8. Plunging into the jungle

In Sherrington's enchanted loom there are 50,000 to 100,000 nerve cells in each cubic millimeter, and each neuron sends

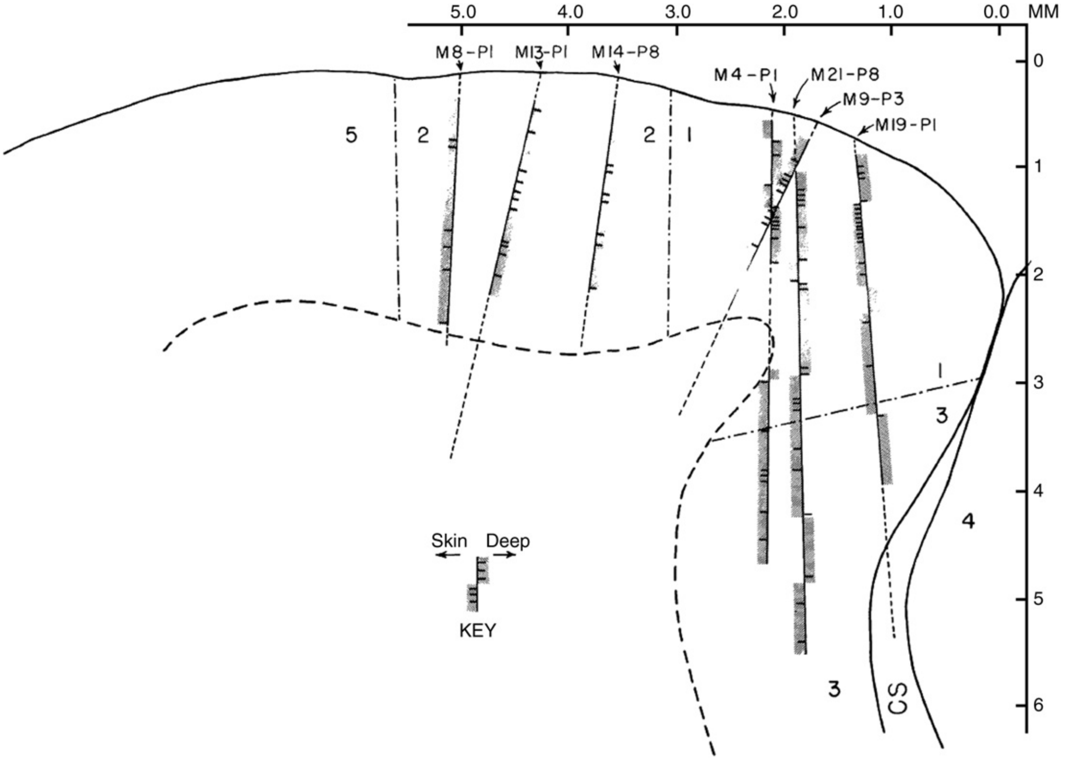

Fig. 4 – Evidence for columnar organization in the neocortex was obtained by Powell and Mountcastle in single neuron electrophysiological studies of somatic sensory cortex in cats and monkeys (Mountcastle, 1957; Powell and Mountcastle, 1959). This figure (Powell and Mountcastle, 1959, modified) shows several microelectrode penetrations made into the postcentral gyrus of anesthetized monkeys. Those made normal to the pial surface encountered neurons in each cellular layer with similar properties of place and modality. By contrast, penetrations parallel to the pial surface and crossing the vertical axis of the cortex encountered a succession of 300–500 μm regions, each containing a group of neurons with identical properties. Sharp transitions were observed from a region with one set properties, to the adjacent region with different properties.

out a single nerve fiber that branches to form a dense meshwork of fibers that enable this single cell to connect to hundreds of other cells. If we take 1 mm^3 of white matter and join all the pieces of axon 'wire' together, then they form a single piece of wire 9 m long. If we take a cubic millimeter of the grey matter and repeat the exercise then after joining up all the pieces of wire, we have a single piece of wire 4 km long. This is because the wires in the grey matter are much thinner than the wires in the white matter. What this tells us is that we are dealing with a structure that is highly connected, and highly connected to itself. Only 1/1000 fibers in the white matter itself connects to a structure other than neocortex. It is this cortical thicket that defeated Cajal and Lorente de No. By contrast, the number of wires that connect our sense organs to the neocortex, or our neocortex to our spinal cord, is remarkably tiny. An eye connects to the thalamus with just over a million fibers, an ear has only 10,000 sensory fibers, but for a concert pianist or a member of the audience, these few fibers connecting ear and hand make a rather dramatic difference to their quality of life. The motor cortex connects to the spinal cord with only 1 million fibers, of which the hand area receives 10,000. Sherrington's *final common path* is a numerical fact.

The major advances in untangling the cortical thickets awaited the development of the powerful tools of electron microscopy, more sophisticated recording and tracing techniques and neurochemical markers, all developed between the late 1950s to late 1970s. Intracellular recordings from cortical neurons showed the presence of inhibitory and excitatory events (Albe-Fessard and Buser, 1953; Phillips, 1959) while electron microscopy indicated the presence of two synaptic morphologies (Gray, 1959) that could be correlated with functional identification of inhibitory and excitatory synapses (Uchizono, 1965). Surprisingly, the Golgi technique also showed it was not yet spent and a new generation of anatomists, with fresh eyes and fresh ideas, used it in combination with these new tools and new concepts like specificity of connections, columns, parallel processing, multiple representations and functional specialization. The result was a far deeper understanding of the principles that underlie the organization of cortical circuits. The idea of a fundamental circuit was encouraged by studies in different species, which showed a remarkable convergence. In the example of the connections made by the thalamus, the diagram made by Powell and colleagues (Fig. 5; Gatter et al., 1978) closely resembles that of Freund et al. (1985), which in turn closely resembles that of White (1981). Yet these diagrams were generated independently in three different species and three different cortical areas. However, the arrows that had been so

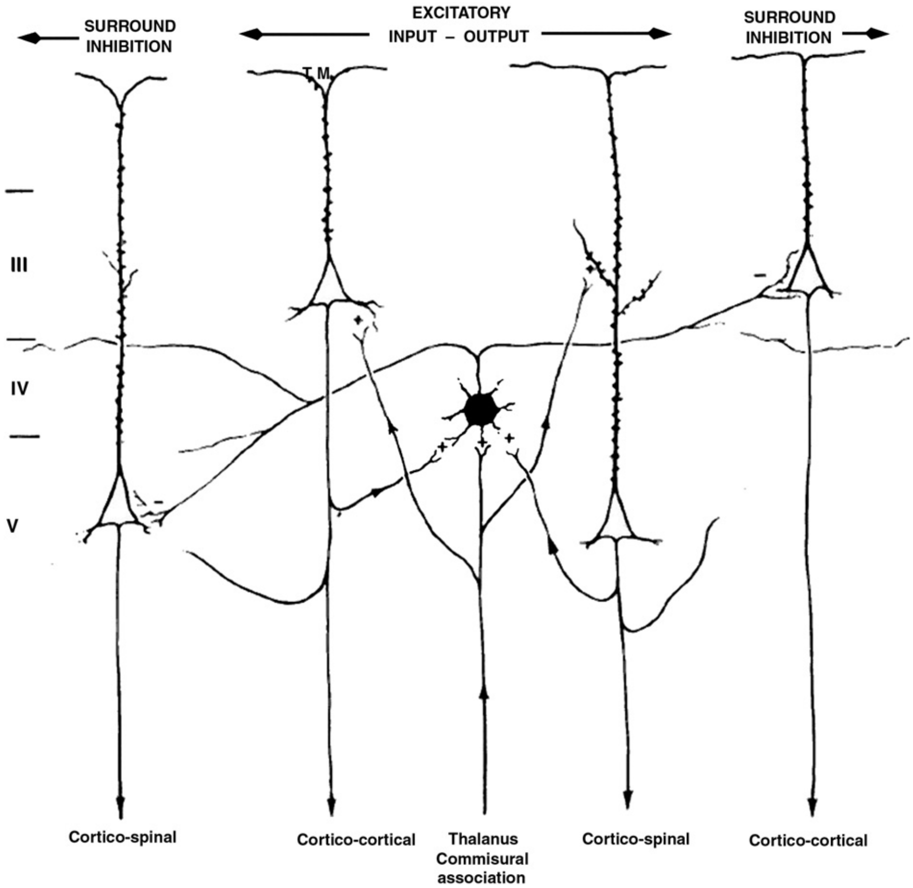

Fig. 5 – Powell and colleagues summarized their correlated light and electron microscopic studies of the intrinsic connections of area 4 of the monkey with this diagram. Monosynaptic thalamic input distributes to both pyramidal and layer IV basket cells. The basket cells then feed back locally to inhibit pyramidal neurons in the superficial (III) and deep (V) layers (Gatter et al., 1978).

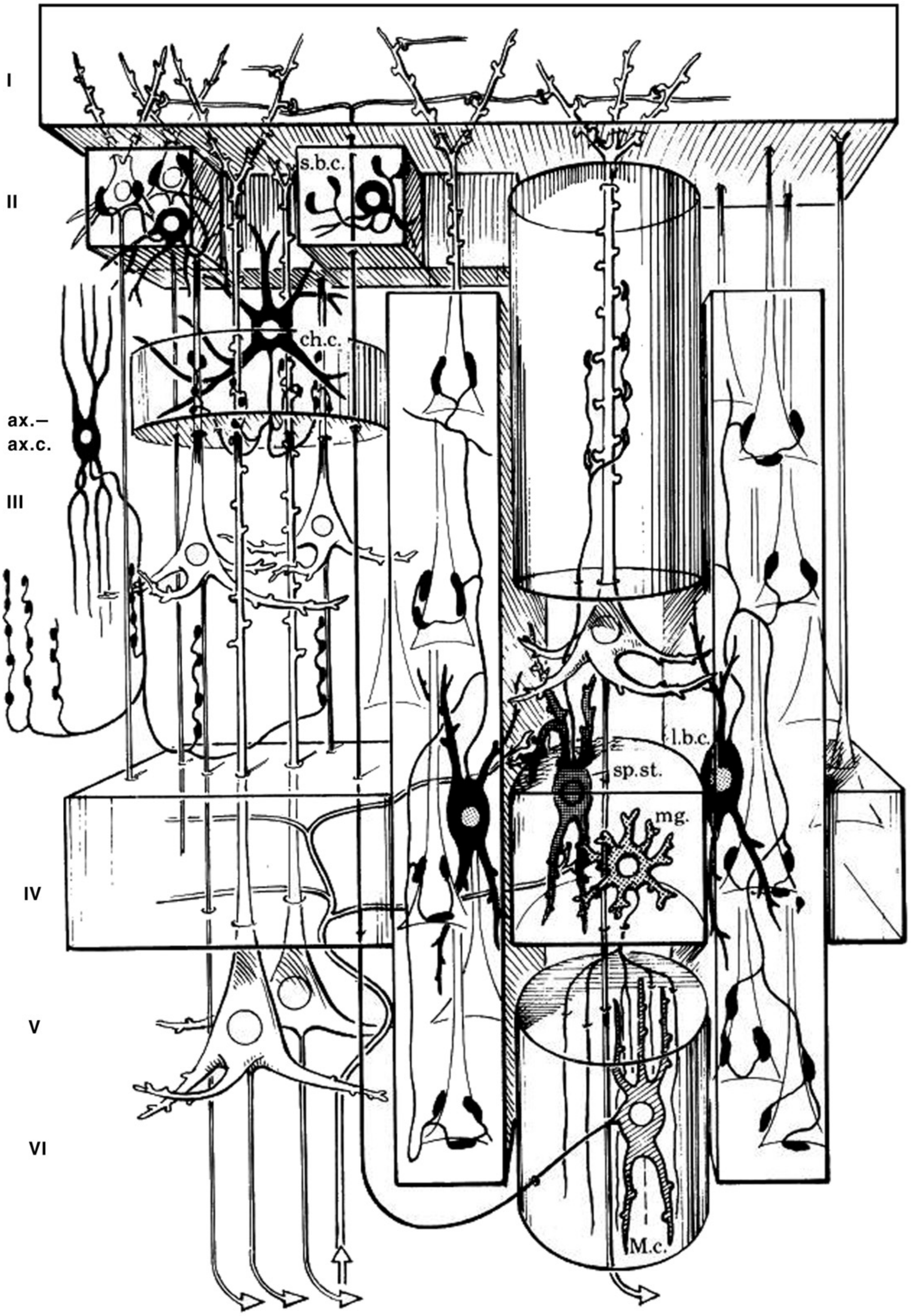

Fig. 6 – Szentagothai proposed that the cerebral cortex is a mosaic of columnar units of 200–300 μm. These units are the basic processors of the cortex. They are composed of similar internal neuronal circuits that have a predominantly vertical organization (an example connection diagram is shown here). The operations performed by these general circuits are made task-specific by longer range connections (not shown) that establish the particular interactions between columns. Within each column, the thalamic afferents excite layer IV spiny stellates (stippled cell in the half cylinder at center right), which in turn excite predominantly the superficial pyramidal neurons. The excitation of the spiny stellates is opposed by local inhibitory neurons (black cells). This inhibition shapes and focuses the excitatory response (Szentágothai, 1978).

emphatic and confident in the diagrams of Cajal, but dwindled in the hands of Lorente de No, by now had vanished altogether. Lorente de No at least partially contributed to this state of affairs, for he stated that unlike the retina or the cerebellum, no single layer could be called a ‘receptor’ layer and no single layer could be called an ‘effector’ layer. Thus there was no way to assign to the layers of the cortex the separate tasks of reception, association, and projection.

9. Cortical jigsaw puzzles

The concept that there exists a basic cortical circuit had not vanished, however, although most cortical anatomists were reluctant to say what it was. Janos Szentagothai, for example, drew elegant diagrams of hypothetical cortical modules (Fig. 6) that showed the relations of the different cell types in different layers (Szentágothai, 1978), but these circuits still did not provide the theoreticians with sufficient details to begin their investigations. David Marr, for example, who continued the long line of attempts to develop a theory of the cerebral cortex, frustratedly concluded that ‘finally, it is unprofitable to attempt a comprehensive survey of cortical cells at this stage, neither the theory, nor the available facts permit more than the merest sketch’ (Marr, 1970). However, this did not mean that there was no connection between ideas of cortical function and structure. In the visual cortex, the idea of hierarchical processing had been encapsulated in the hugely influential hypothetical circuits for simple and complex and hypercomplex cells proposed by David Hubel and Torsten Wiesel in the early 1960s. These same orientation selective cells had begun to feature in many different models of vision, most notably those of David Marr and colleagues (who nevertheless insisted theirs was a principled ‘top-down’ approach to understanding vision). The anatomical substrate for the hierarchy of processing was later developed by Charles Gilbert and Torsten Wiesel in their circuit for the cat visual cortex (Gilbert, 1983; Gilbert and Wiesel, 1983). This circuit (Fig. 7) was based on data from *in vivo* experiments where functionally identified neurons had been intracellularly labeled, showed a logical sequence of interlaminar processing that accounted qualitatively for the receptive field structures that they had determined with single unit recording. Ironically, the same circuit could have been constructed by Cajal, for it relied on the same application of the law of dynamic polarization and jigsaw piecing together of individual neurons to decide who was connected to whom. Although Gilbert and Wiesel’s circuit is based on the difficult technique of intracellular recording *in vivo*, their basic components for the interlaminar circuits are apparent in data obtained from studies of many cortical areas, albeit by less arduous means than intracellular recording *in vivo* (see Douglas and Martin, 2004).

10. Recurrent themes

The modern circuits derived from the visual cortex concentrated on correlating the laminar differences in receptive field properties with the interlaminar or lateral intercolumnar connections. The existence of the local collaterals of pyramidal cells was well known to Cajal, for it formed the basis of his

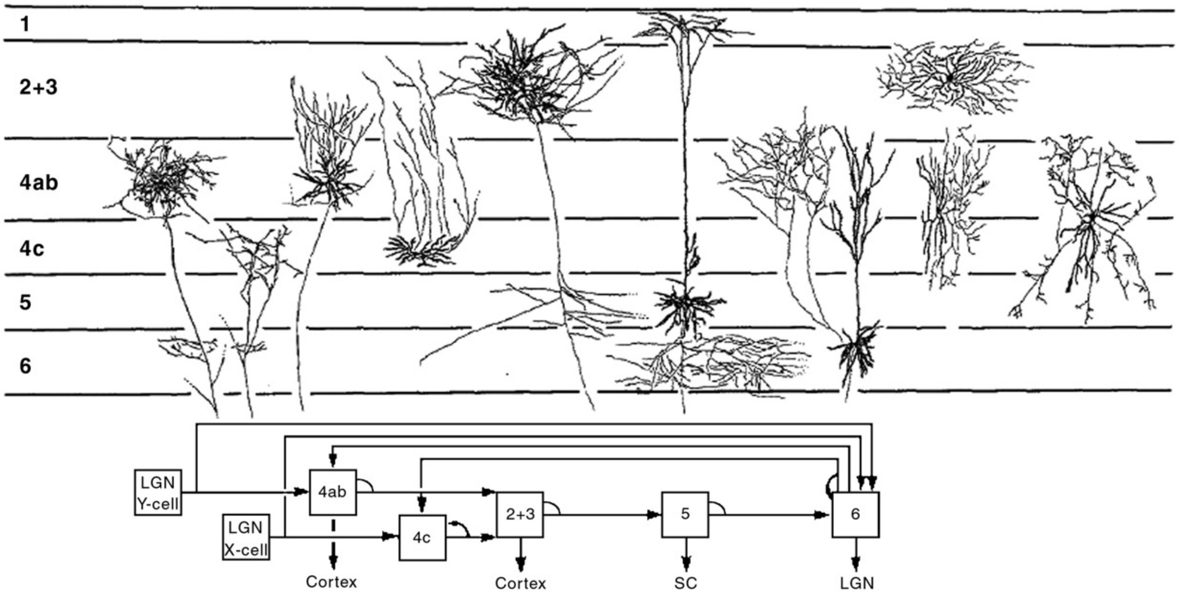

Fig. 7 – Gilbert and Wiesel provided one of the first functional interpretations of a defined anatomical circuit based on their intracellular recordings and reconstructions of individual cells filled with horseradish peroxidase (HRP) in cat visual cortex (Gilbert, 1983; Gilbert and Wiesel, 1983). Their labeling method revealed for the first the laminar preferences of the axons of different types of neurons. By using the simple rule that axons connected to neurons whose somata were located in the layer to which the axons project, Gilbert and Wiesel developed a simple circuit for cat area 17 (V1) that was consistent with the hypothetical circuits developed by Hubel and Wiesel (1962) two decades earlier on the basis of receptive field structures.

law of neural avalanche (see below). Similarly, the local collaterals feature in Lorente de No's circuits, but without a grasp of neuronal biophysics and of the relative influences of the inhibitory and excitatory cells, it was difficult to go much further. Estimates of the length of the local axons of an average cortical cell, based on the volume of neuropil occupied by axon, predicted that each cortical cell would have a local axonal plexus that was a staggering 40 mm long and formed several thousand synapses (Braitenberg and Schüz, 1998). However, with the cortical physiology very much dominated by the visual system and by the opinion of the visual savants that receptive fields could most simply be explained by feedforward circuits, there was no incentive to explore the role of local collaterals. This lack of interest in the details of the structure occurred despite the fact that the new intracellular labeling techniques had revealed that the local axons of single cells were highly elaborated, particularly in the vicinity of the dendritic tree. However, the experimental evidence that the local collaterals formed recurrent excitatory and inhibitory circuits was compelling and had important theoretical consequences.

The elements of the recurrent circuit, and the notion that it formed an elemental cortical circuit, was encapsulated by Douglas, Martin and Whitteridge in a 'canonical' circuit for the neocortex (Fig. 8; Douglas et al., 1989; Douglas and Martin, 1991; Binzegger et al., 2004). This circuit was based on structural and physiological evidence derived from the visual cortex of the adult cat, which implied that a small afferent input to the cortex was amplified by recurrent excitatory activity that could be gated or modulated by an embedded recurrent circuit of inhibitory neurons. Inhibitory and excitatory neurons are co-activated. This circuit explained for the first time the otherwise puzzling observation that inhibitory neurons occupy the same functional column as their major targets and thus share their stimulus specificity. Although in its model instantiation the 'canonical' circuit is almost banal in its simplicity, this interpretation of the structure and function of the cortical column has been invaluable for computational models. It was used as the basis for not only re-examining the traditional problems of orientation selectivity (Somers et al., 1995; Ben-Yishai et al., 1995; Douglas et al., 1994) and direction selectivity (Douglas et al., 1995) in visual cortex, but also stimulating wider ranging explorations of the

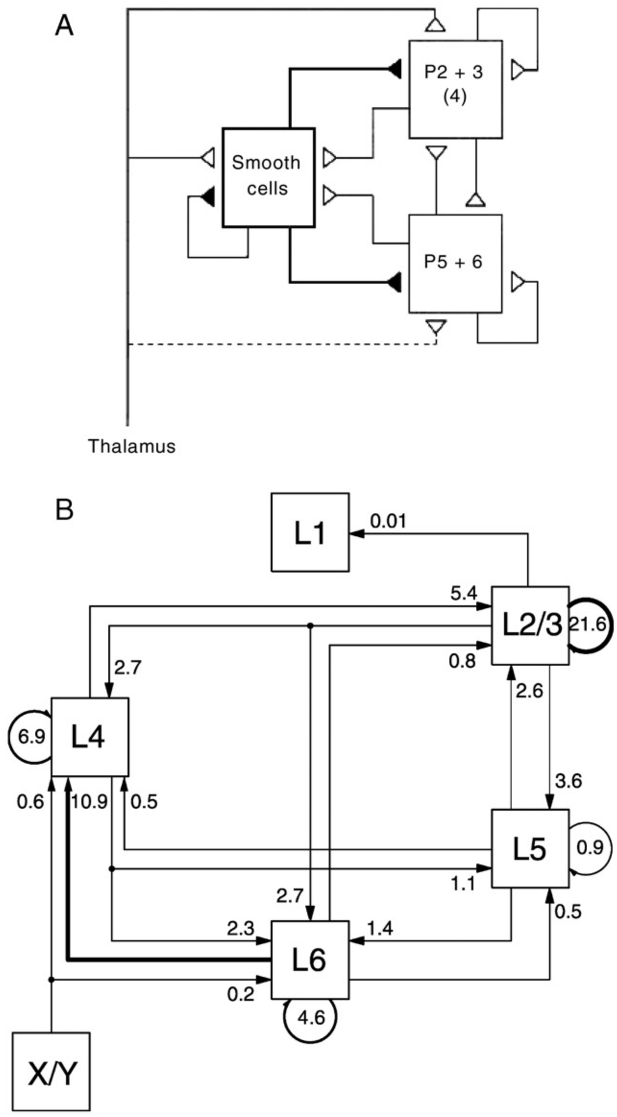

Fig. 8 – (A) Original diagram of the 'canonical microcircuit for the neocortex' (Douglas and Martin, 1991). This circuit successfully modeled the intracellular responses of cortical neurons to pulse stimulation of thalamic afferents. The circuit proposes that the cortex is composed of three dominant populations of neurons that interact with one another. One population is inhibitory (smooth cells, filled synapses), and two are excitatory (open synapses). The latter represent superficial (P2+3) and deep (P5+6) layer pyramidal neurons, respectively. The layer 4 spiny stellate cells (4) are incorporated with the superficial group of pyramidal cells. Some neurons within each population receive excitatory input from the thalamus. Continuous versus dashed lines indicate that thalamic drive to the superficial group is stronger. The inhibitory inputs activate both GABAA and GABAB receptors on pyramidal cells. The thick continuous line connecting smooth cells to P5+6 indicate that the inhibitory input to the deep pyramidal population is relatively greater than that to the superficial population. However, the increased inhibition is due to enhanced GABAA drive only. The GABAB inputs to P5+6 are similar to those applied to P2+3. (B) A more recent version of the canonical microcircuit, refined by quantitative neuroanatomical studies (Binzegger et al., 2004). Only the connections between the dominant excitatory cell types are shown in this partial diagram. Each arrow is labeled with a number indicating the proportion of all the excitatory synapses in area 17 that are formed between the various types of excitatory neurons. Total number of synapses between excitatory neurons is 13.6×10^{10}. The proportion of asymmetric unassigned synapses that the excitatory neurons in each layer receive is 0.1% (layer 1), 6% (layer 2/3), 10% (layer 4), 2% (layer 5), and 12% (layer 6). These synapses are presumably formed by the afferents originating outside area 17. Additional maps of connections for excitatory to inhibitory neurons, etc., can be found in Binzegger et al. (2004).

dynamical properties of cortical circuits, chaos (van Vreeswijk and Sompolinsky, 1996), Hebbian learning in recurrent networks (Amit et al., 1994), persistent activity in prefrontal cortex (Miller et al., 2003). The quantitative anatomical and physiological details of this model are now only emerging through detailed measurements of the synaptic connections and biophysics of the neurons.

The cat visual cortex has one huge advantage of any other cortical area in any other species in that it is the only cortical area where years of quantitative anatomy have provided many of the numbers required to make genuine quantitative estimates of the connections. Similar efforts are also being made for the rodent barrel cortex, but with rather a different strategy. The rodent project exploits strongly reductionist methods to study all the elements of neuronal biophysics, morphology, and gene expression, so as to derive the large number parameters thought necessary for an isomorphic bootstrap simulation of the whole circuit. In the cat our approach has been first to derive common principles of structural and functional organization, and then to explore to what extent the quantitative details match these predictions. This approach has a painterly quality, it begins at low resolution and works up to higher resolutions. The rodent program proceeds in the opposite direction and adopts something like a Humpty Dumpty strategy: many eggs are disassembled in the hope that one egg can be put together again, at least *in silico*. Whether all the Kings Men (and IBM) can put a cortical column together again remains for the future to reveal.

11. Uniformalism

The central question of the degree of uniformity of cortex in different species has been a difficult thing to measure. Powell and colleagues (see Powell, 1981) took a simple approach, albeit with provocative results. They sampled areas of cortex in mouse, rat, cat, old world monkey and man, and counted the number of cells contained in a rectangle of arbitrary dimensions (25×30 μm) though the entire thickness of the cortex. With exception of area 17 in primates, the numbers they collected were similar across species and across areas. Primate area 17 had numbers that were more than double the counts for all other areas. Their conclusion was surprising to many and remains controversial, perhaps, because no attempt has been made to replicate it using modern stereological techniques. Powell's conviction that there was a basic uniformity in structure of the neocortex did not, however, rest on this single study, but his many quantitative ultrastructural studies, which showed the constancy in the proportions of the major cell types, and their maps of local and long distance connections of the cortex. Powell's view of cortex brought into discussion ideas of the evolution and genetic specification of the neocortex: his work convinced him that cortex was built of repeated modules, which increase in number as the cortex increases in area.

Powell recognized that his concept of a basic uniformity of cortex was somewhat at odds with the view of cortical differentiation seen from cortical cytoarchitectonics. Perhaps little recognized and considered, however, is his observation that the changes in the proportions of afferent and efferent projections may change gradually, so that cytoarchitectural changes may also occur in a graded way. If true, this view would fundamentally shift our understanding of the functional localization of cortex that have dominated our thinking for the past 100 years. He also pointed out that the long pathways that connect to the local cortical circuits need to be considered as a whole, since activity in one brain region.

> 'will inevitably and invariably affect the function of several other parts, if not the whole of the cortex on the same or both sides. This is the very basic anatomical fact underlying what is perhaps the most important and essential function of the cortex, the integration and interpretation of information from several different sensory pathways and the formulation of a response to them.' (Powell, 1981)

12. Matter and minds

In 1895 Cajal had proposed histological mechanisms for association, ideation, and attention. As he later concluded this paper was not too successful, because, 'unfounded imagination has run riot in the whole venturesome lucubration.' However, one concept that survived was the law of neural avalanche, 'which is formulated thus: every peripheral impression received by the dendrites (sensory) of a single cell is propagated towards the centers in the fashion of an avalanche; or, in other words, the number of neurons concerned in the conduction increases progressively from the periphery to the cerebrum' (Cajal, 1937, p. 461). For Cajal, the pyramidal cells were the 'psychic' cells of the cortex and of course these existed in the largest number in the human cerebral cortex and were inevitably associated with cognition. Yet, when considering the origin of the intellect, Cajal reflected that it was not the sheer number of cerebral neurons that was the critical factor, but the richness of their connections. But even then, the exceptional qualities of the human brain seemed to require something more, and to pursue this idea, Cajal again exploited his insight that the Golgi stain works best on the fetal or neonatal brain. He gained access to a plentiful supply of fresh human fetuses from a nearby maternity hospital. After 2 years of intensive study, his conclusion was that the superiority of the human brain arose from,' the prodigious abundance and unaccustomed wealth of forms of the so-called neurons with short axons' (Cajal, 1937, p. 481). We would today call these the inhibitory neurons. Although he thought that these types might exist in primitive forms and sizes in the brains of higher mammals like dogs and monkeys, he considered the neurons like the double tufted cells, the basket cells and other 'dwarf elements' with short or with tufted axons, as being peculiar to the human cortex. However, Cajal did not study non-human primates, whose neocortex shares many features with *Homo sapiens*. Modern quantitative estimates of the proportion of inhibitory neurons in the different regions of cortex in different species come up with the same average: 15–20% of the cortical neurons are inhibitory neurons. Thus, the origin of Cajal's observations may lie more in the capriciousness of the

Golgi method than in some exceptional changes in the cellular composition of human cortex relative to other animals.

Cajal's fascination was also for the intracellular morphology. The then recently discovered neurofibrils, the Nissl granules and the Golgi apparatus (he was a bit upset that Golgi had beaten him to the first description) led him to speculate that traits like habit, talent, and genius may also have their origin in 'the most subtle warp of the nervous protoplasm' (Cajal, 1937, p. 460). Ironically, his success in developing the neuron doctrine meant that most neuroscientists after Cajal took the neuron as the basic unit of the brain and did not have much interest in what was beneath the cell membrane. However, the advances in molecular biology have re-inspired some theoreticians to re-explore the connection of intracellular processes to cognition. For example, the hypothesis of quantum consciousness of Hamerhof and Penrose proposes that tubulin, the basis of the microtubules that form the cytoskeletal structures, implements quantum computations that are intimately involved in generating consciousness (Hameroff, 2001; Penrose, 2001), although the mechanisms and processes have yet to be discovered. Quantum physical interactions are also at the heart of Beck and Eccles' solution to the origin of consciousness (Beck and Eccles, 1992). For them the critical interaction occurs at the synapse, where the release of synaptic vesicles is modulated by quantum physical interactions at the presynaptic grid (Beck and Eccles, 1992). Most physicists, however, take the view that all the physical processes in the brain are explainable in terms of the theories of classical physics (Koch and Hepp, 2006). Barlow has not taken the quantum leap, but he too has reconsidered the possible role of intracellular processes in performing cortical computations (Barlow, 1996).

Sherrington's experiments on binocular fusion had led him to the erroneous conclusion that neurons driven by right and left eye were not connected spatially, only temporally. The implication of this was that the brain circuits did not follow the reflex arcs he had revealed in the spinal cord, a view that Lorente de No later refuted. How was one then to understand the organization of the cerebral hemispheres? On the one hand there was the law of neural avalanche of Cajal, and on the other, the principle of convergence and the final common path of Sherrington. Put together, they gave rise to one explanation that there was a convergence centrally onto a single 'pontifical' nerve cell. This Sherrington rejected: 'Yet I cannot but think that its limitless postulation leads not so much to explanation of the high degree of units of the individual mind as to an ultimate fallacy which Professor James has trenchantly termed that of *the pontifical cell*' (Sherrington, 1906, p. 381). The alternative proposed by Sherrington was the mind as, 'a million-fold democracy whose each unit is a cell'.

In present times this debate goes on and the pontifical cell has transfigured into the grandmother cell. The idea that single neurons code for perceptually significant events has been developed over most of the long working life of Horace Barlow. His ground-breaking paper on feature detection by the frog retina led him inexorably to another Neuron Doctrine, his Central Dogma for neurobiology (Barlow, 1972). His mentor, E. D. Adrian had as early as 1920, proposed that sensations arising from the brain could be explained by the frequency of action potentials generated in the afferent nerve fibers of peripheral sense organs (see Adrian, 1932). Barlow cleverly integrated into his Neuron Doctrine a number of different streams of thought from psychology, information theory, ethology, and neurophysiology. The support for Barlow's Neuron Doctrine has waxed and waned as different fashions of coding in neural networks have come and gone. However, the experimental evidence that single neurons can exhibit highly selective responses to sensory stimuli is now well-established. The recent work in humans (Quiroga et al., 2005; Rutishauser et al., 2006) for example shows that the 'cardinal cells', as Barlow called them, are selective for faces and for people, words and objects associated with those faces. This is a major advance but leaves the relation between mind and brain still the philosophical conundrum it ever was.

Sherrington asked himself whether mind was a product of evolution and quickly came to the clear answer — 'yes'. 'Mind emerged from a general development of cell aggregates into animals with brains. Our parable would preach acceptance of energy and mind as a working biological unity although we cannot describe the how of that unity.' Perhaps this is unsurprising, given that Sherrington's philosophical beliefs have been described as 'evolutionary pantheism' (Granit, 1966). He saw Nature as a boundless unity. 'If a definition has to exclude as well as to include, it must lean on a logical boundary of what it defines; the term life has no such boundary from lifeless' (*Man* Chapter 3). Cajal, also struggling to understand how the brain produced cognition, was unsure how much could be attributed to the forces of evolution. He began his career as a hardened materialist: 'I boasted at that time, not without a certain amount of petulance, unshakably materialistic views,' he wrote in his autobiography (Cajal, 1937, p. 446). In the *Advice to a Young Investigator* (Cajal, 1999) he describes how early in his career he looked down the microscope at blood corpuscles flowing in a frog's mesentery and was suddenly struck with the conviction that, 'Life seems to be pure mechanism'. However, towards the end of his life he qualified that view. In an endnote added to his account of his epiphany in seeing the mesenteric blood flow he later wrote:

> 'Today I do not subscribe unreservedly to this mechanistic concept, nor do I adhere strictly to the physicochemical interpretation of life. The origin and morphology of cells, organs, heredity, evolution, and so on include phenomenon that depend on incomprehensible absolute causes, notwithstanding the vaunted promise of Darwinism and the postulates of Loeb's school of biochemistry' (Cajal, 1999, p. 64, end note p. 74)

13. Deeds and words

Both Cajal and Sherrington were artists, imaginative, widely read, charismatic, hugely energetic, enormously fluent with prose and poetry. In their work they ever sought the bigger picture, the integration of small facts into larger concepts. They had formidable powers of observation. Ragnar Granit recalled the time when he and Jack Eccles strode across the University Parks in Oxford one bright spring lunchtime after some morning rain. They met Sir Charles coming the other way. He stopped and asked them, 'have you noticed that all the earthworms this morning are crawling in the same direction? Phototropism or what?' (Granit, 1966). Sherrington reported on Cajal's drawing skills at the preparation for the Croonian Lecture:

> 'Such scanty illustrations as he vouchsafed for the preparations he demonstrated were a few slight, rapid sketches of points taken here and there — depicted, however, by a master's hand.' (Sherrington, In: Cannon, 1949, p. xiii)

Although Sherrington published many single-author papers, his laboratory saw a stream of bright students and distinguished visitors, Granit, Eccles, Penfield and Cushing among them, whom he inspired and who came to occupy chairs throughout Europe, the British colonies, and North America. This was a true 'neural avalanche'. Cajal too, founded a school of anatomy, made indelible as the Cajal Insitute in Madrid, where his ghost still sits at the microscope and watches over his heirs. Sherrington spent his scientific life in the intellectual capitals of the world. Cajal by contrast had to make his own way and create single-handedly an environment where he could compete on an international scale, which he did brilliantly.

In his memoir on Cajal, Sherrington described a striking quality of Cajal's mind, which to a large extent was a counterpart to Sherrington's inclinations to metaphor:

> 'A trait very noticeable in him was that in describing what the microscope showed he spoke habitually as though it were a living scene……The intense anthropomorphism of his descriptions of what the preparations showed was at first startling to accept….We must, if we would enter adequately into Cajal's thought in this field, suppose his entrance, through his microscope, into a world populated by tiny beings actuated by motives and strivings and satisfactions not very remotely different from our own…. Listening to him I asked myself how far this capacity for anthropomorphizing might not contribute to his success as an investigator. I never met anyone else in whom it was so marked.' (Sherrington, In: Cannon, 1949)

Anyone browsing through the early scientific literature that is the foundation of modern neuroscience will soon discover that in the formulaic, bland, and often semi-literate writing of contemporary science, we have lost an undeniably human presence. The passionately engaged, literate author, in energetic pursuit of nature's secrets, is a now an endangered species. Both Sherrington and Cajal may have written too many words, their style may now be dated, and their prose too self-consciously purple for modern tastes. But over their long scientific careers they provided us with astonishing discoveries and recorded them in vivid and memorable images. Their reflections on what they had found was often profound. Both projected a sense of wonder about nature and were, in the words of Cajal, 'like the entymologist in pursuit of brightly colored butterflies, [hunting] in the flower garden of the grey matter, cells with delicate and elegant forms, the mysterious butterflies of the soul, the beating of whose wings may some day – who knows? – clarify the secret of mental life' (Cajal, 1937, p. 363).

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