

EXTRAPYRAMIDAL SYSTEM, MOTOR GANGLIA AND MOVEMENT DISORDERS

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ABSTRACT

The pyramidal tract, pyramidal syndrome and involuntary movement disorders related to the extrapyramidal pathways are described. A review of the evolution and growth of the neurobiological and clinical knowledge of non-voluntary movement control, which have led up to the recent attempts to better integrate these two discipline components, is attempted. Presently, animal models of involuntary movement disorders are available which, for the first time, permit the study of the role played by different subcortical nuclei in pathological conditions. However, a critical analysis suggests that neurobiological and clinical data are still far from being totally integrated.

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Neurological syndromes characterized by motor disabilities are usually classified either as pyramidal, extrapyramidal or cerebellar. These terms denote different collections of symptoms, which can be readily recognized during examination. Cerebellar signs indicate a motor syndrome of the cerebellum and cerebellar connections, which is clearly consistent with experimental anatomical and physiological knowledge. The pyramidal syndrome also presents a coherent clinical picture: it is characterized by reduced voluntary strength, abnormal muscle tone and reflexes, and the Babinski sign. Its anatomical correlates were originally thought to consist of a

pyramidal tract lesion. However, as discussed below, it is now clear that they definitely extend beyond the anatomical limits of this motor pathway. The extrapyramidal syndromes constitute a heterogeneous assortment of clinical entities, which were grouped together during the first half of this century and are interpreted as being due to a dysfunction of some non-pyramidal and non-cerebellar centres devoted to non-voluntary movement control. The pyramidal, extrapyramidal and cerebellar anatomical correlates focus on the role of several subcortical grey structures and of a variety of connecting pathways. It is not paradoxical to say that, while the concept of the extrapyramidal system (whose impairment is thought to bring about extrapyramidal diseases) essentially relies on the study of clinico-anatomical material, the use of the expression "extrapyramidal" has been often criticised on the same grounds /1,2,3/.

Recent studies have provided much knowledge about the physiopathology of involuntary, extrapyramidal, motor control, which has not yet been integrated with existing information. Therefore, the need for a revision of current classifications seems necessary. Considering that terminology directly reflects "the methodology of reason" /4/: this paper explores the historical development of the concept of the extrapyramidal motor system and evaluates whether a comparison of current neurobiological and clinical knowledge may lead to a more comprehensive picture and thus a revised terminology.

THE HISTORICAL BACKGROUND

Bulbar pyramids were the first element of the motor system to be studied morphologically. Their first description was by Vieussens /5/. The pyramidal decussation was later reported by Mistichelli /6/ and by Pourfour du Petit /7/, while its first diagram was included in Duverney's treatise /8/. The discovery that pyramids are formed by fibre bundles conveying motor impulses ended some long existing controversies. According to Magendie /9/, "very few questions have generated so much research as those concerned with the anatomy and physiology of anterior pyramids".

The earliest theory about the organization of the motor centres located in the cerebral hemispheres originated from phrenology (a theory firmly advocated by well-known anatomists, such as Gall) and also from the controversy about its validity. The official decline of phrenology as a scientific theory was hastened by the work of Flourens /10/, who experimentally demonstrated that the cerebral cortex is electrically non-excitabile and that it acts as a whole without separate functional centres. Flourens' formulations were authoritative and each of his statements, unlike phrenology, was supported by a specific experiment. He also devoted a large part of his analysis to the problem of a scientific method. Therefore, although Flourens' "laws on nervous action" were disproved by later experimental studies, they paved the way for important contributions based on accurate scientific methodology.¹ One such finding was Broca's /12/ discovery of the anatomical and functional specializations in the pallium, which experimentally confirmed some earlier phrenological propositions.

Following some intuitive comments by Gall and Spurzheim /13/, in 1853 Türk /14/ found that the bulbar pyramids are composed of bundles of axons contained in a long system of descending corticospinal pathways. He studied the course of this tract, which he called "pyramidal", and observed that lesions at the level of the internal capsule are commonly found in patients with spastic hemiplegia. Almost two decades later, Fritsch and Hitzig /15/ showed that electrical stimulation of the frontal lobe in the dog induces movements of the contralateral limbs. In 1875, Jackson /16/ suggested the presence of a somatotopic distribution, which was then experimentally demonstrated at the turn of the century by Grünbaum and Sherrington /17,18/. The site of origin of the pyramidal tract was identified in 1909 by Holmes and May /19/, who observed that, when it is sectioned at the level of the cervical spinal cord, retrograde degeneration affects only Betz's giant cells in

Brodman's area 4. Briefly, it can be said that, following these and other studies, a rather accurate concept of the functional anatomy of the pyramidal tract had started to crystallize towards the end of the last century.

By that time, however, the development of new research methods was generating new data which was at odds with the previous information. It was Brown-Séquard /20/ who, with the aim of inducing an experimental pyramidal syndrome, first performed pyramidotomies in animals. He observed that, even after severing the pyramids, a stimulation of the cerebral cortex would produce vigorous movements of the limbs. Subsequent research showed that the pyramidal tract could not be the only descending system responsible for motor control. Using the preliminary data from studies of bilateral pyramidotomies in dogs, in 1895 Starlinger /21/ drew the following conclusions: "1) in the dog, the pyramidal tract plays a secondary role in motor control; 2) in the dog there must be a pathway outside the pyramidal tract, capable of transferring impulses from the cerebral cortex to the muscle". The term "extra-pyramidal" was used three years later in 1898 by Prus /22/.

In the light of present knowledge, Starlinger's first statement sounds rather radical. Data from studies using pyramidotomies have clearly shown that the most severe clinical signs are observed in the highest phylogenetic ranks. In fact, according to Tower /23,24/, the clinical picture observed in the chimpanzee is more complex than that seen in lower monkeys. In chimpanzees, the experimental pyramidal syndrome particularly affects fine motor movements of the hand. Residual motor ability shows neither precision, fineness nor versatility. Hypotonia and the Babinski sign are also present. Subsequent research /25,26,27/ has expanded and substantially confirmed these findings. The clinical picture of the pyramidal syndrome, which naturally occurs in man, is accentuated by symptoms brought about by damage to non-pyramidal tracts coursing through the internal capsule. Therefore, the clinical pyramidal syndrome is not a pyramidal tract syndrome (see Table 1).

¹ According to Popper /11/, dogmatic thinking, which is "prescientific", is a stage that is needed if critical thinking is to be possible. Critical thinking must have before it something to criticize, and this must be the result of dogmatic thinking. Flourens' theories were scientific because they ruled out the occurrence of some possible events. In fact, according to Popper /11/, "the more a theory forbids, the more it tells us."

Table 1
Clinical Anatomical Correlates

Clinico-anatomical set	Clinical coherence	Anatomical coherence
Cerebellar	Yes	Yes
Pyramidal	Yes	No
Extrapyramidal	No	No

EXTRAPYRAMIDAL SYNDROMES

Twenty years after Luciani /28/ discovered the cortical pathogenesis of epilepsy, in 1878, Prus /22/ disproved Unverricht's theory of a diffusion of epileptic discharge along the surface of the brain (principle of irradiation), although he admitted that the pyramidal tract did not take part in the conduction. He stated that "the conduction of excitation from the motor cortex to the medulla proceeds along the motor pathway which I call extrapyramidal, running from the cerebral cortex to the medulla and the spinal cord. This tract travels through the superior part of the midbrain and decussates in the medulla". Thus, according to Prus, the extrapyramidal tract consisted of a single anatomical connection which ran parallel to the pyramidal pathway. By the beginning of the nineteenth century, Monakow /29/ introduced the concept of diaschisis, i.e., the loss of function caused by cerebral lesions in areas which are remote from the lesion but which are neuronally connected to it. This physiological concept suggested the existence of a complex anatomical organization of cortical and subcortical brain centres. In 1907, in a physiological study on the corticospinal tract, Rothmann /30/ interpreted some events previously described by Monakow /29/ as examples of diaschisis depending upon the presence of extrapyramidal connections. He stated that "extrapyramidal pathways [...] must be able to transmit some motor impulses from cerebral cortex to the spinal cord. Extrapyramidal conduction may be of great importance for the acquisition of new movements, while the pyramidal tract, which directly connects the cerebral cortex with the spinal cord, is essentially used for movements that have been already acquired". The term extrapyramidal was therefore used as a *deus ex machina* to explain some inconsistencies in the experimental data available at that time. In discussing the pathogenesis of the disease bearing his name, in 1912 Wilson /31/ first introduced the concept of the extrapyramidal system as a coherent functional anatomical entity.

In the early years of this century, the search for a functional role of subcortical grey nuclei was particularly

active. The method of study was usually clinico-anatomical, consisting of a correlation of clinical data with anatomical data obtained from autopsy. Mingazzini /32,33,34/ proposed that the lenticular nucleus was involved in motor control by means of discrete subsets characterized by different functional roles. The specifics of the theory were developed by other Italian neurologists. Franceschi /35/ found that spastic laughter and crying were usually associated with a lesion of the lenticular nucleus. Piazza /36/ reported the clinico-anatomical correlates of lesions located in the lenticular nucleus which were associated with either motor deficiency (usually contralateral hemiparesis or dysarthria) or contralateral involuntary movements. Eventually, Mingazzini /37/ described the "lenticular syndrome" as having pyramidal signs and sensory deficits on the contralateral side, ipsilateral anisocoria and, sometimes, dysarthria.

One early experimental approach to the understanding of extrapyramidal system functions was carried out by Vogt and Vogt /38,39/, who tried to delimit the extrapyramidal motor areas by determining the effects of cortical stimulation before and after isolation of the stimulated areas from the primary motor cortex. Dana /40/ studied some cases of acute gas poisoning associated with unilateral or bilateral haemorrhagic softening of the basal ganglia. Contrary to Mingazzini, he deduced that "the corpus striatum has not any independent or specific motor function. It probably has some supplementary motor function, and especially in connection with articulation". In 1911, Oppenheim and Vogt described two cases of "congenital pseudobulbar infantile paralysis." Post-mortem examination of one of the brains showed atrophy with bilateral marble-like appearance (*état marbré*) of the caudate nucleus, the putamen, and the pallidum. The internal capsule was intact and rather hypertrophic. Among the clinical signs, a spastic contraction of the limbs and face was a prominent feature. Thus, Vogt /41/ defined the "syndrome of the corpus striatum", characterized essentially by "spasms, accompanied by more or less serious athetoid movements, rhythmic oscillations, associated movements, spastic laughter and crying, without almost any paralytic signs, without sensory disturbances or intellectual deficiency: in other words, a pure double athetosis".

Cécile Vogt's syndrome represented the first naturally occurring condition characterized by a clear-cut sparing of the pyramidal tract. This resulted in the first reliable clinico-anatomical correlations. A few years later, Wilson /31/ used a similar approach to demonstrate that hepatolenticular degeneration is not due to a lesion of

the pyramidal tract. He extensively used the terms "extrapyramidal system" and "extrapyramidal pathways". His deductive logic was based on the following considerations: "(a) The pyramidal tracts must not be too severely injured. If they are, then no voluntary movements occur. [...] (b) A lesion of the pyramidal system is not by itself sufficient to produce involuntary movements. Innumerable cases of hemiplegia occur where involuntary movements are conspicuously absent. There is no case of involuntary movement on record pathologically in which the lesion did not involve, directly or indirectly, certain areas of grey matter at the base of the brain, or in the mid-brain. (c) The assumption, therefore, is strong that other, extrapyramidal paths must be injured. What are these extrapyramidal paths? There are two that concern us in this connection, one afferent and the other efferent (Fig. 1). The former is the cerebello-rubro-thalamo-cortical path, which is well recognized anatomically: from the nucleus dentatus, via the superior cerebellar peduncle, to the nucleus ruber of the opposite side, and thence to the inferior and external division of the optic thalamus, and so to the sensory and motor cortex. There can be no doubt that with lesions of this system certain involuntary movements are prone to occur. The latter is the lenticulo-rubrospinal system, which is perhaps less well known." After discussing earlier electrophysiologic data on experimental lesions, Wilson concluded that "(e) Destructive lesions of the extrapyramidal paths in some way allow involuntary movements to occur." Incidentally, it may be noted that the extrapyramidal pathways described by Wilson are in fact cerebellar, and that both involve the red nucleus, which has no connections with the corpus striatum and is chiefly influenced by the cerebellum and the cerebral cortex. In fact, in this essay, the red nucleus will not be considered as part of the basal ganglia.

For the first time, Wilson's formulation explicitly correlated a specific, although ill-defined, anatomical system with a coherent set of clinical signs. This was the first step in a new interpretation of motor disturbances, which successively distinguished two main functional anatomical domains: the corticospinal system, responsible for voluntary movements; and the extrapyramidal system, related to non-voluntary motor control. This simple and rather attractive definition changed the semantic value of the term extrapyramidal from its original meaning of "non-pyramidal" to that of "other than pyramidal". Therefore, according to Gil's formulation /42/, the logical relationship between the categories *pyramidal* and *extrapyramidal* evolved from a non-antagonistic

dualism to an antagonistic scheme with a mutually exclusive association.

Some experimental data also supported a logical dichotomy between two mutually exclusive categories. Brown /43/ reported that a postural flexion of the upper extremity, maintained in the ape by electrical stimulation of the midbrain tegmentum, could be promptly changed into a strong phasic flexion by stimulating the cerebral peduncle containing the pyramidal fibres. This evidence was also interpreted by Wilson /44,45/ to mean that a prevailing posture, induced by stimulation of a non-pyramidal structure, can be reversed by stimulation of the pyramidal system. A separate relationship was also suggested a few years later by Strümpell /46/: he differentiated the "myostatic" system, with the corpus striatum as the main component, from the "myodynamic" voluntary system having the cerebral cortex as its principal unit.

Strümpell's theory was authoritative, particularly in the mid-European scientific circle. However, the "amyostatic syndrome" he identified was based more on axiomatic postulates than on empirical data. Anatomical, physiological and clinical correlates of the amyostatic syndrome were thoroughly analysed in the September 1921 meeting of the German Neurological Society /47/. As reported by Calligaris /48/, by the end of the same decade this theoretical framework was widely criticised.

A clinically distinctive nature of the extrapyramidal system was emphasised after World War I by the discovery of new disorders and by the theoretical reassessment of motor system functions. Encephalitis lethargica, described by Economo in 1917 /49/, appeared in micro-epidemic or sporadic form throughout many of the following years. It was characterized by abnormal movements, such as tics, torsion spasms, myoclonus, etc. Post-encephalitic parkinsonism was one of the most frequent sequelae. The first description of parkinsonian symptoms in patients suffering from lethargic encephalitis was by Marie and Lévy /50/. Involuntary movements were described later /51,52/. Sterling /53/ proposed that motor abnormalities associated with encephalic lethargica could represent a particular form of "extrapyramidal epilepsy."

Kleist /54/ was the first to classify all motor disturbances known to be associated with lesions of subcortical structures as extrapyramidal diseases. A few years later, in a series of papers published in the early '20s, Wimmer /55,56,57,58,59/ listed the following diseases as extrapyramidal: Wilson's disease (pseudosclerosis); progressive infantile torsion spasms; striatal syn-

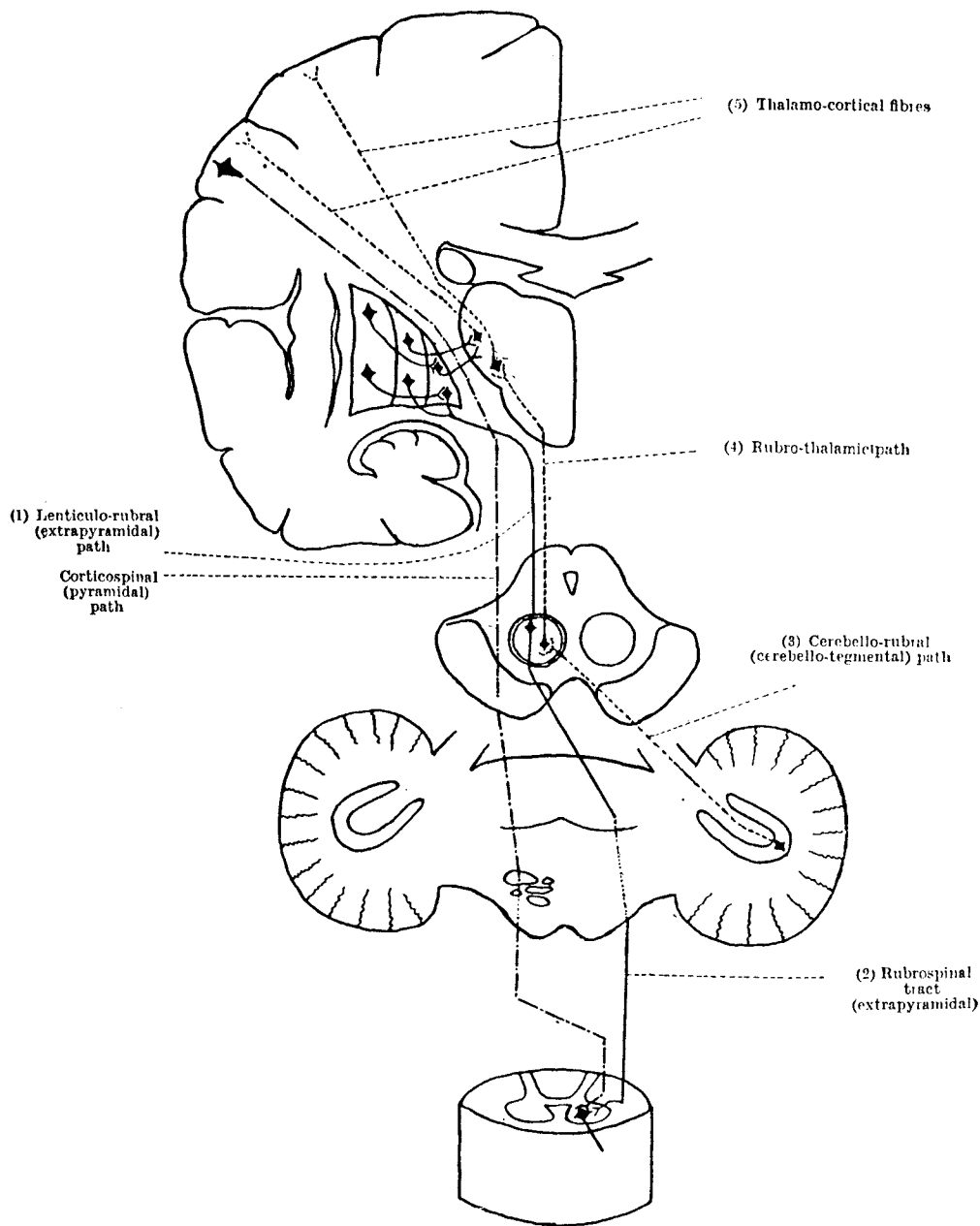


Fig. 1: Diagram used by Wilson /31/ to summarize the relations of the pyramidal, extrapyramidal and cerebellar systems: (1) and (2) constitute the lenticulo-rubrospinal path (efferent); (3), (4) and (5) the cerebello-rubro-thalamic path (afferent). In this simple diagram efferent motor pathways constitute two parallel systems; the only differences between the two are in the sites of origin and in the polysynaptic organization, which characterizes the extrapyramidal path. As observed by Meyers /70/ this dichotomy corresponds to the Boolean algebraic equation: $P \cdot E = 0$ (where P and E correspond to the pyramidal and extrapyramidal systems, respectively). (From Wilson /31/, by courtesy of Oxford University Press)

dromes in patients with either neuroleues or infantile congenital encephalopathy; and striatal syndromes following carbon monoxide intoxications. In 1922, Hallervorden and Spatz /60/ described a "peculiar disease of the extrapyramidal system with particular involvement of the globus pallidum and the substantia nigra." In their monographs on extrapyramidal disorders, Jakob /61/ and Lewy /62/ tried to draw conclusive correlations between anatomy, physiology, and clinical symptoms.

In his address to the 49th annual meeting of the American Neurological Association, Wilson /45/ summarized the three cardinal signs of extrapyramidal motor system lesions: (1) variability in muscle tone: generally hypertonia, or even "dystonia", affecting all muscle groups of a given area, with no preference for either flexor or extensor muscles; (2) appearance of involuntary movements, usually tremor or choreoathetosis; (3) absence of paralysis. In Italy, Calligaris' text /48/ on the extrapyramidal system was a catalogue of all motor disabilities known at that time. It also surprisingly included disorders of the peripheral nervous system and of the muscles. The putative anatomical substrate of extrapyramidal disorders depicted by Calligaris (Fig. 2) was clearly more complex than that sketched 15 years earlier by Wilson /31/.

It is interesting to note an example of the extent to which dichotomous thought has affected scientific theorists in reference to movement disorders. As late as 1967, in his report on the physiology of myoclonus, Halliday /63/ proposed a theoretical distinction of this disorder into three main categories: pyramidal; extrapyramidal; and segmental myoclonus. While Halliday's pyramidal myoclonus corresponds to what was later defined as cortical reflex myoclonus /64/, his definition of the extrapyramidal type was quite unclear; he "included under this heading a number of other forms of muscle jerking", which "are examples of extrapyramidal basal ganglia movement disorders, not myoclonus" /65/. In this case, therefore, the identification of an extrapyramidal form of the disease clearly reflected the challenge of making a correct clinical diagnosis. This leads to the general question as to whether the identification of extrapyramidal disorders or forms of diseases is simply a measure of our neurological illiteracy.

MOTOR GANGLIA

A comprehensive concept of the extrapyramidal system arose from clinical observation before being applied to neurobiological analysis. This is just the opposite of what occurred in the evolution of thought

above the pyramidal system, since the study of the pyramids and of the corticospinal tract antedated clinical interpretations. In this light, it should be mentioned that experimental lesions of the pyramidal system (i.e., experimental pyramidal syndromes) were successfully performed by early researchers, although the similarity of the experimentally produced signs to naturally occurring clinical signs has often been debated. On the contrary, attempts to produce symptoms of extrapyramidal diseases by means of experimental lesions have failed until recently. Classical morphological studies in patients with extrapyramidal disorders have indeed demonstrated a subcortical structural pathology, but they have failed to indicate clear-cut clinical anatomical correlates.² It should also be recalled that, before the morphology of the corpus striatum was studied by the Vogts /66/, it had been almost ignored by anatomists. Retzius' /67/ monograph, for example, which reviews anatomical knowledge of the nineteenth century, paid little attention to the basal ganglia, as compared to other brain regions.

The concept of extrapyramidal system and extrapyramidal disorders had flourished until quite recently /68/. Perhaps the first critical analysis of this concept was set forth by Bucy /69/, who pointed out that the idea of the extrapyramidal system had undergone major changes over the previous quarter century, and that this neural system was incompletely understood, both anatomically and physiologically. Meyers /3/ commented that it "may mean that the extrapyramidal concept is but a term for high-order abstraction, referents for which are not demonstrable in the phenomenal world. If so, and provided that its usage in this sense were generally appreciated, there could be no serious objection to its retention in neurologic jargon, for science abounds in and advances by just such 'as-if' formulations, for example, neutrons, mesons, atoms, [...]. It may also mean that under the term 'extrapyramidal system', our neurologic forebears unwittingly lumped together a number of genuinely discrete but unidentified neural systems, the difference between which are comparable to those now presumed to exist between the pyramidal and extrapyramidal systems." Bucy /2/ concluded that "it is urged that the terms pyramidal tract, pyramidal syndrome, and extrapyramidal tract or system be discarded and that renewed effort be made to discover

² Probably the most important exception to this statement is chorea. Meynert /70/ and Broadbent /71/ noted gross embolic foci in the neostriatum of patients having infectious chorea. In 1895 Anton /72/ provided microscopic evidence of damage to the basal ganglia.

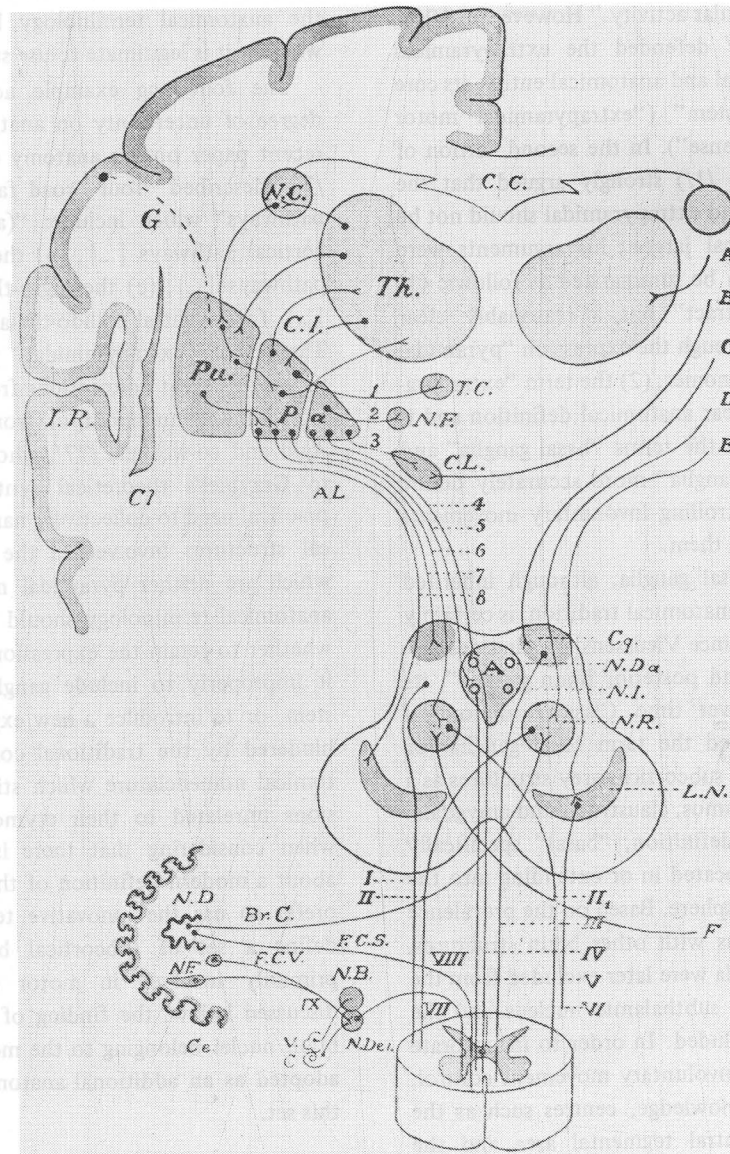


Fig. 2: Schematic drawing of extrapyramidal motor pathways, according to Calligaris /48/. After reviewing diagrams previously published by Italian authors (Mingazzini, Ayala, Sterzi, Bernardini, Furno, Negro, Gamna and Omedei-Zorini) and foreign authors (Edinger, Monakow, Wilson, Vogt, Lewy, Förster, Lhermitte, Chatelin, Bing, Flatau, Jakob, Foix and Nicolesco), Calligaris concluded that "extrapyramidal pathways appear as an inextricable maze, which cannot be schematically summarized". Abbreviations for nuclei: *A.*, aqueduct; *A.L.*, ansa lenticularis; *Br.C.*, superior cerebellar peduncle; *C.*, cochlea; *Ce.*, cerebellum; *C.I.*, capsula interna; *C.L.*, subthalamic nucleus; *Cl.*, claustrum; *C.q.*, inferior colliculus; *I.R.*, insula of Rheil; *L.N.*, substantia nigra; *N.B.*, Bechterew's nucleus; *N.C.*, caudate nucleus; *N.D.*, dentate nucleus; *N.Da.*, Darschewitsch's nucleus; *N.Dei.*, Deiters' nucleus; *N.F.*, nucleus of Forel's field, fastigial nucleus; *N.I.*, interstitial nucleus; *N.R.*, red nucleus; *Pa.*, globus pallidum; *Pu.*, putamen; *T.C.*, tuber cinereum; *Th.*, thalamus; *V.*, vestibulum. Abbreviations for tracts: *1*, pallido-cinereum or pallido-infundibular tract; *2*, pallidal projection to Forel's field nucleus; *3*, pallido-subthalamic tract; *4*, pallido-Darschewitsch tract; *5*, pallidal projection to the interstitial nucleus; *6*, pallido-rubral tract; *7*, pallido-tectal tract; *8*, pallido-nigral tract; *I*, reticulospinal tract; *II*, *II₁*, rubrospinal tracts; *III*, tectospinal tract; *IV*, Darschewitschspinal tract; *V*, interstitial-spinal tract; *VI*, nigro-pedunculo-spinal tract; *VII*, vestibulo-spinal tract; *VIII*, *F.C.S.*, cerebello-spinal tract; *IX*, *F.C.V.*, cerebello-vestibular tract; *A*, cortico-thalamic tract; *B*, cortico-hypothalamic tract; *C*, cortico-tectal tract; *D*, cortico-rubral tract; *E*, cortico-nigral tract; *F*, cerebello-rubral tract; *G*, cortico-lenticular tract. (From Calligaris /48/)

and define the neural mechanism responsible for the control of skeletal muscular activity.” However, in 1960, Jung and Hassler /73/ defended the extrapyramidal motor system as a clinical and anatomical entity, its core being the “striatal system” (“extrapyramidal motor system in the narrow sense”). In the second edition of his treatise Brodl (see /1/) strongly argued that the expressions pyramidal and extrapyramidal should not be accepted neuroanatomical jargon; his arguments were well supported, and can be summarized as follows: (1) the term “pyramidal tract” has a reasonably clear anatomical meaning, although the expression “pyramidal tract syndrome” is a misnomer; (2) the term “extrapyramidal system” has no clear anatomical definition and is clinically misleading; (3) the terms “basal ganglia” and “diseases of the basal ganglia” more accurately define the cerebral nuclei controlling involuntary movements and the diseases affecting them.

The definition of basal ganglia, although inherited from the early classical anatomical tradition, is certainly not without ambiguity. Since Vieussens’ /5/ first description of the “anterior and posterior brain ganglia”, its meaning has changed over time. Classical anatomical terminology later adopted the term basal ganglia (or nuclei) to label the main subcortical grey structures as a whole, i.e., striatum, thalamus, claustrum, and amygdala. In fact, by anatomical definition, “basal” specifically refers to any structure located in or extending into the basal part of a brain hemisphere. Based on the prevalence of functional connections with other brain structures, the thalamus and amygdala were later excluded from the basal ganglia,³ while the subthalamic nucleus and the substantia nigra were included. In order to incorporate all structures related to involuntary movement control, as defined by current knowledge, centres such as the substantia nigra, the ventral tegmental area and the pedunculopontine nucleus, which are located outside the hemispheres and therefore are not basal, should be included in the basal ganglia. An additional source of misunderstanding originated from the term “corpus striatum”, which was first introduced by Willis /75/ to indicate the caudate nucleus, and later used by others as a synonym for the basal ganglia. According to Dana /40/, for example, “the corpus striatum consists of three parts, the caudate nucleus, the lenticular nucleus, and the nucleus amygdalae into which the tail of the caudate

nucleus runs”. Hence, the complexity and ambiguity of the anatomical terminology leads to the question of whether it is legitimate to use such classic definitions.

The following example accounts for the current degree of uncertainty on anatomical terminology. In a recent paper on the anatomy of basal ganglia, Graybiel /76/ described “four broad families of extrapyramidal pathways” which include: “(a) the cerebello-thalamo-cortical pathways [...], (b) the pallido-thalamo-cortical pathways [...], (c) the nigro-thalamo-cortical pathways [...], (d) a ventral pallido-thalamo-cortical connection”. These four “extrapyramidal” pathways, which in fact include efferent connections from the cerebellum, were later called “main output from the basal ganglia” by Agid and co-workers /77/, who made specific reference to Graybiel’s theoretical synthesis. Since there is a practical need to collectively name a number of anatomical structures involved in the control of movements, which are neither pyramidal nor cerebellar, a suitable anatomical terminology should be used. The dilemma is whether to retain the expression “basal ganglia” and use it improperly to include ganglia located in the brain stem, or to introduce a new expression which could be hindered by the traditional conservatism of neuroanatomical nomenclature which still retains several expressions unrelated to their etymological meaning⁴. Still, when considering that there is no general agreement about a modern definition of the basal ganglia, I would prefer to use the innovative term “motor ganglia” to define a set of subcortical brain nuclei which are primarily involved in motor control (Table 2). As discussed below, the finding of reciprocal links among brain nuclei belonging to the motor ganglia can also be adopted as an additional anatomical criterion to define this set.

MOVEMENT DISORDERS

Recent years have led to a better understanding of extrapyramidal disorders. In fact, not only have new classifications been proposed for disorders which were

³ This definition is not universally accepted. Carpenter /74/, for instance, includes the amygdala among the basal ganglia, while Brodl /1/ does not. In classic textbooks the amygdala is also referred to as *archistriatum*.

⁴ The nucleus accumbens provides an interesting example of the evolution of anatomical terminology. It was first described in Monotremata as *nucleus accumbens septi* /87/, a Latin expression meaning “septal nucleus in a sloping position.” Later, when it was understood that it is part of the basal ganglia, the genitive *septi* was omitted. Luckily, the popular English translation of this Latin name (“nucleus leaning toward the septum”, see /88/) is incorrect, so that, according to a proper translation, the nucleus accumbens retains a meaningful name.

Table 2
The Motor Ganglia

A. Corpus striatum	Neostriatum	Caudate nucleus Putamen ¹
	Paleostriatum ² (globus pallidum)	Internal segment External segment
B. Subthalamic nucleus		
C. Substantia nigra	Pars compacta Pars reticulata	
D. Ventral tegmental area		
E. Pedunculopontine nucleus		

¹ Includes the nucleus accumbens and ventral striatum

² Includes the ventral pallidum

already known, but several new associations of symptoms have also been identified (see /78,79/ for a comprehensive coverage). This has created more thorough clinical anatomical correlations, although it has not brought an end to the search for a proper terminology suitable for both the clinician and the neurobiologist. The expression "movement disorders", originally used by Gerstmann and Schilder in the 1920s /80,81,82,83,84,85,86/, has been recently re-introduced to indicate "that group of neurological dysfunctions in which either a paucity of voluntary movements or excess of involuntary movements occur" /78/. This term is quite satisfactory not only for the specialist, who treats such diseases, but also for other physicians and for non-medical personnel, who can readily use it to identify diseases and refer the patients to the most appropriate specialist. The use of this straightforward clinical definition eliminates all the ambiguity related to the use of the term extrapyramidal, and retains the concept of the extrapyramidal system, which originated from clinical observations before it was applied to neurobiological research (see above). Therefore, having unravelled the Gordian knot of ambiguity, two questions arise: (1) is it possible to achieve a comprehensive neurobiological understanding of the clinical entities defined as movement disorders? (2) what is the relationship between movement disorders and the anatomical entity called motor ganglia?

The first question will be dealt with first. If an affirmative answer is to be given, the solution must be quite different from the framework assembled around the classic idea of the extrapyramidal system. Such a classic view is summarized by Jung and Hassler's /73/

anatomical synopsis, which is the most evolved attempt to define the coherent and comprehensive set of motor pathways under the term extrapyramidal system. These authors elaborated on Wilson's dualism, and proposed that pyramidal and extrapyramidal pathways constitute two parallel descending systems, characterized by quantitative and qualitative differences. The first mainly consist of a more complex organization of the extrapyramidal pathways, which are connected with different thalamic nuclei and cortical territories. In fact, there is just one pyramidal tract while, according to Jung and Hassler /73/ extrapyramidal pathways consist of five main tracts (i.e., "systems of the putamen, of the caudate and ruber, of the vestibular and interstitial nucleus, of the reticular formation, and of the nigra") all projecting to the spinal cord (Fig. 3). Qualitative differences include a different nature of pyramidal and extrapyramidal control of motor activity, which is interpreted in the light of existing dualistic theories on nervous function (e.g., according to Hess' /89/ formulation, the pyramidal system is "teleokinetic", i.e., goal-directed, while the extrapyramidal is "ereismatic", i.e., supportive). Jung and Hassler /73/ also identified as extrapyramidal the clinical pictures observed in experimental and natural pathological conditions, characterized by lesions of the extrapyramidal system. This view, which largely relies on old experiments performed using classical anatomical and physiological techniques, must be regarded as obsolete.

During the last twenty years, the development of new anatomical methodologies has produced a more detailed knowledge of the intrinsic organization of the brain. In particular, the chemical identity of neurones and their discrete topographical arrangement have been studied by means of histochemical and immunohistochemical techniques /90/. Also, the hodology of the central nervous system has been re-written by using axonal tract tracing methods /91/. An enormous amount of knowledge has been acquired by means of these techniques. For example, the midbrain efferent tract, which in 1964 was recognized as a pure dopaminergic system /92/, was only a few years later found to have a complex neurochemical composition /93/ (Fig. 4).

The classical analytical approach, aimed at defining different anatomical substrates for each individual function, provided a valuable guideline for experimental studies, at a time when new powerful techniques were causing a rapid increase in knowledge. However, the large amount of neurobiological data now available require revised conceptualizations, and necessitate new attempts to achieve a comprehensive unified terminology.

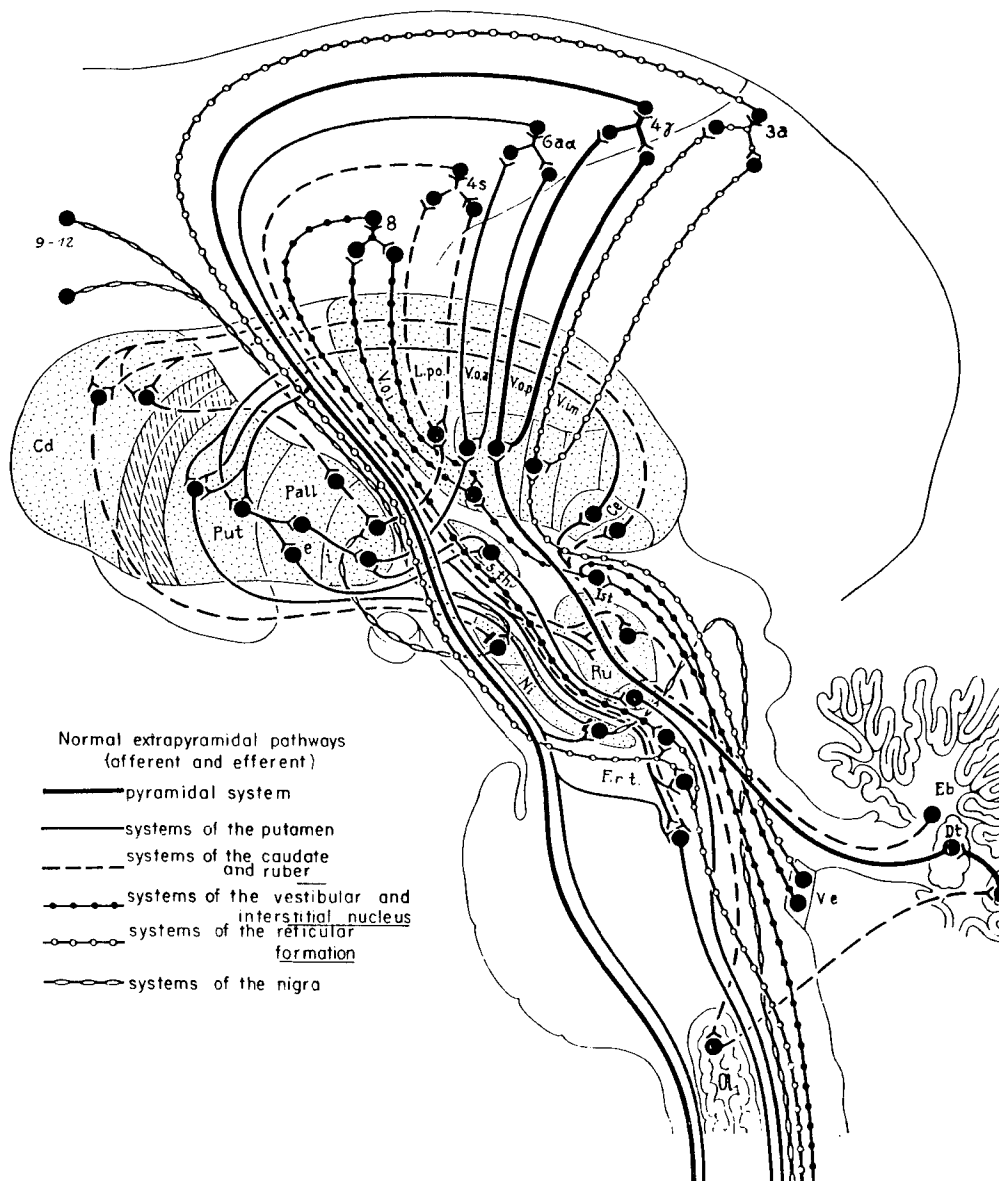


Fig. 3: Diagram of the organization of the pyramidal and extrapyramidal systems, as proposed by Jung and Hassler /73/. This is the most complete attempt to define the extrapyramidal system as a coherent and comprehensive set. A dualistic view is also evident here. Afferent connections to both the pyramidal and extrapyramidal systems are thought to arise from the cerebellum (from the dentate and emboliform nuclei, respectively); they are seen as parallel and independent tracts. Efferent pathways from the caudate nucleus reach the substantia nigra and the pallidal complex. Efferent pathways from the putamen are connected to the substantia nigra and to the thalamus (after passing through the internal pallidum). According to this scheme, the efferent mechanisms are the reticulospinal tracts, the pyramidal tract and the central tegmental tract to the inferior olive, which acts as a feedback mechanism through the cerebellum. Abbreviations: *Cd*, caudate nucleus; *Ce*, centromedian nucleus; *Dt*, dentate nucleus; *Eb*, emboliform nucleus; *F.rt*, reticular formation; *Ist*, interstitial nucleus; *L.po*, nucleus lateropolaris (probably the reticular nucleus); *Ni*, substantia nigra; *Ol*, inferior olive; *Pall.e*, globus pallidum, external segment; *Pall.i*, globus pallidum, internal segment; *Put*, putamen; *Ru*, red nucleus; *Ve*, vestibular nuclei; *V.im*, ventral intermediate (lateral) nucleus; *V.o.a.*, ventral oral (anterior) nucleus anterior part; *V.o.i.*, ventral oral (anterior) nucleus, inner part; *V.o.p.*, ventral oral (anterior) nucleus, posterior part; numbers refer to cortical areas according to Brodmann's classification. (From Jung and Hassler /4/, by courtesy of the American Physiological Society)

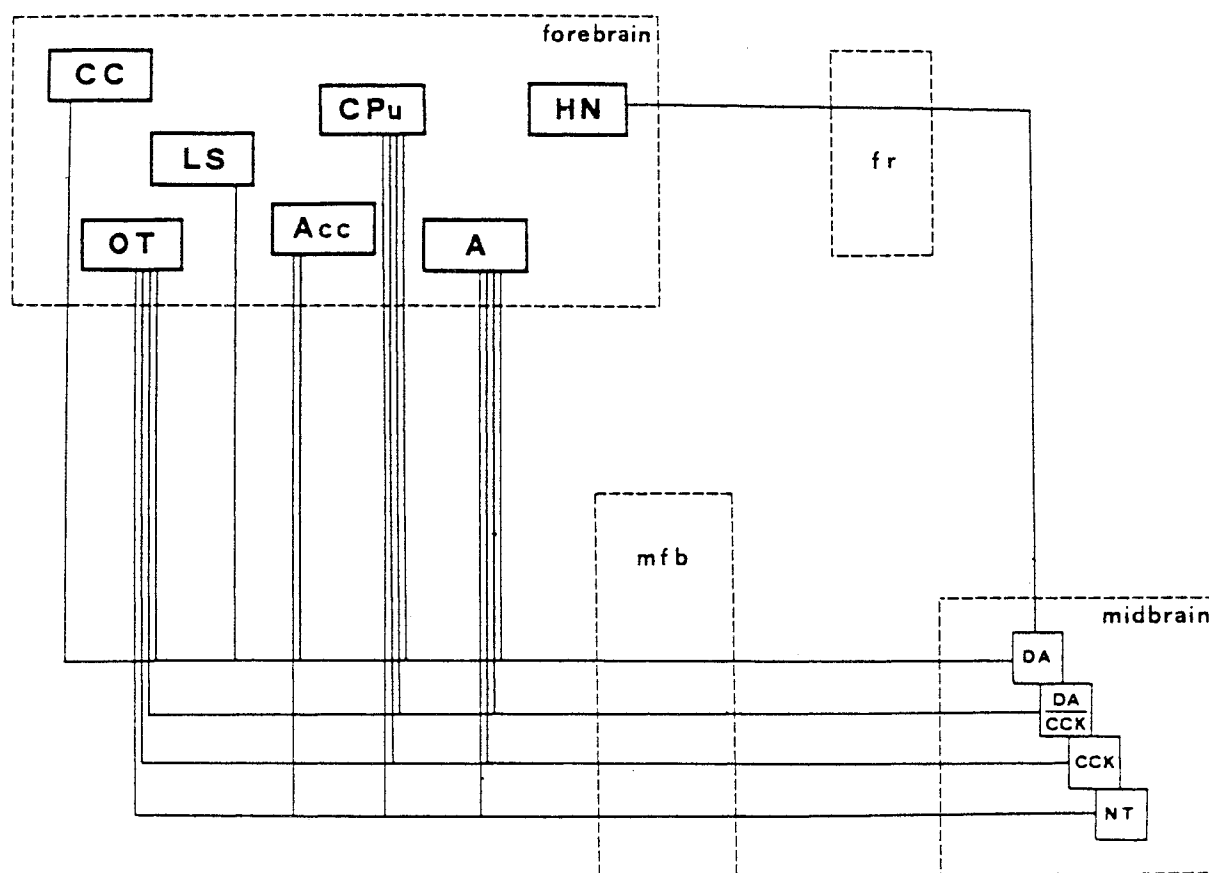


Fig. 4: Diagram of the organization of the midbrain efferent system, which corresponds to just one of the connections depicted by June and Hassler /4/. The increase in analytical knowledge has been enormous. Cell bodies which are located in the midbrain contain dopamine (DA), cholecystokinin (CCK), or neurotensin (NT); they project to several rostral forebrain regions via the medial forebrain bundle (mfb) and the fasciculus retroflexus (fr). Forebrain target sites are abbreviated as follows: Acc, nucleus accumbens; CC, cerebral cortex; CPu, neostriatum; HN, habenular nuclei; LS, lateral septum; OT, olfactory tubercle. (From Albanese and Altavista /93/, by courtesy of Masson Italia Periodici)

Based on the available data dualistic or triadic interpretations seem untenable and integrated analyses would appear more valid. For example, many recent hodological and physiological experiments indicate an interdependence of the motor ganglia and other forebrain regions which are characterized by well established sensorimotor or limbic competences /94,95/.

EPILOGUE

Anatomical and physiological research performed in recent years has identified two specific patterns of organization in the motor ganglia, Feedback and Parallelism.

Feedback. Following some earlier speculations /96,97,98,99/, Penney and Young /100/ proposed that one feature of the motor ganglia consists of their

organization into feedback loops. Figure 5 depicts four such closed loops. The main loop is a positive feedback circuit travelling from the motor cortex through the striatum, medial globus pallidum, and thalamus to return to the cortex. A second loop reciprocally connects the globus pallidum with the subthalamic nucleus. The third is the nigro-striato-nigral loop. Finally, the fourth loop links the neostriatum to the globus pallidum, which in turn projects back to the neostriatum via the thalamus.

Parallelism. According to DeLong and coworkers /101/, the motor ganglia contain segregated, parallel, cortico-subcortical loops subserving sensorimotor and associative functions. The dual scheme of organization, originally proposed by these authors, has been later expanded to a set of five motor ganglia-thalamo-cortical parallel circuits (Fig. 6) /102/. Thus, the motor ganglia can "be viewed as components of multiple parallel,

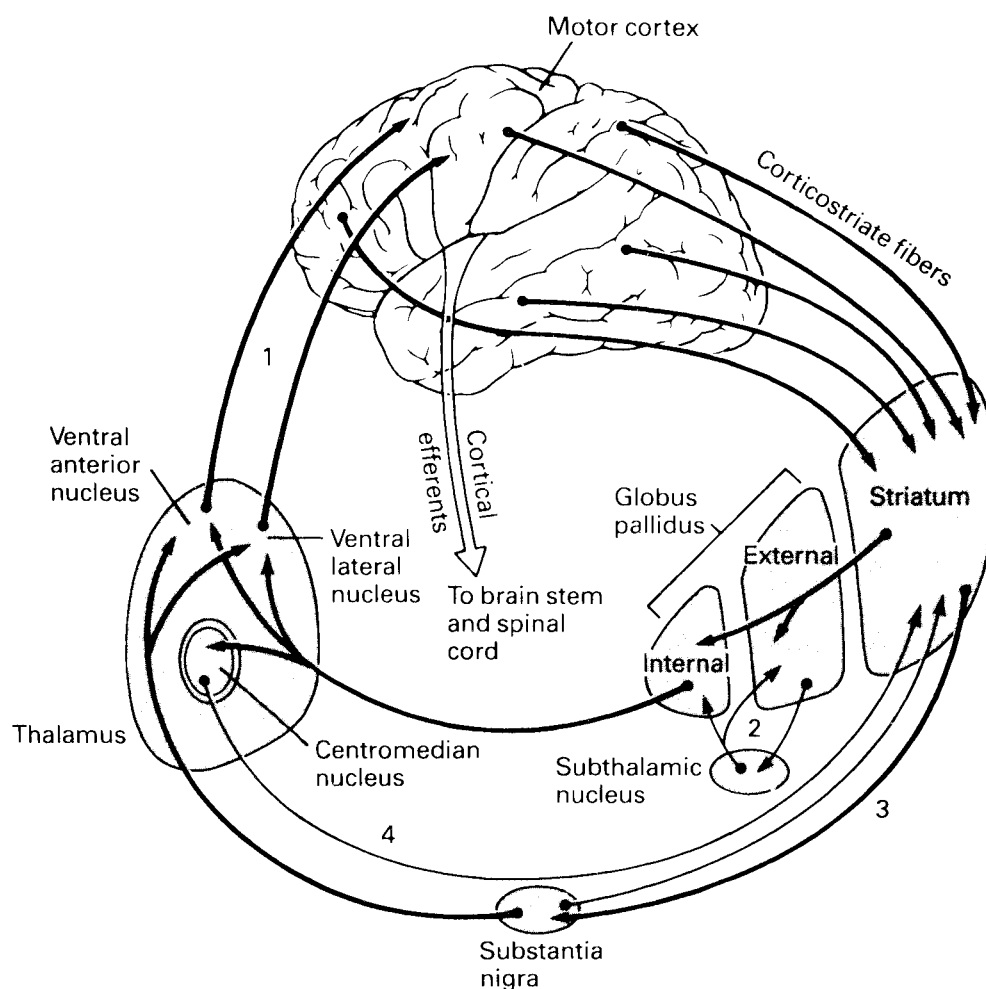


Fig. 5: A simple scheme of the functional hodology of the basal ganglia consisting of four interconnected loops. The first, and the most important, runs from the neocortex to the basal ganglia and thalamus and then back to the frontal cortex. The second runs from the external segment of the globus pallidum to the subthalamic nucleus and back to both segments of the globus pallidum. The third loop runs from the striatum to the substantia nigra and then back to the striatum. The fourth loop runs from the striatum through the globus pallidum and centromedian thalamic nucleus back to the striatum. (From Côté and Crutcher /133/, adapted from DeLong /116/. Copyright 1985, by Elsevier Science Publishing Company)

segregated circuits. Each [... of them] appears to receive input from several separate but functionally related cortical areas, traverse specific portions of the basal ganglia and thalamus, and project back upon one of the cortical areas providing input to the circuit, thus forming a partially 'closed' loop" /102/.

Based on the presence of feedback loops, motor ganglia may be defined as a set of brain nuclei controlling non-voluntary movement, which are reciprocally connected by a number of closed anatomical loops. This principle of organization is currently considered by many as a specific feature of the motor ganglia. Heimer /103/ considered the presence of a feedback loop through the thalamus and the cerebral cortex as a valid

argument supporting the striatal nature of the nucleus accumbens and of the olfactory tubercle. Also, it must be remembered that most pathways interconnecting with the motor ganglia are inhibitory (e.g., see /104/). This explains why the whole system is rather stable, as it is based on a continuous flow of inhibitory feedback information. Although it has always been accepted that the corpus striatum as a whole is the core of the motor ganglia, some differential functions of the neo- and paleostriatum have been elucidated quite recently. The neostriatum, which is chiefly afferent, collects information from several brain regions (i.e., cerebral cortex, thalamus, midbrain tegmentum, subthalamic nucleus, pedunculopontine nucleus, etc. /74/). In addition, func-

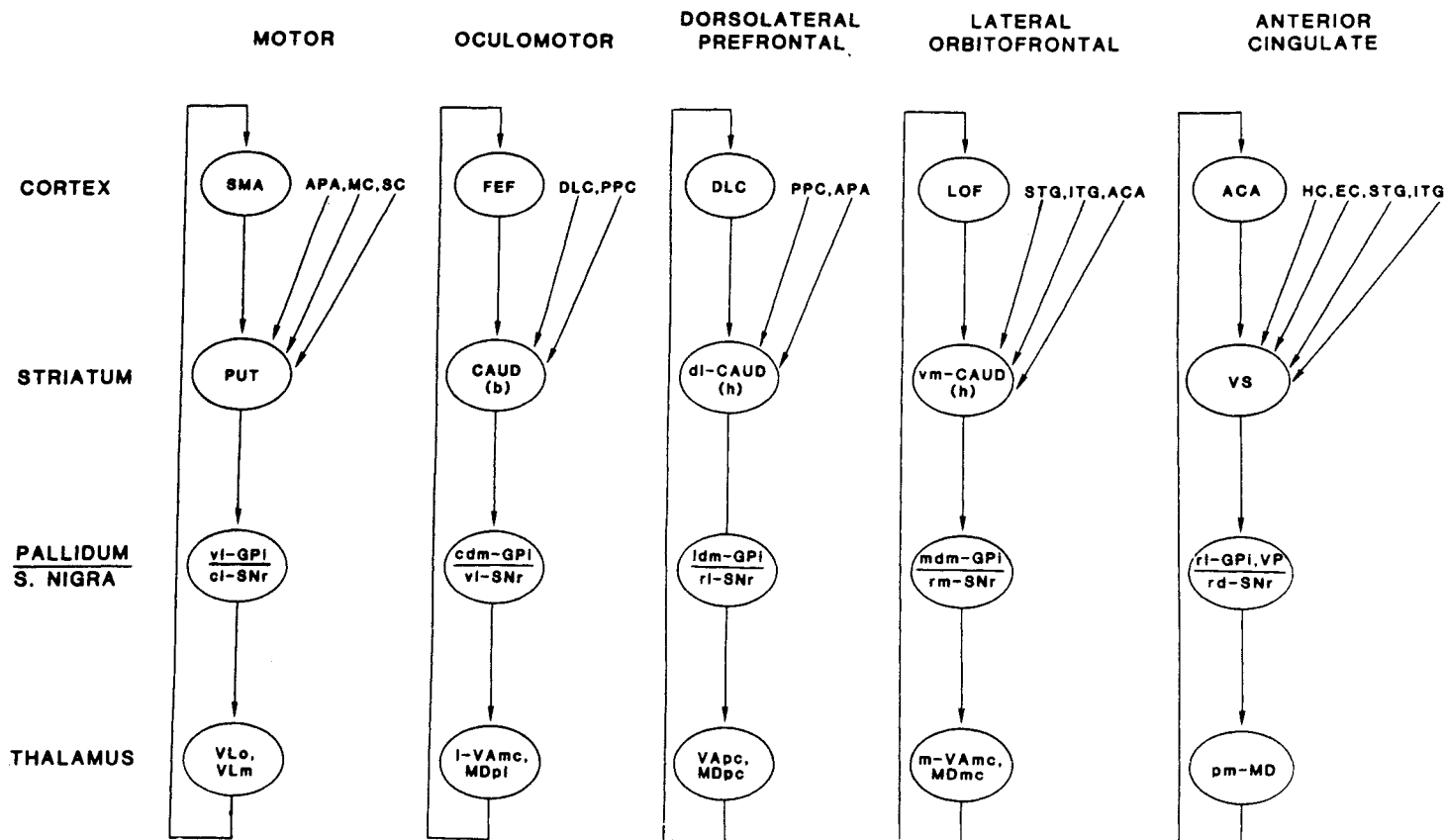


Fig. 6: Schematic diagram of the postulated parallel organization of the five motor ganglia-thalamo-cortical circuits. According to Alexander and coworkers /102/, "each circuit engages specific regions of the cerebral cortex, striatum, pallidum, substantia nigra and thalamus". Abbreviations: *ACA*, anterior cingulate area; *APA*, arcuate premotor area; *CAUD*, caudate nucleus, (b) body, (h) head; *DLC*, dorsolateral prefrontal cortex; *EC*, entorhinal cortex; *FEF*, frontal eye fields; *GPI*, internal segment of globus pallidum; *HC*, hippocampal cortex; *ITG*, interior temporal gyrus; *LOF*, lateral orbitofrontal cortex; *MC*, motor cortex; *MDmc*, pars magnocellularis of nucleus medialis dorsalis; *MDpc*, pars parvocellularis of nucleus medialis dorsalis; *MDpl*, pars paralamellaris of nucleus medialis dorsalis; *PPC*, posterior parietal cortex; *PUT*, putamen; *SC*, somatosensory cortex; *SMA*, supplementary motor area; *SNr*, pars reticulata of substantia nigra; *STG*, superior temporal gyrus; *VAmc*, pars magnocellularis of nucleus ventralis anterior; *VApC*, pars parvocellularis of nucleus ventralis anterior; *VLm*, pars medialis of nucleus ventralis lateralis; *VLo*, pars oralis of nucleus ventralis lateralis; *VP*, ventral pallidum; *VS*, ventral striatum. Prefixes: *cl-*, caudolateral; *cdm-*, caudal dorsomedial; *dl-*, dorsolateral; *l-*, lateral; *ldm-*, lateral dorsomedial; *m-*, medial; *mdm-*, medial dorsomedial; *pm-*, posteromedial; *rd-*, rostradorsal; *rl-*, rostromedial; *rm-*, rostromedial; *vl-*, ventrolateral; *vm-*, ventromedial. (From Alexander and coworkers /102/, reproduced with permission. Copyright 1986 by Annual Reviews Inc.)

tional tasks of the caudate nucleus and of the putamen are specifically segregated.

In the paleostriatum, the internal segment of the globus pallidum is the main efferent site of the motor ganglia, which chiefly projects to the thalamus via the ansa lenticularis. During transfer of information from the neostriatum to the internal pallidal segment, data are processed according to two main principles. First, the **convergence** occurring along the striatopallidal pathway explains the smaller capacity of the ansa lenticularis as compared to the neostriatal afferent pathways. As shown by Percheron and coworkers /105/ dendritic branches of pallidal neurones, which form disc shaped receptive fields lying perpendicular to the incoming striatopallidal tract, are primarily responsible for the concentration of information. Second, data are **filtered** by means of serial and parallel transfer along feedback loops originating in the neostriatum and in the globus pallidum. In the neostriatum data are mainly altered by information contained in the midbrain (striato-nigro-striatal loop). In the external pallidal segment, data are principally filtered by information contained in the subthalamic nucleus (pallido-subthalamo-pallidal loop). Finally, when data have reached the internal pallidal segment, they are mainly influenced by the pedunculopontine nucleus (pallido-tegmental-pallidal loop). In addition to the above mentioned disynaptic loops, other polysynaptic loops account for additional information modulation. Eventually, the motor ganglia convey some information to the thalamus (Figs. 5,6) where data are subject to further alterations before reaching the frontal lobe cortex.

This schematic picture makes it clear that the corticospinal tract is the main final pathway for descending information elaborated in the motor part of the motor ganglia. Additional information is also funnelled through the tectospinal and reticulospinal tracts, which originate directly in the motor ganglia and descend to the spinal cord. These pathways are mainly devoted to visuomotor integration and gamma motoneurone control /106/. therefore, although they are capable of directly affecting spinal cord neurones, motor ganglia exert their influence primarily on the cerebral cortex. Such organization is opposite Jung and Hassler's /73/ classic concept of the extrapyramidal system, which consisted of several descending pathways running parallel to the corticospinal neurones. In addition, the functional anatomical organization of the motor ganglia also differs from that of the cerebellum, which is reciprocally connected with both the cerebral cortex and the spinal cord. Hence, while the organization of cerebellar pathways is consistent with

the main function of the cerebellum, which acts as a centre for integrating movement commands and the movements themselves (see /107/), the organization of the motor ganglia is consistent with the view that they act as a processor of motor programmes and commands. The architectural organization of motor ganglia is also in sharp contrast with that of the cerebellum; the first are patchy and redundant while the latter displays a crystalline geometry. The quality of information processed in the motor ganglia is therefore highly specific and it differs significantly from that occurring in the cerebellum.

Although it is still poorly understood, the relationship between the motor ganglia and movement disorders is definitely a very close one. In addition to classic clinico-anatomical studies, a large amount of new information has appeared in recent years due to the availability of experimental animal models for movement disorders. The expectations of having made experimental replicas of the human diseases were disappointing in most cases. However, the study of experimental movement disorders in animals significantly improved our knowledge about the functional arrangement of the motor ganglia in normal and abnormal conditions. Interestingly, progress has occurred chiefly through those studies in which no over-bold attempts to draw correlates with human diseases were made.

Following the observations of a long-lasting depletion of noradrenaline from peripheral sympathetically innervated organs /108,109/, Thoenen and Tranzer /110/ observed that 6-hydroxydopamine is capable of producing a "chemical sympathectomy". This neurotoxin was later injected directly into the brain or into the cerebro-spinal fluid to perform chemically specific lesions of catecholaminergic neurones /111,112/.

Ungerstedt /113/ observed spontaneous rotation and a unilateral sensorimotor impairment in rats which received a unilateral injection of 6-hydroxydopamine into the nigrostriatal pathway. This approach provided the first measurable experimental condition characterized by a selective damage of the dopaminergic neostriatal tract. In fact, Ungerstedt's model was effectively used, not only to test the efficacy of several anti-parkinsonian drugs (l-DOPA /113/, apomorphine /114/, ergot derivatives /115/, etc.), but also to show that grafts of foetal dopaminergic nerve cells may partially restore normal motor conditions /116,117/. Similar results were later shown in primates. Unilateral injections of 6-hydroxydopamine in the lateral hypothalamus of monkeys /118/ causes a unilateral hypokinesia resembling that observed after large coagulations of the substantia nigra /119/. In

summary, this line of research has been able to highlight many aspects which are relevant to the understanding of Parkinson's disease. It has also shown that animals treated with 6-hydroxydopamine cannot be used as experimental models for an idiopathic human disease which is characterized by a diffuse impairment of central dopaminergic pathways /120/ and by some additional biochemical and pathological features (see also /121/).

Unlike 6-hydroxydopamine, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) crosses the blood-brain barrier and poisoned human beings /122/ before it was recognized as a useful experimental tool for animal studies /123/. However, the value of the MPTP model for inducing Parkinson's disease is controversial (see a review by Langston /124/). On the one hand, the finding of eosinophilic inclusions in aged monkeys treated with MPTP /125/ has provided a striking similarity with human Lewy bodies, which are an important feature of Parkinson's disease; on the other hand the recent finding of an even pattern of dopamine loss in the corpus striatum /126/ is clearly at variance with biochemical data obtained from patients with idiopathic Parkinson's disease /127/. It can be seen from experimental and clinical evidence that MPTP is neither just a dopaminergic neurotoxin (such as 6-hydroxydopamine) nor a normal agent for the human idiopathic disease. Therefore, any attempt to solve this controversy fulfils some expectations which disappointing others. The significant point, nonetheless, is that a neurotoxic tool is presently available which permits the exploration of the motor ganglia organization in normal and abnormal conditions. DeLong /128/ showed that, after MPTP poisoning, spontaneous tonic activity of neurones located in the internal segment of the pallidum is increased, while that of neurones located in the external segment is reduced. Also, physiological balance between the two pallidal segments is altered and the selectivity of signal processing between them is significantly impaired.

Several other experimental animal models for movement disorders have been described. As reviewed by Crossman /129/, a number of dyskinetic syndromes can be experimentally produced in primates. Crossman and coworkers /130/ have studied the functional role played by neurones located in the subthalamic nucleus in monkeys affected by different kinds of movement disorders. When bicuculline is injected in the subthalamic nucleus, or in the lateral pallidal segment, hemiballism or hemichorea occur. Both syndromes are characterized by decreased neural activity in the medial pallidal segment and in the subthalamic nucleus. On the contrary, MPTP-induced parkinsonism is associated with increased

activity in the striatum and in the subthalamic nucleus.

In conclusion, the availability of experimental models for movement disorders offers new possibilities for exploring the normal and abnormal organization of the motor ganglia. These animal models are definitely more important for their use as neurobiological tools than they are for clinical work. However, they make it possible to focus on new and old issues about diseases, which require clinically related analysis in order to be answered. To this end, the study of MPTP-induced parkinsonism has focused on the following two problems, which are of primary importance in the understanding of Parkinson's disease: (1) the influence of environmental pollutants, which may act as exogenous toxic factors; and (2) the possibility that the entire pathological process may occur in the nerve terminals. The first issue has been addressed by studies on the epidemiology of Parkinson's disease (see /131/132/), while, due to the difficulty in finding a proper methodological approach, the second issue is a difficult challenge for research in man.

CONCLUSIONS

1. The "extrapyramidal system" does not exist. This anatomical term has only a historical value, because it implies the existence of a set of multiple descending pathways coursing outside the pyramids.
2. The "motor ganglia" are a coherent set of brain structures distributed throughout the brain, which are devoted to processing motor programmes and commands. For reasons of clarity, the term "basal ganglia" should be avoided.
3. The expression "movement disorders" is a simple and handy way of describing a group of diseases, which are characterized by complex, and sometimes heterogeneous, clinical signs. The expression "extrapyramidal disorders" can be used as a synonym of movement disorders.
4. Movement disorders are evidently associated with alterations in information processing within the motor ganglia. However, it is clear that, until a thorough neurobiological understanding of the functions of the motor ganglia is achieved, research progress may be hindered, rather than quickened, by inappropriate clinical anatomical correlations.
5. In contrast to a fairly good knowledge of the functional organization of motor systems, analytical studies of their neural modelling have not been pursued yet. The study of non-linear neural networks /134/, which constitute the motor ganglia, are expected to provide the first measurable theories about their general organization.

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