Lawrence and Kuypers (1968a, b) revisited: copies of the original filmed material from their classic papers in *Brain*

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This article aims to reintroduce two classic papers on motor control published in *Brain* in 1968, in which Lawrence and Kuypers reported their systematic studies of the effects of lesions to the corticospinal system (Lawrence and Kuypers, 1968a), and subsequently to the descending brainstem pathways (Lawrence and Kuypers, 1968b) in the Old World macaque monkey. They showed that the capacity for independent movements of the digits was permanently lost after a complete, bilateral lesion of the corticospinal system. These studies also revealed that the brainstem pathways contribute to fundamentally different aspects of motor control, with one set of pathways (the ventromedial system) involved in the control of head, trunk and girdle movements, while the other, lateral set of fibres control movements of the extremity such as reach and grasp. There is still much to learn today from these papers. However, an important part of their scientific legacy, the films illustrating the different cases, has long been unavailable. Much of this filmed material is now made available again in video format accessible on the *Brain* web site, complete with supplementary notes and histological detail. This article summarizes this newly available material for these classic papers in *Brain*.

**Keywords:** monkey; pyramidal tract; corticospinal; lesion; motor system

**Introduction**

In 1968, Don Lawrence and Hans (Henricus) Kuypers published two landmark papers in *Brain*, reporting the effects of surgical interruption of the descending pathways on the motor capacities of Old World Rhesus (macaque) monkeys. These studies were prompted by Kuypers’ realization of the striking differences in the pattern of spinal termination of the cortical and subcortical descending pathways (Kuypers et al., 1962; Kuypers, 1973 and below). This led him to hypothesize that these pathways might control different components of motor performance. The lesion studies confirmed this hypothesis by showing the different roles of the corticospinal tract and of the lateral and ventromedial brainstem pathways in motor control of the trunk, and of the proximal and distal limb segments (Fig. 1 and below).

The overall idea of the experimental approach was to first study the effect on motor behaviour of a complete bilateral pyramidalotomy that cut all the descending corticospinal fibres, but which
avoided damage to adjoining brainstem structures (Lawrence and Kuypers, 1968a). Once the effects of the initial pyramidotomy had been fully studied, the effects of additional lesions of the two major brainstem pathways that receive cortical inputs were studied. These lesions interrupted either the ventromedial descending brainstem pathways or the lateral brainstem pathways (Lawrence and Kuypers, 1968b). This approach allowed the functional contribution of these ‘subcorticospinal’ systems (i.e. brainstem motor systems receiving cortical input) to be assessed.

The original papers in Brain were supplemented by filming (16 mm) the behaviour of the monkeys, filmed before and at various times after the different types of lesion. These films were an essential part of the original study, because they richly complemented the behavioural descriptions provided in the papers, together with still shots of the histological material. Sadly, these films have been unavailable for a long time.

The new Supplementary material to these papers contains digital copies of the original film sequences in a series of 20 MP4 files, and a downloadable file explaining each film sequence is also available. This file contains the photographic plates taken from the papers to illustrate the lesions made, together with notes highlighting the main points of the histology and the monkeys’ behaviour. The original films, and these copies, follow the same sequence of histology and behaviour as in the Plates in the original 1968 papers, although not all the cases are shown (6/10 animals used in the 1968a paper and 7/14 in the 1968b paper). For cross-referencing with the original papers, plate and figure numbers are given in the notes before each film sequence. The notes are based on the text, figure legends and Supplementary material provided by Don Lawrence. The films were taken in Cleveland between 1963 and 1966.

Hans Kuypers returned from the USA to The Netherlands in the late 1960s, to establish a Department of Anatomy at the newly founded medical school in Rotterdam (now the Erasmus Medical Centre). In 1984, Kuypers was elected to the Professorship of Anatomy at the University of Cambridge, in England, where he died suddenly in 1989, at the age of 64. Don Lawrence joined Kuypers in Rotterdam from 1968–72. He moved to the Department of Neurology and Neurosurgery of the Faculty of Medicine at McGill University in Montreal in 1972. He is now retired and living in Montreal.

Anatomical background to the Lawrence and Kuypers studies

Kuypers and his colleagues had previously shown that corticospinal neurons located in the precentral gyrus (area 4, primary motor cortex, blue in Fig. 1) project to the dorsolateral region of the intermediate or internuncial zone of the spinal grey matter, concerned with control of the extremity: the hand and digits in the upper limb, the foot and toes in the lower limb. Neurons in this region of the intermediate zone are thought to relay excitation to motor neurons innervating muscles of the extremity. This projection descends mostly contraterally as the lateral corticospinal tract. Corticospinal neurons originating in the primary motor cortex (M1) with axons in this tract also project directly to the lateral motor neuronal cell groups, which supply the muscles of the extremity: the hand and digit muscles (Fig. 1; Kuypers et al., 1962; Lemon, 2008). Some corticospinal fibres descend ipsilaterally, and project bilaterally to the ventromedial intermediate zone;
controlling trunk and girdle muscles. Finally, corticospinal fibres originating from the postcentral gyrus (primary somatosensory cortex) terminate mostly in the dorsal horn (extreme left section in Fig. 1) and avoid the rest of the spinal grey matter. The three parallel influences of the whole corticospinal outflow, on the dorsal horn, intermediate zone and motor neurons in the ventral horn are indicated at the bottom of Fig. 1.

The pathways arising in the brainstem are grouped into medial and lateral systems, according to their differing terminal distribution in the spinal grey matter (Fig. 1). The lateral system (red in Fig. 1) comprises mostly rubrospinal fibres that arise from the caudal, magnocellular red nucleus and which descend contralaterally to terminate in the dorsal and lateral parts of the intermediate zone, again concerned with control of the extremity. The medial system (green in Fig. 1) is made up by fibres from the tectum, the interstitial nucleus of Cajal, the vestibular complex and the pontine and medullary medial reticular formation. Fibres belonging to this system descend ipsilaterally and terminate bilaterally, mainly in the ventromedial parts of the intermediate zone, concerned with control of trunk and girdle muscles. The cells of origin of these brainstem pathways receive numerous cortical projections, and Kuypers referred to them as ‘subcorticospinal’.

Since the terminal distributions of some corticospinal fibres are bilateral and overlap with those of the ventromedial and lateral brainstem systems, in order to study the function of these systems in isolation, it was necessary to first completely eliminate the influence of the corticospinal fibres on both sides. A previous, extensive study by Tower (1940) had focused mostly on the influence of the corticospinal tracts, at the upper level of the medulla oblongata.

What were the main issues in motor control at the time of the original investigation?

In 1968, there were a number of controversial arguments ongoing regarding the control of movement, and these provided the backdrop to the studies. For example, there was the debate, originally started by Hughlings Jackson, as to whether or not the cortex could be shown to be particularly important for ‘voluntary’ movements. In addition, with the introduction of intracortical microstimulation there were new contributions to the debate as to whether there was cortical representation of muscles or of movements. The nature of spasticity, and the poverty and weakness of movement after cortical damage or stroke was also being debated, as were disconnection syndromes and the phenomenon of diaschisis.

The straightforward premise of the Lawrence and Kuypers’ studies was that acute loss of the primary cerebral output tract to the neuromuscular ‘final common path’ of Sherrington would inform both the normal and adaptive functions of motor cortex and forebrain.

Original material newly available on the Brain web site

What can we learn today from this material?

The Lawrence and Kuypers papers are part of the classic archive of Brain (see van Gijn, 2004), and are two of the mostly highly cited Brain papers for that decade of research. The reason we have put this material together is because we believe there are important lessons that can still be learned from these classic studies. The findings remain important for both the experimental science and clinical neurology of motor control. While there are some differences between humans and rhesus monkeys in the organization of descending pathways for motor control, this model is still the best available for understanding the motor effects of stroke, spinal injury and motor neuron disease. Therefore, detailed and careful studies showing the motor capacities that remain after lesions of the descending pathways are particularly valuable.

It is also important to realize that for ethical and practical reasons, it is unlikely that these studies will be repeated on the scale undertaken by Lawrence and Kuypers: their work involved 41 adult monkeys, and the cases illustrated were carefully chosen after the full extent of the lesions had been thoroughly analysed. This allowed them to analyse the behavioural results from groups of animals with very similar lesions.

The first of the 1968 papers showed without question that the corticospinal tract does not have exclusive control over limb movements, and that monkeys can run, walk and climb within days of a bilateral pyramidotomy, albeit with a fluidity and speed of movements that was far from normal. The manifest efficacy of this early performance demonstrates the redundant function of the corticospinal output as far as these motor functions are concerned, and it was of course too early for substitutive plasticity.

However, at this early post-lesional stage, these same animals were completely unable to use their hands and digits to retrieve food rewards. Thus, while the hands could be used as part of a whole body movement (such as in climbing), they could not be used for more isolated actions such as the reach and grasp of food. Denny-Brown and Botterell (1948) had earlier commented on the fact that motor cortex lesions also caused a ‘depression of all motor function’ that was ‘graded in terms of emotional drive and complexity of integration with general motor behaviour rather than in terms of specific muscles or categories of movement’. By studying the same monkey for several months after pyramidotomy, Lawrence and Kuypers showed that the corticospinal tract alone is able to provide ‘the capacity for further fractionation of movements’, as exemplified by independent digit movements. Thus, these movements, so characteristic of primate hand function, were permanently lost after pyramidotomy. However, their studies also revealed that these capacities showed a remarkable degree of recovery after incomplete lesions.

The second 1968 paper showed the importance of the lateral brainstem pathways in control of the extremities in reach and
The original papers

The effects of bilateral pyramidal lesions (Lawrence and Kuypers, 1968a)

In the first series of experiments (Part I), Lawrence and Kuypers investigated the behavioural effects of bilateral interruption of the pyramidal tract, at the level of the medulla. Lesions were made by a parapharyngeal approach. The pyramids were interrupted between the caudal border of the pons and rostral tip of the inferior olive (Fig. 2). Eight of the 41 cases had a complete bilateral pyramidotomy without involvement of adjacent structures such as the medial lemniscus or inferior olive. A remarkable feature of this study is that most of these animals survived for months after the very difficult operations in which the bilateral lesions were made.

Supplementary Video 1 shows film footage of a normal macaque reaching and grasping for food presented in a pair of forceps, and using fine finger movements to extract food morsels from a Klüver board. This board specifically challenged the monkey’s ability to use relatively independent digit movements to retrieve food from the smallest wells on the board. A total of six cases are then shown, some with a complete pyramidotomy (Supplementary Videos 2–4 and 6), and others with incomplete lesions (Supplementary Video 5) or with involvement of other brainstem structures (Supplementary Videos 7 and 8). The films compare behaviour a few days after the pyramidotomy (Supplementary Videos 3 and 6) with that observed several months post-lesion (Supplementary Videos 2, 4, 5, 7 and 8).

A variety of motor behaviours are shown, including tests of skilled hand and finger function, but also of reaching, walking, running and climbing. One of most striking cases is that shown in Chapter 6 (Case MDY), filmed just 4 days after a complete bilateral pyramidotomy that largely spared any adjoining structures. The initial film sequences show the monkey was able to walk, run and climb up a cage at this early postoperative stage, although the monkey’s movements are somewhat unsteady. What is remarkable is the capacity of the monkey to use its hands to ‘firmly grip the cage bars’ and to pull itself into the cage or to climb up it. However, when food was offered to the monkey while it was seated in its home cage, it was completely unable to use its hands to retrieve even large pieces of fruit, and instead the monkey lowered its head towards the board and attempted to bite it. Thus, at ‘this early post-operative phase’ these monkeys ‘were apparently unable to use their extremities, especially their hands, independently of total body movements;’ and ‘After two or three such fruitless attempts they usually gave up reaching for food until 8–16 days after the operation. Yet, during this same period, they could use their hands to firmly grip the cage bars.’

The case involving an incomplete pyramidotomy (Supplementary Video 5, Case MDW, filmed 2 months after the lesion) is also of great interest because it shows that the monkey was able to use the (left) hand and fingers contralateral to the pyramid where there was significant sparing, far better than the right hand contralateral to the fully transected pyramid. This strong contrast with the complete pyramidotomy cases has important lessons for our understanding of the potential for recovery after incomplete spinal lesions. It is remarkable that a total, bilateral pyramidal lesion was required to completely abolish the capacity for skilled independent digit movements, which is controlled by a highly crossed system in the primate (Brinkman and Kuypers, 1972). Recent discoveries relevant to this result have highlighted the spontaneous plasticity of corticospinal projections after spinal lesions, with marked reconstitution of pre-lesion axon density arising from axon sprouts that can cross the midline (Rosenzweig et al., 2010).

The effects of lesions of the descending brainstem pathways (Lawrence and Kuypers, 1968b)

In this second series of experiments, Lawrence and Kuypers reported the effects of lesions made to interrupt either the
ventromedial or lateral brainstem descending pathways. These lesions were made 2–8 months after bilateral interruption of the corticospinal pathways. Examination of the monkeys after these lesions was completely consistent with the contrasting pattern of termination in the spinal cord of these pathways (see above).

Supplementary Videos 9–13 (Part IIa) show two cases with lesions to the ventromedial pathways. The ventromedial pathways descend paramedially through the brainstem into the spinal cord and were interrupted by an incision through the floor of the fourth ventricle into the medial reticular formation (Fig. 3). Case MCA (Supplementary Videos 9–11) shows a striking contrast between the monkey’s ability to right itself, walk and climb 4 months after a bilateral pyramidotomy (Supplementary Video 9) compared with the very limited degree of any head, trunk and shoulder movement 1 month after a medial reticular lesion (Supplementary Videos 10 and 11). However, the capacity to use the hand to grasp food is not affected (Supplementary Video 11). Similarly, Case MBM shows that after a medial reticular lesion, the capacity to sit unsupported is lost (Supplementary Video 12) and the gait is very unsteady, but the monkey can still grasp the cage bars (Supplementary Video 13).

Supplementary Videos 14–20 (Part IIb) show four cases with lesions of the lateral brainstem pathway. The lateral brainstem pathway is derived largely from the magnocellular portion of the red nucleus in the midbrain and consists of crossed rubrospinal fibres; these were interrupted on the right side by an electrolytic lesion at the medullary or pontine level. Case MDH (Supplementary Video 14) with a lateral medullary lesion, shows that the monkey was unable to use the right hand (ipsilateral to the lesion and contralateral to the red nucleus showing retrograde cell loss) to pick up food. There is a characteristic flexion of the arm and extension of the fingers. A control lesion to the gracile and cuneate nuclei on the opposite side of the brainstem showed that the deficit in hand function was not due to the medullary lesion interrupting ascending sensory lemniscal fibres. A similar case (MCP) is shown in Supplementary Videos 18 and 19.

There was a similar loss of the capacity to grasp in Case MDU (Supplementary Videos 15 and 16), with a lateral pontine lesion. It also shows the arm flexion and digit extension. When the lesion spared the rubrospinal tract (as judged by the normal pattern of cell staining in the red nucleus), there was only a transient loss of grasp (Case MEA, Supplementary Video 17). Finally, in Case MCT (Supplementary Video 20) spinal lesions aimed at the lateral funiculus at the first or second cervical segment, which also interrupted the rubrospinal fibres, produced a similar motor deficit, without any detectable sensory (tactile) deficit, as demonstrated in the final sequence of this video. It is noteworthy that cage grasping during climbing could survive both lateral pontine (Supplementary Video 16) and medial reticular lesions (Supplementary Video 13).

**Figure 3** Semi-diagrammatic representation of brainstem sections of a monkey with a bilateral pyramidotomy plus a lesion of the ventromedial brainstem pathways (lesion in solid black, resulting gliosis shaded). BC = brachium conjunctivum; PY = pyramidal tract; SV = spinal trigeminal nucleus; VC = vestibular complex; VII = facial n. (Kuypers, 1973).

**Summary and conclusions**

The findings of the combined studies (Parts I and II) led Lawrence and Kuypers to the following conclusions: (i) the ventromedial brainstem pathways are the basic system by which the brain controls movement. This control is concerned especially with maintenance of posture, integration of body–limb movements and with directing the course of locomotion; (ii) the lateral brainstem pathways superimpose upon this the capacity for the independent use of the extremities, particularly of the hand; and (iii) the corticospinal pathways mediate a control similar to that of both brainstem pathways and, in addition, provide the capacity for further fractionation of movements as exemplified by relatively independent finger movements.

The purpose of this short paper has been to reintroduce these important papers to the current readership of *Brain*, and in particular to make the filmed material more accessible to modern scientists. Our comments are therefore made very much along the lines of the original papers. However, as an addendum, made in the light of current research on repair and rehabilitation after brain or spinal injury, it is interesting to note that Lawrence and Kuypers did not discuss the possible mechanisms underlying the recovery they saw in the weeks and months following lesions of the descending pathways. In fact, they purposely focused on their experimental observations and were not distracted by speculating on the reasons for the gradual recovery. All of the lesions would have deprived spinal interneurons and, directly or indirectly, motor neurons of significant synaptic input from the descending pathways. The recovery after the lesions presumably included adaptation to the input exerted by the remaining pathways. It may also have included a significant amount of plasticity and reorganization, which has been revealed in numerous experiments.
carried out since 1968 and which have been, to some extent, inspired by these classic papers.

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Supplementary material

Supplementary material is available at Brain online.

References


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