In expressing a liking for people who are ‘witty, world-wise, opinionated, argumentative, iconoclastic, intolerant of fools, and original to the level of eccentricity’, Patrick (‘Pat’) Wall (1925–2001) was largely describing himself (see The Guardian 16 August 2001; Alex May, Oxford Dictionary of National Biography, Jan 2005). His opinions were often couched in forthright terms, to the amusement of many and at the cost of a few; they espoused leftwing politics and the opposition of authoritarian doctrines. Over time, Wall substituted socialism with anarchism. He opposed the treatment of prisoners in Northern Ireland by the British Army; and was an outspoken member of the Gardiner Committee on the effects of rubber bullets. Pat Wall studied pain, deriving novel mechanistic concepts that advanced knowledge on plasticity and functions of the spinal cord. His legacy is the gate control theory of pain, developed with Ronald Melzack (see Brain 1962; 84: 331–56). This was influenced by his observation that the intensity of pain is unrelated to the amount of tissue damage, and by studies on phantom pain and causalgia in the Yom Kippur War (1973). His work led to the development of transcutaneous electrical nerve stimulation and dorsal column stimulation. Wall’s scientific doctrine was to choose a subject ignored by others, write a book on it, and start a journal. To that end, he was the first editor-in-chief of the journal Pain (founded in 1975), co-editor with Melzack of the definitive Textbook of Pain (1983); and author of The Challenge of Pain (1982). He also wrote a novel [TRIO – The Revolting Intellectuals Organisation (1966)]. His lectures to students were irresistible. After qualification from the Middlesex Hospital Medical School in 1948, Pat Wall worked in the US at Yale, University of Chicago and Harvard before being appointed professor at the Massachusetts Institute of Technology (1960). But, uncomfortable with interest from the CIA on the political affiliations of his research group, he returned to work with J.Z. (John Zachary) Young (1907–97) at University College London in 1967. In retirement (from 1990), Wall was based at St Thomas’s Hospital in London. His work was recognized by election to Fellowship of the Royal Society (1989), and by award of the Society’s Royal Medal (1999). His interest in neuroscience was precocious. It was stimulated by Paul Glees (1909–99) who also taught Oliver Sacks, Wall’s fellow student in Oxford and at the Middlesex Hospital Medical School. Glees had moved from his native Germany in the 1930s, first to Cambridge, and then to Oxford at the suggestion of (Sir Wilfrid) Le Gros Clark (1895–1971) where he interacted with (Sir) Hugh Cairns (1896–1952) and Solly (Lord) Zuckerman (1904–93). His contributions were in devising a novel silver staining method; pioneering early work on neural transplantation; and studies on glia. Glees returned to Germany in 1961 to head the Institute of Neuroanatomy and Embryology in Göttingen. It was Glees who suggested to Pat Wall, then a scholar of Christ Church, Oxford, that he work on the anatomy of the subthalamic nucleus. By the age of 21 Wall had already published two papers, one in Nature (Glees et al., An ensheathed rotating knife for causing brain lesions. Nature 1947; 160: 365); and his first, appearing a year earlier, in Brain.

It is the lack of knowledge on its fibre connections that prompts Glees and Wall to study afferent and efferent pathways of the subthalamic nucleus. In passing, they gather new information on the relationship between the centromedian nucleus of the thalamus and the subthalamic region. This they consider to comprise the zona incerta and the fields of Forel, the subthalamic nucleus or corpus Luysii, the red nucleus, the substantia nigra and the entopeduncular nucleus. The region is bounded ventrally by the hypothalamus, dorsally by the thalamus, and laterally by the internal capsule. Based on the existing literature, from a physiological perspective, the subthalamic nucleus concerns movement. Most commentators agree that lesions of this structure are associated with hemichorea; the transition from walking to a decerebrate animal occurs when the subthalamic nucleus is disconnected from the brainstem; and stimulation of the region produces running movements in cats. Existing knowledge on the anatomy suggests that this biconvex lens-shaped nucleus contains large and small cell parts and may show somatotopic differentiation. The main afferent supply is from the globus pallidus via the subthalamic fasciculus. Input is also received from the substantia nigra and the red nucleus. The tractus opticus accessory, present in lower mammals, is lost in primates. More controversial is whether there are direct fibre connections from the cortex to the subthalamic nucleus. There are also inputs from the lateral nucleus of the hypothalamus and the contralateral...
subthalamic and lenticular nuclei. Efferent connections are with the ipsilateral lenticular nucleus, the substantia nigra and red nucleus. Taken together,

"it may be concluded that there [is] very little information in the literature to indicate that the subthalamic nucleus is anything but a relay station for descending fibres."

Now, Drs Glees and Wall study five young monkeys anaesthetized with Nembutal; and with area 4 of the cortex identified by movement in the contralateral limbs triggered by low voltage stimulation. A thin insulating needle is then inserted vertically through a point 4 mm anterior to the central fissure and 6 mm from the midline, and lowered 29 mm at which stage a high frequency, high-voltage current is passed for 1–20 s before the needle is withdrawn. The animals are sacrificed after several weeks and the brains stained with the Swank-Davenport method.

MSL2 is studied at 26 days and has a lesion of the medial part of the lateral thalamic nucleus and inner third of the subthalamic nucleus reaching to the substantia nigra. Degeneration is seen in the interthalamic commissure connecting the two lateral thalamic nuclei; in the supramamillary commissure linking the opposite subthalamic nucleus; and in the red nucleus. Fibres are seen to degenerate that pass from the lateral thalamic nucleus to the internal division of the globus pallidus; and to the centromedian nucleus and midbrain including the superior colliculus. MSL3 is sacrificed at 37 days; the lesion affects the lateral thalamic nucleus, the tip of the internal pallidal division and the optic tract, extending down to the lateral border of the subthalamic nucleus and the internal capsule. Degeneration is seen in fibres connecting the pallidum and subthalamic nucleus; the centromedian thalamic nucleus; and those entering the ipsilateral substantia nigra, the red nucleus and the contralateral ventral tegmental decussation. MSL5 studied at 37 days has a lesion of the medial border of the subthalamic nucleus and lateral portion of the substantia nigra. Degeneration is prominent in connections with the pallidum; and, via the tegmental decussation, the red nucleus on both sides. The damage focused on the substantia nigra is associated with degeneration of fibres projecting to the superior colliculus and centromedian nucleus. MSL10 is sacrificed at 16 days and has a lesion of the anterior portion of the centromedian thalamic nucleus and field of Forel but the subthalamic nucleus is spared. Degeneration in this animal is therefore confined to projections of the cortex, incidentally injured, and those connecting the thalamus to the globus pallidus and red nucleus.

'The great wealth of fibres streaming through the region partially explains the many contradictory statements about the actual connections within the subthalamic region itself.'

Decrying lack of coherence in the available literature, the authors lean much on the prior work of Dr Glees describing connections within the basal ganglia (see Brain 1945; 68: 331–346) in which a preliminary view on the anatomy of the subthalamic nucleus, especially fibres passing to and from the pallidum or en route to the tegmental field of Forel, has already been expressed. That there is a rich afferent input to the subthalamic nucleus from the pallidum is not disputed, although whether this originates predominantly from the external division is less clear. The authors also confirm that fibres from the substantia nigra converge at the ventral surface of the subthalamic nucleus, where some terminate (Fig. 1). The authors' material leaves open the issue of whether there is an afferent projection from the red nucleus to the subthalamic region. Considering the efferent connections, the authors express surprise that, despite its dense concentration of nuclei, the subthalamic nucleus appears to lack any major long-distance connection (Fig. 2). Most of its fibres pass to the globus pallidus via the internal capsule. On this Jules Dejerine (1849–1917) has offered a view:

'en résumé, le corps du Luys dépend essentiellement du corps strié; il dégénère chaque fois que le globus pallidus, le putamen et le noyau caudé sont détruits.'

It seems likely that degeneration within the red nucleus is reinforced when both the pallidum and subthalamic nucleus are lesioned because the subthalamic nucleus contributes fibres reaching the supramamillary commissure and the ventral tegmentum. The explanation is that the combined lesion captures the subthalamic-pre-rubral fibres which pass caudally towards the interpeduncular nucleus. These apart, the subthalamic nucleus receives some projections from the ipsilateral ventral and centromedian thalamic nuclei. Extending their observations further, Glees and Wall comment on connections of the substantia nigra but, on the afferent side, can only contribute the view that there are connections from the cortex. They do, however, provide evidence for an efferent cortical bundle that passes to the subthalamic nucleus via the ventromedial part of the pallidum; and with some reciprocal
fibrres that take the same course from the subthalamic nucleus. Furthermore, there is a pathway connecting the substantia nigra to the centromedian nucleus of the thalamus. Their view is that the centromedian nucleus is not a typical thalamic component in the sense of having cortical connections but, rather, a relay station for midbrain impulses to the pallidum (Fig. 3). And Alfred Meyer (1895–1990) has already emphasized the connection of this thalamic nucleus to the frontal lobe (see Brain 1947; 70: 18–49; and Brain 2014; 137: 1266–71). Others—especially well demonstrated in Dejerine’s patient ‘Richard’—have argued for connection between the substantia nigra and the anterior colliculus on each side. The evidence from MSL10 in which Forel’s field is damaged in the presence of an intact subthalamic nucleus allows the conclusion that a pathway runs from Forel’s field to enter the central grey matter and the oculomotor nuclei that contributes to a pathway connecting the posterior hypothalamus with the tegmental and lower cranial nerve nuclei, and to which the centromedian and dorsomedial nuclei of the thalamus make a contribution. Since the subthalamic nucleus is part of the substantia nigra group of cells which has split off and become closely associated with the globus pallidus, and has no long pathways that terminate within its structures, it seems likely that, functionally, the subthalamic nucleus reinforces the suppressor system of the cortex that projects onto the caudate nucleus and globus pallidus.

Self-evidently, interest remains in studying the connections of brain systems, as two pieces in the current issue emphasize. Also presented within our ‘Dorsal Column’, Jan Voogd reviews the Atlas of human brain connections by Marco Catani and Michel Thiebaut de Schotten (2012: see page …) in which diffusion tensor tractography is used to map long association, commissural and projection systems of the cerebral hemispheres. The authors place their observations in an historical context; and Professor Voogd is also faithful to the history of how fibre systems were elucidated before and after introduction of the method that detects degeneration following strategic lesioning of defined structures. Professor Voogd debates the merits and demerits of living anatomy in humans versus histological and physiological studies in primates around the functional anatomy of the superior longitudinal and arcuate fasciculi and the instructive neurology of disconnection syndromes, raising some concerns about the insufficient resolution of tractography based on group studies in man. On page …, Ignacio Obeso and colleagues from London (UK), Havana (Cuba), and Navarra and Madrid (Spain) study patients who have undergone unilateral subthalamotomy to assess whether the subthalamic nucleus has a role in adjusting the thresholds to response or is concerned more with inhibiting and resolving potential conflicts in how to respond. Using behavioural testing, they conclude that the subthalamic nucleus has to do with response inhibition, modulating how information is allowed to accumulate and at what point a response is engaged so that accuracy does not suffer at the expense of speed. It follows that the subthalamic nucleus is part of the cerebral apparatus that provides inhibition on too rapid and indiscriminate a response to the call for action.

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