TIMELINE

Insights into the life and work of Sir Charles Sherrington

Zoltán Molnár and Richard E. Brown

Abstract | Much of the original historical data behind the greatest discoveries in neuroscience are now lost. However, a recently rediscovered box of histological slides belonging to Sir Charles Sherrington, a pioneer in spinal cord and motor control research, has survived at the University of Oxford since 1936. Sherrington coined the term 'synapse', developed the concept of inhibition in neuronal function, demonstrated the integration of sensory and motor actions of the nervous system, and examined the synaptic activity of single neurons and their integration into neuronal circuits. Here, we explore Sherrington's lifetime of discoveries, with reference to histological specimens from his box of slides.

Sir Charles Sherrington was one of the outstanding physiologists of his time. He coined the term 'synapse'[1], established the importance of inhibition in neuronal function[2] and wrote the first book that integrated the sensory and motor actions of the nervous system[3]. Furthermore, Sherrington and his colleagues made numerous experimental and conceptual advances towards the definition of neuronal circuits and towards our understanding of the properties of synaptic activity. The concepts of the motor unit, inhibition and convergence are now so deeply embedded in our thinking that it is difficult to imagine what the field of systems neurophysiology was like before Sherrington[4,5].

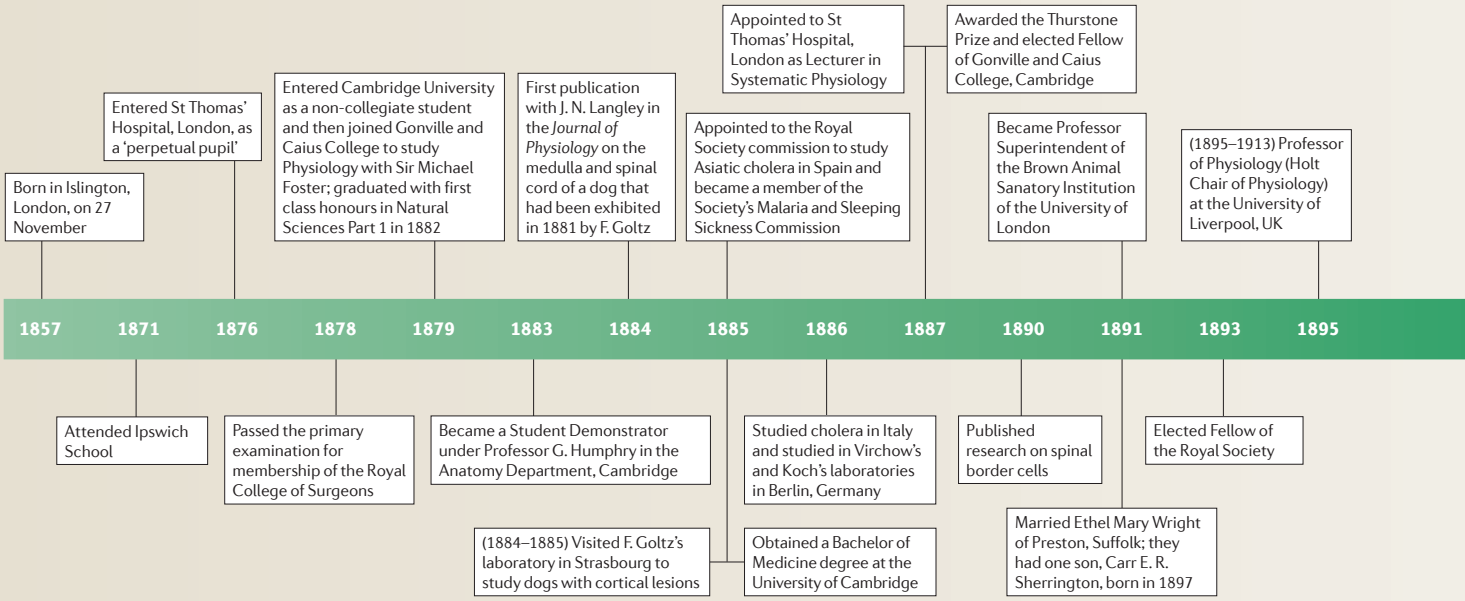
Sherrington's work on tone (posture), including decerebrate rigidity, the ipsilateral flexor reflex, the crossed extensor reflex and the stretch reflex (including the tendon jerk reflex), has been instrumental to our understanding of how neuronal circuits operate[3]. Sherrington also proposed the law of reciprocal innervation, which states that when a muscle contracts there is a simultaneous inhibition of its antagonist. These ideas led Sherrington to establish the concept of active inhibition, which he regarded as essential for coordinated movement[2]. His work on spinal reflexes and inhibition was recognized with the Nobel Prize in Physiology or Medicine in 1932 (TIMELINE).

Many of Sherrington's papers and much of his scientific correspondence are held in archives in the Sherrington Room of the Department of Physiology, Anatomy and Genetics at the University of Oxford, UK (see The National Archives website) and in an archive set up by William Gibson at the University of British Columbia (UBC) in Vancouver, Canada (see the UBC Library website). Some of his laboratory apparatus, as well as some of his personal belongings, have survived and are exhibited at the University of Oxford[6] (Supplementary information S1 (figure)). In addition to these artefacts, a wooden box bearing Sherrington's name and containing 21 drawers of glass microscope slides was recently rediscovered (Supplementary information S1 (figure)). This box has been kept on various shelves and under benches in several offices, in the Physiology Department at the University of Oxford since Sherrington retired in 1936. The glass histology demonstration slides are of neural and other tissues, stained and labelled, from work done throughout Sherrington's life. The contents of the box are now available on the University of Oxford website. The discovery of these slides provided us with the motivation for a new assessment of Sherrington's life and work. In this article, we highlight the histological work that provided the basis for many of Sherrington's neuroanatomical and neurophysiological studies; from his early work on cortical localization, bacteriology and haematology to the more widely known work on spinal cord circuits, motor unit convergence and muscle spindles.

Early work on cortical localization

Sherrington's first research experience took place while he was a medical student at the University of Cambridge, UK, where he worked with his college tutor, John Newport Langley, from 1882 to 1884. During this period cortical localization was becoming the central issue in neurology[7]. At the 1881 meeting of the Physiological Section of the International Medical Congress, held in London, there was a debate on the localization of function in the cortex between Friedrich Leopold Goltz and David Ferrier[8,9]. Ferrier showed that a monkey with lesions to the motor cortex exhibited localized paralysis, which supported the idea that motor functions are localized to particular cortical regions. By contrast, Goltz showed that a dog that had similar lesions exhibited very little paralysis or sensorimotor deficit. This suggested that there was no localization of motor and sensory functions in the cortex[7] (Supplementary information S2 (figure)). It was agreed that a committee of four scientists — William Gowers, Edward Emanuel Klein, Edward Albert Schäfer and John Newport Langley — would examine the brains of these animals. Sherrington worked on the dog brain with Langley[10], and at the 1884 meeting of the Physiological Society, Langley and Sherrington[11] presented their analysis of the degeneration of the nerve tracts in the right half of the medulla oblongata and the spinal cord of Goltz's dog. They correlated the pattern of neural degeneration with the location of the lesions. The results demonstrated that not all of the corticospinal projections in this dog had degenerated and that the observed motor functions were produced by the projections that were still intact. The work therefore supported Langley's observations of localization of motor function in the monkey[7].

Timeline | **The life and work of Charles Scott Sherrington**



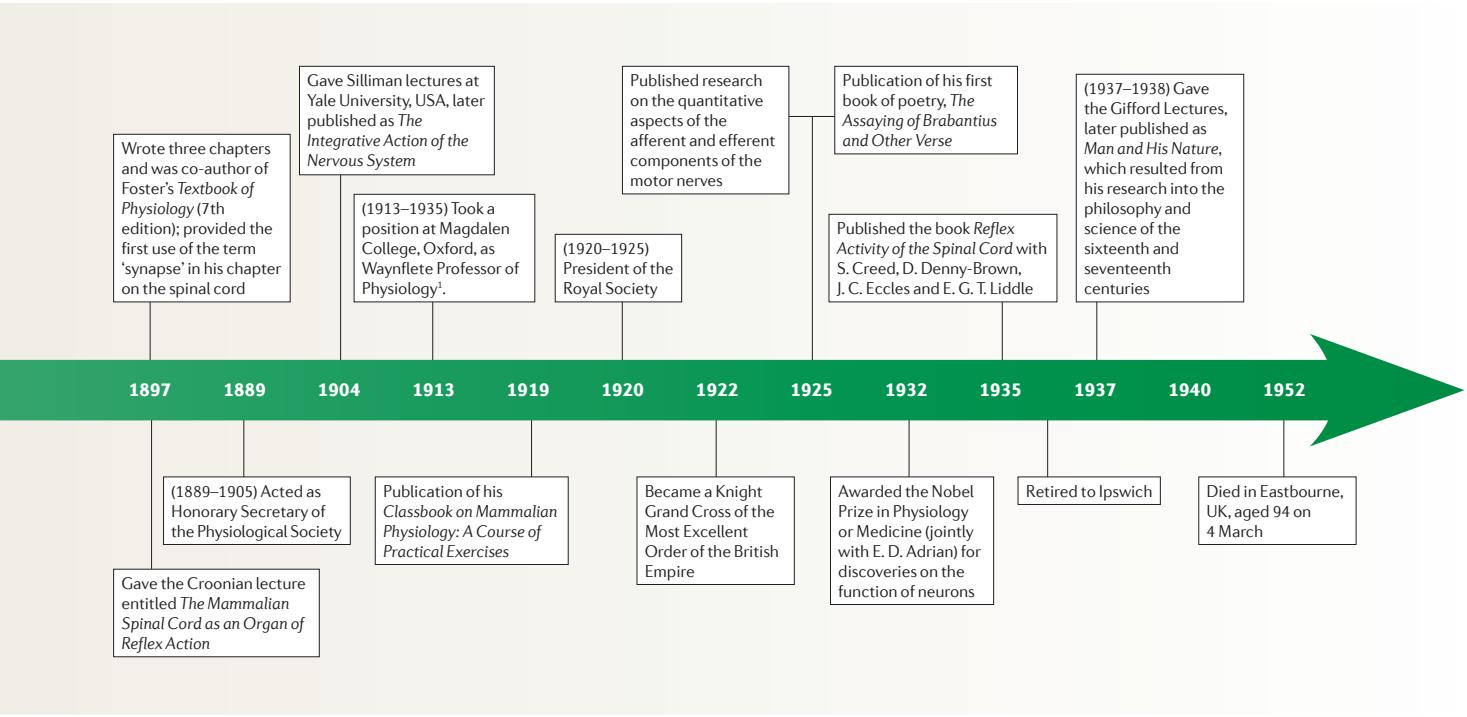
During their study of the brain of Goltz's dog, Langley and Sherrington[11] found neural degeneration "of a peculiar kind", which they thought might be due to tertiary degeneration, as this dog had received multiple operations at different times. Sherrington went to Goltz's laboratory in Strasbourg in the winter of 1884–1885 to determine whether the patterns of nerve degeneration in the spinal cord varied with the site of the initial lesion in the 'cord-area' of the cortex (his preferred term for the area of the motor cortex with projections to the spinal cord)[12]. He examined the degeneration of the spinal cord in dogs for up to 11 months after the removal of the cortical cord area, and showed that cortical lesions elicited widespread degeneration in a specific sector of the descending corticobulbar and corticospinal pathways and that the pattern of degeneration depended on the time since the lesion was made[12] (Supplementary information S2 (figure)). The results confirmed that some but not all of the descending motor pathways had been damaged after Goltz's original lesions. This early exposure to spinal cord research influenced Sherrington for the rest of his career. Although the recently rediscovered box of his slides does not contain sections relating to these particular experiments, there are a number of preparations of cat brains in which various lesions were performed and degenerated fibres stained, illustrating Sherrington's continued interest in this area of research.

Sherrington returned to work on cortical localization with Albert S. F. Grünbaum during his years at the University of Liverpool, UK (1895–1913), and produced the first maps of cortical localization of motor function in primates[13,14] (Supplementary information S2 (figure)). Further evidence of his ongoing interest in the field of cortical localization and ongoing contact with colleagues with similar interests can be found in the box of slides. For example, the box contains samples originating from Gustav Theodor Fritsch, a German anatomist and physiologist (Supplementary information S3 (figure)) who is best known for his work with the neuropsychiatrist Eduard Hitzig on the use of electrostimulation to determine the sites of motor control in the brain[15].

Bacteriology and haematology

Sherrington also contributed to research in bacteriology and haematology in the early stages of his career, although his work in these areas is not as well known today as his discoveries in neuroscience (Supplementary information S4 (figure)). In the summer of 1885, Sherrington, Charles S. Roy and J. Graham Brown were sent by the University of Cambridge and the Association for Research in Medicine to investigate an outbreak of cholera in Spain, where they performed 25 post-mortem examinations and described a microorganism (Schizomycetes) that they claimed was found in all 25 cases[16] (Supplementary information S4 (figure)). In 1886, Sherrington visited Venetia and Puglia in Italy, where he studied another 25 fatal cases of cholera. He conducted his microscopical investigations of these cases in the laboratory of Rudolf L. K. Virchow in Berlin, Germany, where he found that: "The comma-shaped bacilli lie in the fundi of the tubular glands of, especially, the ileum, and in the tissue in which those glands are imbedded in the immediate vicinity of the glands."[17]

Sherrington's box of slides contains a single section of cholera autopsy material, which could be related to the two publications that Sherrington produced during this time (Supplementary information S4 (figure)). In addition, the box contains slides showing haematological preparations, blood, pathological changes in leucocytes, blood clotting and bone marrow, indicating Sherrington's continued interest in these issues throughout his career (Supplementary information S4 (figure)). In 1891, Sherrington was appointed Professor Superintendent of the Brown Animal Sanatory Institution of the University of London, UK, following the departure of John Burdon Sanderson[18]. It was during this time that Sherrington and Armand Ruffer developed a diphtheria vaccine that was first used in 1894 by Sherrington on his own nephew[19].



Spinal cord research

From the time that he was a student at Cambridge, Sherrington was exposed to the work of Walter Holbrook Gaskell (1847–1914) (FIG. 1a). It was probably due to Gaskell's influence that Sherrington shifted his research interests from the cerebral cortex to the spinal cord. Sherrington[20] later wrote: "My own work began by chance at the wrong end — the cortex-pyramidal degenerations, etc. It was certainly through Gaskell that I very soon felt that. One could not talk with him long without realising that the cord offered a better point to attack physiologically." Indeed, the majority of the histological sections in the box at the University of Oxford are from the spinal cord.

When he returned from Germany in 1887, Sherrington was appointed a Fellow of Caius College, University of Cambridge, and a lecturer in physiology at St Thomas' Hospital in London, where he used the Physiological Laboratory to continue his work on the spinal cord of the dog. In addition, Sherrington conducted post-mortem examinations of the spinal cords of two patients from St Thomas' Hospital. In the first case, Hadden and Sherrington[21] traced the degenerating motor fibres in the spinal cord of a 63-year-old man who died following a haemorrhage in the "motor part of the left internal capsule". They showed that the pattern of spinal axon degeneration agreed with observations made on a dog with lesions in the same area. In the second case[22], they were able to trace the connection of the anterolateral spinal tract to the cerebellum in a 35-year-old man who died following a prolonged bout of back pain and inability to walk. These studies allowed Sherrington to compare the degeneration of spinal nerves in humans with his observations of degeneration in the dog brain. Sherrington's continued interest in the spinal cord is reflected in the slides from the box, which show human cases of syringomyelia and tabes dorsalis as well as spinal cord and medulla preparations from monkeys, cats and humans (Supplementary information S5 (box)).

Spinal border cells

Border cells were originally described by Gaskell[23], who gave the name to the neurons scattered at the periphery of the lateral column in the spinal cord of the alligator. In Sherrington's box there are several spinal cord slides with labels pointing to cells at the edge of the spinal cord (or spinal border cells) (FIG. 1c,d). These are the sections that led Sherrington[24], while working at Cambridge and at St Thomas' Hospital, to describe a group of large nerve cells in the ventrolateral grey matter of the lumbar spinal cord of monkeys and cats as 'outlying nerve cells'. Later, in one of his last publications from the University of Oxford[25], he called these neurons 'spinal border cells' because they were located predominantly along the lateral border of the ventral horn. Sherrington was interested in these cells because he suspected that they caused the sustained tonic inhibition of extensor muscle α-motor neurons in the cervical enlargement. Only much later were these cells identified as spinocerebellar tract neurons[26]. Acute spinal injuries caudal to the cervical enlargement and cranial to border-cell neurons result in sudden deprivation of tonic inhibition of cervical enlargement neurons and cause their excitation. This excitation results in the extensor hypertonia observed in the thoracic limbs. Because Schiff[27] described this syndrome in amphibian spinal cord before Sherrington, it is usually referred to as the Schiff–Sherrington phenomenon[28]. This work provides an excellent example of the way Sherrington combined anatomical and physiological approaches to understand the interactions among spinal circuits that regulate reflex action by inhibition.

Spinal cord circuits

During the early stages of his work on spinal reflexes of rhesus monkeys at Cambridge, St Thomas' Hospital and later at Liverpool, where he held the position of Holt Professor of Physiology (1895–1913), Sherrington laid the anatomical and physiological foundations of our current understanding of spinal cord circuits by carefully describing the distribution of efferent fibres in spinal nerves of the lumbosacral plexus of frogs, rats, rabbits,

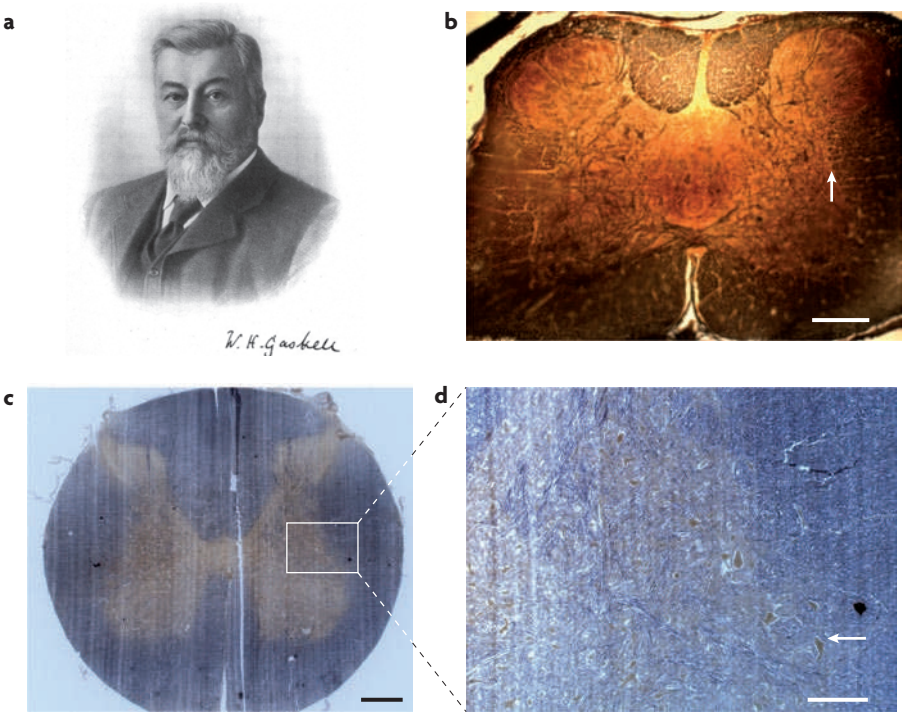


Figure 1 | **Early work on the border cells of the spinal cord. a** | Walter Holbrook Gaskell, who originally described 'border cells' at the periphery of the lateral column in the spinal cord of the alligator[23]. **b** | A preparation of an amphibian spinal cord, taken from the box of Sherrington's slides found at the University of Oxford. The outlying border cells of Gaskell are more apparent in the white matter surrounding the grey matter. The arrow indicates the white matter–grey matter boundary. Sherrington described similar cells in mammals, including in humans, dogs and bonnet monkeys[24]. The scale bar represents 200 μm. **c** | A photograph of one of the slides labelled "Spinal border cells". These slides may be related to Sherrington's publications on this subject[24,25]. Sherrington identified isolated nerve cells in the white matter of the spinal cord of rabbits, cats, dogs, calves, monkeys and humans. These were present not only in the deeper portions of the lateral column but also in the anterior and posterior columns. The scale bar represents 500 μm. **d** | High-power view of the region indicated by box in **c**. The arrow indicates an example of a cell at the white matter–grey matter boundary. The scale bar represents 200 μm. Image **a** is reproduced, with permission, courtesy of the Wellcome Library, London, UK.

cats, dogs and rhesus monkeys[29]. Using platinum electrodes he stimulated the ventral efferent spinal roots of rhesus monkeys and cats and examined the movements produced. In this way, he mapped out the muscles activated by each branch of the efferent spinal nerves and showed that the contraction of each of the limb muscles could be evoked by stimulation of two or three different spinal roots[29]. He also showed that the cutaneous sensory fields of the afferent spinal nerves were contiguous, and he coined the term 'sensory spinal skin-field' to describe the skin area activating each sensory spinal nerve branch[30]. In this way, he was able to define both the sensory and motor aspects of the spinal reflex. When he ablated areas of the motor cortex, he could determine exactly which spinal nerves were affected by determining sensory and motor deficits in the reflexes.

Sherrington's use of the 'successive degeneration method' which he developed with Ernest Edward Laslett at the Thompson Yates Laboratory of Physiology in Liverpool[31], enabled him to make two spinal transections at different times and then analyse the degeneration caused by the second cut. This technique allowed him to identify afferent arcs from the sensory receptors in the skin to the spinal cord and efferent pathways from motor neurons to the flexor muscles, which are involved in the scratching reflex, the shaking reflex and a number of other reflexes in dogs[3,31]. This method resulted in Sherrington's development of the 'final common path' concept for the efferent motor nerve stimulation of muscles[32]. This research is reflected in the superb preparations of dorsal root ganglion cells and sympathetic paravertebral ganglion cells that are found in the box of slides (FIG. 2).

Inhibition and decerebrate rigidity

The concept of reciprocal inhibition was one of Sherrington's most important discoveries. This work began with his careful description of the anatomy of motor neurons and their innervation of muscles when he was at St Thomas' Hospital[29]. He continued to analyse the action of antagonistic muscles[33] and developed the concept of reciprocal innervation of these muscles while he was at Liverpool[34] and Oxford[35]. From this work he was able to show that contraction of a muscle is accompanied by the simultaneous inhibition of the antagonistic muscles. This work culminated in his Nobel Prize lecture on Reciprocal Inhibition in 1932 (REF. 2).

Decerebrate rigidity was discovered in 1896 when Sherrington was at the University of Liverpool and fully described in 1898 (REF. 36). Sherrington noted that following removal of the cerebral hemispheres there was a rigidity of certain joints, including the elbow, knee and neck. He found this phenomenon in monkeys, dogs, cats, rabbits and guinea pigs and determined that it was due to spasms of the extensor muscles as a result of afferent stimulation from the sensory fibres in the muscle itself. This rigidity could be inhibited by stimulating antagonistic muscles directly or by stimulating brain regions that control these muscles, providing a clear example of the power of reciprocal inhibition.

Motor unit convergence

Once Sherrington had worked out the pattern of motor neuron stimulation of muscles, defined the distribution of the motor nerve roots to each muscle (while at St Thomas' Hospital in 1892)[29] and understood the actions of antagonistic muscles (also discovered while at St Thomas Hospital in 1893 (REF. 30) and later studied at Liverpool[4,34]), he was able to use his methods of successive degeneration[31] and electrical stimulation to determine the final common path of neuromuscular stimulation[32]. This allowed him to determine that two or more efferent motor nerve endings converge onto one muscle fibre, a breakthrough he made at the University of Oxford and presented in his Ferrier Lecture in 1929 (REF. 37).

There are several serial nerve sections in Sherrington's box (FIG. 3c). These sections were prepared when he worked at the University of Oxford (1913–1936) and were used for three main purposes: to determine the site of nerve-fibre branching in relation to the neuromuscular endplates, to follow the path of the nerve fibres to muscle tissue

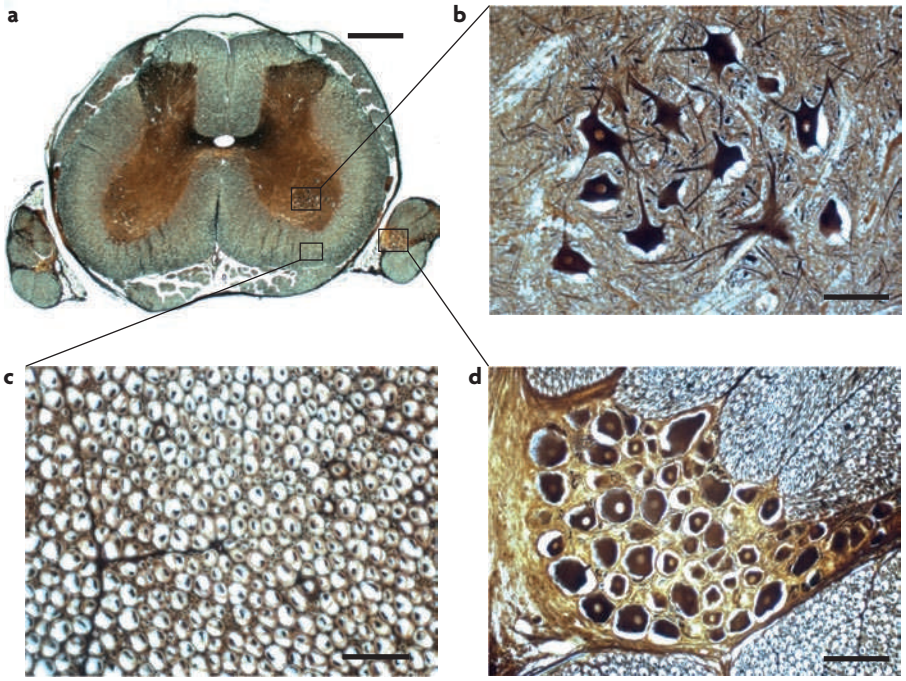


Figure 2 | **Histological preparation of cat spinal cord with ventral horn motor neurons, dorsal root ganglion and paravertebral sympathetic ganglion. a** | Histological section of cat lumbar spinal cord, stained with Cajal's silver stain. The slide is from Sherrington's box, found at the University of Oxford. The scale bar represents 1 mm. **b** | High-power view of ventral horn motor neurons from the region indicated in **a**. The scale bar represents 100 μm. **c** | High-power view of fibres in the white matter in **a**. The scale bar represents 50 μm. **d** | High-power view of the paravertebral sympathetic ganglion in **a**. The scale bar represents 100 μm. These slides reveal the extremely high quality of histological analysis in Sherrington's laboratory. Sherrington probably performed most of the analysis by himself.

and muscle spindle organs and to estimate the proportions of afferent and efferent nerves by ablating the sensory dorsal root ganglia and quantifying the degenerating nerve fibres (FIG. 3e,f). Sherrington examined the number of fibres throughout the length of the nerve to establish the size of the motor unit — that is, the number of muscle fibres innervated by the branches of a single motor neuron — in different muscles, and the overlap between the innervation patterns of different motor nerves in the muscle. In addition, Sherrington observed increased muscle contraction after simultaneous stimulation of two efferent motor neurons converging on a muscle fibre. This effect was related to the 'subliminal fringe' effect[38], which occurs when subthreshold activation of muscle fibres facilitates suprathreshold stimulation to increase muscle contractions. Based on these findings, Sherrington[37] emphasized that several motor neurons innervate a particular muscle and that several afferent fibres converge on an individual motor neuron in the spinal cord. His combined anatomical and physiological observations enabled him to correlate neural convergence with the functional interactions between various nerves and determine how the multiple innervations could elicit a motor response as an integrated response of several components of the circuit. Sherrington established the concept of facilitation of synaptic activity by showing that although a single stimulus was insufficient to fire a motor neuron, subthreshold firing of two or more motor neurons could summate and facilitate motor neuron firing. Through his painstaking dissections, he could show which nerves interacted in the control of each muscle.

Muscle spindles

Sherrington's work emphasized that muscle is an important sensory organ. In the box are several slides containing serial nerve sections that were dissected after 2 weeks of degeneration following the removal of the dorsal root ganglion and stained with osmic acid (FIG. 3f). By removing the sensory spinal roots and allowing the motor nerves to remain intact, Sherrington concluded[39] that only 60% of the fibres in the muscle nerves were motor axons, whereas 40% of the fibres originated from the dorsal root ganglion and carried sensory input from the muscles to the spinal cord; he therefore showed that muscles are also sense organs. Sherrington traced nerves to the muscle and examined the concentration of muscle spindles and sensory receptors in the muscle, and found great variability between species[39]. In his 1924 Linacre Lecture, Sherrington postulated that small- and large-diameter motor neuron axons might serve different functions[40], although this was missed by subsequent studies[5]. Indeed, the functional significance of the reflex arc — which consists of small anterior horn nerve cells (γ-motor neurons) and their smaller diameter fibres (intrafusal fibres, which elicit contraction of intrafusal fibres of the muscle spindle and thereby initiate afferent impulses to motor neurons) — was not understood until much later[4,41]. The role of the γ-motor neurons and of their actions on muscle spindles subsequently became the subject of intense studies by Sherrington and others[42].

Although Kühne[43] was the first to describe the muscle spindle, Sherrington was one of the first to emphasize the sensory role of the muscles in tonus and posture. The discovery of sensory fibres in muscle spindles provided Sherrington with evidence that when a muscle is stretched, it sends proprioceptive information on the state of the muscle length to the spinal cord, which allows the animal to regulate its motor movements[38]. While at St Thomas' Hospital, Sherrington[36] also showed that sensory fibres from the muscles have an important role in decerebrate rigidity. These interests are reflected in several preparations of afferent nerve endings and muscle spindles that were found in Sherrington's box of slides. Indeed, many of the slides illustrate these receptors, including the Paccinian corpuscle, Meissner organ, Golgi tendon organ and muscle spindle (FIG. 4c,d), some of which may have contributed to Sherrington's publication 'Further note on the sensory nerves of muscles' from 1897 (REF. 57).

When studying the afferent nerve endings in muscle, Sherrington contacted Angelo Ruffini (1864–1929), a lecturer in histology at the University of Bologna, Italy, who had published papers on nerve endings in muscle[44,45]. Ruffini had sent copies of his papers to Sherrington in 1896 and a correspondence developed between them[46]. From these letters we know that in 1898 Ruffini sent Sherrington a box of microscopical preparations of muscle spindles and cutaneous receptors in the skin, which Sherrington wanted to use for his chapter on cutaneous receptors in Schäfer's *Textbook of Physiology*[47]. We found these 11 slides

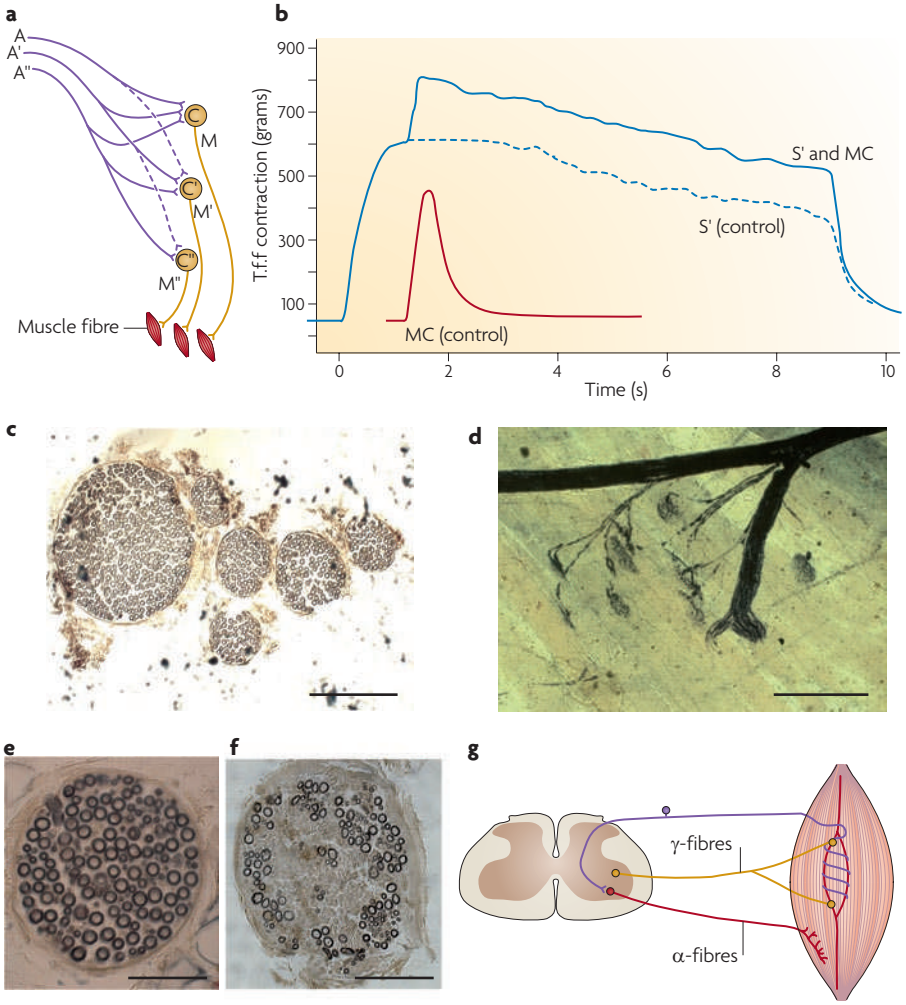


Figure 3 | **Fundamental concepts of muscle innervation. a** | Sherringtons schematic diagram[35] illustrating the convergence of afferent input on three motor neurons in the spinal cord. Three afferent nerves (A, A′ and A″) send multiple terminal branches to multiple motor neurons (C, C′ and C″). Each nerve converges on a motor neuron with a different synaptic density (solid and broken lines illustrate projections with different strengths). Motor neurons innervate muscle fibres in motor units (M, M′ and M″). **b** | Recordings by Denny-Brown and Sherrington in 1928 (REF. 38) of the contractions of the tensor fasciae femoris (T.f.f.) muscle elicited after the stimulation of the internal saphenous (S') or musculocutaneous (MC) nerves in cat spinal cord that has been separated at the level of the midbrain. Increased muscle contraction was observed after simultaneous stimulation of both nerves (S' and MC). **c** | Photomicrograph of an osmium-stained cross section through the nerve supplying the rectus femoris muscle in a cat, from Sherrington's box of slides found at the University of Oxford. This is one of a number of serial sections used to trace the fibres along the length of the nerve. The scale bar represents 200 μm. **d** | A slide from Sherrington's box showing silver-impregnated phrenic nerve branches and neuromuscular end-plates from the diaphragm of a cat. The slide shows that individual fibres detach from the fascicles as they approach the muscle and neuromuscular junctions. This end-plate has been photographed from the same slide as FIG. 4d. The slide was placed next to those of Ruffini, but it does not carry Ruffini's signature. The scale bar represents 100 μm. **e** | Cross section through a nerve stained with osmic acid. The nerve contains fibres of various diameters (including α- and γ-fibres). Sherrington collected serial sections along the nerve and used them to quantify the individual fibres to assess branching along their path. The scale bar represents 50 μm. **f** | Cross section of a nerve prepared 2 weeks after the removal of the dorsal root ganglion. Observation of the proportions of afferent and efferent nerves present after ablation of the dorsal root ganglion on these sections contributed to understanding of the reciprocal innervations of the muscles. Eccles and Sherrington[54] identified a large sensory component of the nerve that degenerated after dorsal root ganglion removal, and two different populations of efferent nerve fibres (α- and γ-fibres) that survived after elimination of the sensory component. The scale bar represents 50 μm. **g** | Schematic overview of the innervation of extrafusal and intrafusal muscle fibres by α- and γ-fibres[52]. Part **a** is reproduced, with permission, from REF. 35 © (1925) Royal Society Publishing. Part **b** is modified, with permission, from REF. 38 © (1928) Blackwell Publishing. Part **g** is modified, with permission, from REF. 55 © (2008) Churchill-Livingstone.

in Sherrington's box (FIG. 4g). Sherrington arranged to have Ruffini's work published in the *Journal of Physiology*. This paper[48] had three plates showing the tissues on the slides that he sent to Sherrington. Ruffini identified them by self-testing and excised these receptors from his own skin (FIG. 4g,h).

The letters between Ruffini and Sherrington are of remarkable interest because they tell a wonderful story of the scientific associations between investigators in different countries. They provide a valuable documentation of the true spirit of science as it was practiced around the turn of the twentieth century[46]. Sherrington and Ruffini corresponded until 1903 and continued to exchange a number of small gifts. The greatest gift that Ruffini provided for Sherrington was their collaboration on the anatomy of the muscle spindles and sensory endings, and Sherrington provided strong support for Ruffini's efforts to publish and promote his scientific work.

Sherrington as a teacher

Sherrington successfully combined academic research and teaching, and was a respected and beloved teacher to his students, many of whom have written fondly about their time in his laboratory[4,5,49,50,51]. Although it has been noted that his lectures often included too much detail and were not as streamlined as most medical students of that time would have liked[52], Sherrington was very popular and was famous for his hospitality[5]. He prepared a number of sophisticated laboratory exercises for his students and published these in a laboratory manual[53]. The experimental illustrations and drawings set the standards for physiology teaching even today. Several of the trays of slides in Sherrington's box contain histological demonstration material used for teaching, some of which are from Sir John Burdon-Sanderson, the first Waynflete Professor of Physiology at Oxford (1882–1905). Others were added by Derek Denny-Brown, who worked with Sherrington at Oxford (1924–1928). Some slides carry the inscription of Santiago Ramón y Cajal; however, this is likely to refer to the method used for staining rather than the origin of the slide (Supplementary information S6 (figure)).

Conclusions

Our examination of the histological slides in Sherrington's box has shown us that, even 100 years later, archival materials can be used for establishing links between original preparations and publications. The slides show the breadth and depth of Sherrington's work and allow us to interpret the original

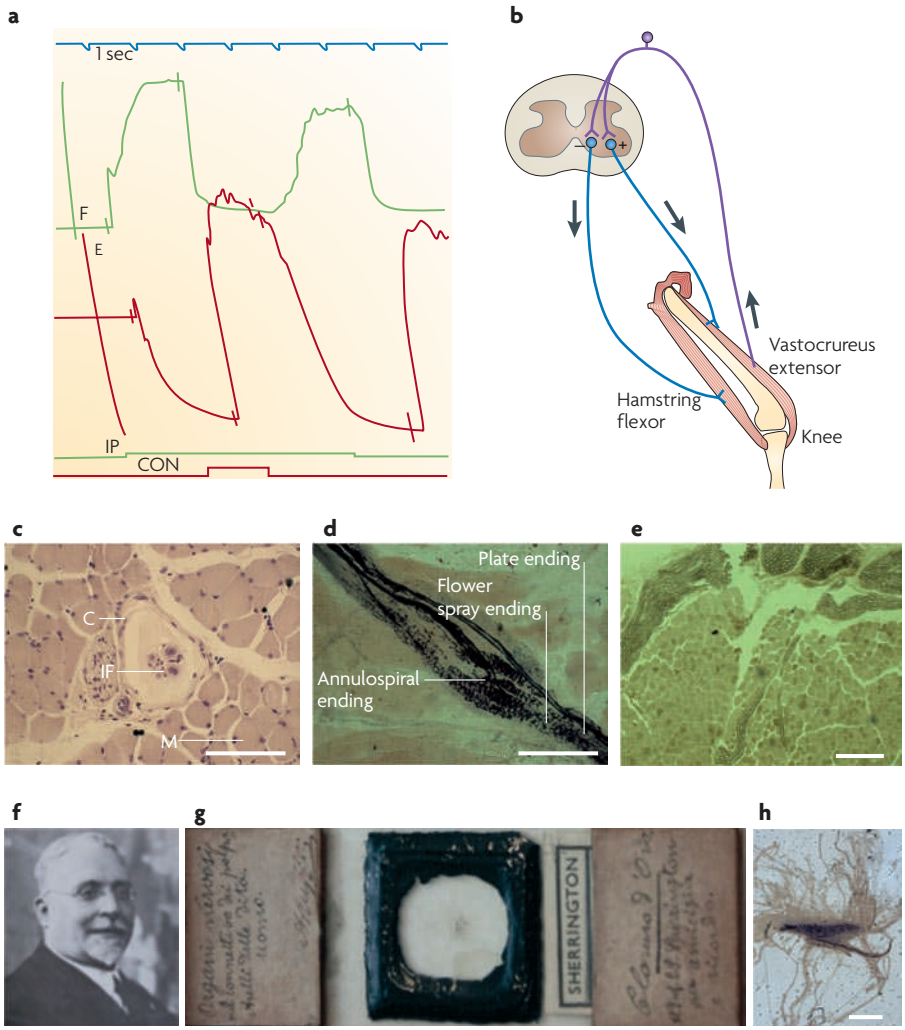


Figure 4 | **Anatomical and physiological dissection of spinal reflexes. a** | The reciprocal effects of antagonistic muscles of the knee[56]. The upper traces are recordings made from the flexor (F) and extensor (E) muscles of the knee. The lower part of the panel indicates the duration of stimulation of the ipsilateral (IP), and contralateral (CON) peroneal nerves which connect to the ipsilateral flexor and contralateral extensor respectively. Contralateral peroneal nerve stimulation inhibited the ipsilateral flexor and activated the contralateral extensor. **b** | Schematic drawing of a spinal circuit proposed to explain the excitation of the extensors and inhibition of flexors by afferent nerves of the ipsilateral extensor[56]. **c** | Cross section through a methylene-blue stained muscle and muscle spindle from the box of Sherrington's slides that was rediscovered at the University of Oxford. Typically, muscle fibres (M) surround a spindle with the spindle capsule (C) enclosing intrafusal fibres (IF) of varying diameters. The scale bar represents 100 µm. **d** | High-power photomicrograph of a silver-impregnated muscle spindle from the same cat phrenic nerve preparation shown in FIG. 3d. The three types of endings found in muscle spindle (annulospiral endings, flower spray endings and plate endings) are shown. Sherrington did not routinely use silver-impregnation in these muscle preparations, suggesting that this slide might have been a gift from Ruffini. The scale bar represents 200 µm. **e** | Photomicrograph of nerve fibres entering the right inferior oblique eye muscle of a monkey. The slide is taken from Sherrington's box. Such slides may be related to an article published in 1897 (REF. 57) in which the relatively small numbers of muscle spindles in the eye muscles of monkey were reported. The scale bar represents 200 µm. **f** | Angelo Ruffini (1864–1929). Ruffini and Sherrington developed a close friendship through correspondence. They exchanged scientific ideas, publications, histological preparations and a number of small personal gifts[46]. **g** | Photomicrograph of one of the 11 slides sent by Ruffini from the University of Bologna to Sherrington in Oxford in 1898. The hand-written label reads: "Organi nervosi nel connettivo del polpa anelli delle dita uomo." ("Nerve ending in the connective tissue from the human finger.") Ruffini dedicated this slide to Sherrington: "Per Prof C.S. Sherrington, per amicizia e ricordo." Ruffini identified the sensory ending by self-testing and by excising these receptors from his own skin. **h** | High-power image from the slide shown in **g** with silver-impregnated sensory organ, now called the Ruffini ending. The scale bar represents 200 µm. Part **a** is reproduced, with permission, from REF. 56 © (1913) The Physiological Society. Part **f** is reproduced, with permission, from REF. 58 © (1979) Piccin Editore.

research materials that have provided the foundations of modern systems neuroscience. In addition, they enable us to appreciate the number of species and techniques used by Sherrington and his colleagues and the very high quality of their histological work. Images taken of slides from this box could be used for practical neuroanatomy teaching today. The slides also give an insight into Sherrington's rich interactions with colleagues, collaborators (including Ruffini and Fritsch) and students (Denny-Brown, Gibson and Eccles). They point to lesser-known areas of Sherrington's research in haematology, bacteriology and sensory receptors, in addition to his more famous work on the spinal cord. The examination of these slides could provoke further insights into the history of systems neuroscience and discussion of Sherrington's contributions to neuroscience. By establishing a web-based repository of Sherrington's slides, we hope to present Sherrington's work to a wider public and facilitate further analysis and online interpretation of this material.

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OPINION

Modelling neurodegeneration in *Saccharomyces cerevisiae*: why cook with baker's yeast?

Vikram Khurana and Susan Lindquist

Abstract | In ageing populations, neurodegenerative diseases increase in prevalence, exacting an enormous toll on individuals and their communities. Multiple complementary experimental approaches are needed to elucidate the mechanisms underlying these complex diseases and to develop novel therapeutics. Here, we describe why the budding yeast *Saccharomyces cerevisiae* has a unique role in the neurodegeneration armamentarium. As the best-understood and most readily analysed eukaryotic organism, *S. cerevisiae* is delivering mechanistic insights into cell-autonomous mechanisms of neurodegeneration at an interactome-wide scale.

Neurodegenerative diseases are among the most pressing public health challenges facing the ageing populations of developed nations. For more than a century, the study of neurodegeneration was confined to relating the devastating clinical phenotype of these diseases to their post-mortem neuropathology. Although the neuropathologic observations have been instrumental in identifying pathologic proteinacious aggregates and patterns of differential neuronal vulnerability, they cannot distinguish causal from epiphenomenal factors in disease pathogenesis. Over the past 15 years we have gained tremendous