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The Unbearable Lightness of the Extrapyramidal System

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The concept of the extrapyramidal system comprises an amalgam of disparate and often conflicting ideas with a tortuous history. To the theoretical neuroscientist or practicing clinician, it promptly evokes semantic associations that are hardly reminiscent of its original meaning. The purpose of this article is to revisit the sources of the extrapyramidal concept and to examine the transformations that it went through from its inception, in the late 1890s, up to the neuroimaging revolution of the 1980s. Our review shows that the use of "extrapyramidal" as a surrogate for the basal ganglia, disorders of movement, or certain manifestations of spastic hemiplegia does not apply to humans; rather, it represents the historical product of the unwarranted translation of results of animal experimentation into the interpretation of clinical findings on human patients, misguided clinico-anatomic deductions, and fanciful phylogenetic notions. We conclude that the extrapyramidal concept is a valid and robust anatomic *concept as long as it strictly refers to the collection of descending fibers originating in a few discrete brainstem tegmental motor nuclei that project to the spinal cord.*

Keywords extrapyramidal system, basal ganglia, pyramidal syndrome, hemiplegia, Babinski sign, history of neurology, movement disorders

Introduction: The Extrapyramidal System at the Dawn of the Neuroimaging Era

In the early 1980s, the extrapyramidal concept encompassed four relatively independent notions expressing a capricious blend of clinico-anatomic observations and the results of experiments on rodents, carnivores, and monkeys:

1. An anatomical collection of nuclei and fiber tracts that received projections from restricted sectors of the cerebral cortex and sent projections to the segmental apparatus of the brainstem and spinal cord through a series of sequential synaptic relays that originated in discrete nuclei of the brainstem tegmentum and followed a retropyramidal course (Denny-Brown, 1966);

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2. A heterogeneous group of syndromes with prominent abnormal involuntary movements and postures (AIMP) and mild or absent symptoms of pyramidal tract injury, that is, spastic paralysis (Barbeau et al., 1981);
3. A collection of subcortical structures, only in part congruent with those of Item 1, which harbored the histopathologic substrates of AIMP (Jakob, 1925) and
4. The pathologic substrate of the core symptoms of spastic hemiplegia (Wiesendanger, 1984).

Exactly which symptoms of the hemiplegic syndrome should be attributed to damage to extrapyramidal structures were never consensually settled.

For a number of reasons that need not concern us at this point, the aforementioned views have always been difficult to reconcile with the sporadic report of patients with spastic hemiplegia due to injuries restricted to one or to both pyramidal tracts (Brown & Fang, 1961; Fisher, 1977; Ropper, Fisher, & Kleinman, 1979; Paulson, Yates, & Paltan-Ortiz, 1986; Tovar-Moll et al., 2007). However, the rarity of such cases and the sophistication of experimental physiology in the decades that preceded the neuroimaging revolution shifted the balance in favor of comparative models as the most acceptable explanations for the human condition (Lawrence & Kuypers, 1968; Wiesendanger, 1984). The present article investigates the roots of the extrapyramidal concept as portrayed in the four main views depicted above in an attempt to shed light on the century-old controversy regarding its validity.

The Birth of the Extrapyramidal System[1]

The term "extrapyramidal" was coined by Johann Prus in 1898 (as translated by Willner & Kennard, 1948).[2] As a physiologist, Prus intended to ascertain whether the pyramidal tracts were the pathways that conveyed experimentally evoked epileptic activity from the cerebral cortex to the cord. He cut the pyramidal tracts in the internal capsule, peduncle, pons, pyramid, and spinal cord, first on one and then on both sides. Experiments were conducted on dogs without narcosis "so as not to reduce the excitability of the cortex" (p. 134). Prus expected that the pyramidal section would stop the seizures, but what he found intrigued him:

> In view of the fact that bilateral transection of the pyramidal tracts does not prevent the appearance of bilateral epileptic attacks, i.e., the transmission of excitation from the cortex to the muscles, it is established beyond doubt that in the case of transection of the pyramidal tracts the pathways by means of which transmission of cortical epilepsy is effected must lie outside the pyramidal tracts and outside the so-called pontine tracts.
>
> To distinguish these apparently motor pathways from pyramidal and pontine tracts we shall call them extrapyramidal tracts. (p. 136)

[1]For the purposes of our argument, it is irrelevant whether different authors refer to the descending tegmental motor fascicles (e.g., reticulospinal, rubrospinal) as retrospinal (Kennedy, 1997), nonpyramidal (Mettler, 1948), or parapyramidal (Marie & Guillain, 1904; Zülch, 1975) because they all refer to the same anatomical construct.

[2]The expression "extrapyramidal tracts" *(Extrapyramidenbahnen)* was used before Prus by Viennese neurologists at the end of the nineteenth century (Anton, 1893). Future studies will have to decide if the priority of the concept, now awarded to Prus, should be shared with other equally committed authors.

To establish the importance of extrapyramidal pathways in the transmission of epilepsy, Prus made several incisions in the midbrain tegmentum at the level of the posterior quadrigeminal plate avoiding the pyramidal and corticopontine tracts. Because epileptic fits could no longer be elicited by cortical stimulation, he postulated that "conduction of cortical epilepsy takes place via centrifugal motor pathways which lie outside the pyramidal, as well as the frontal and temporo-occipital tracts, and which I have called extrapyramidal tracts" (p. 137). A possible function of this "so far unknown centrifugal, *i.e.*, motor, pathway" was also advanced:

> As far as the significance of the extrapyramidal tracts is concerned, I believe [. . .] that the extrapyramidal tracts conduct excitation mainly for the associated movements and not the special movements (Sonder-bewegungen) in Munk's sense. (p. 139)

The Extrapyramidal System Steps Out Into the Clinic

Although the idea of descending tegmental (i.e., retropyramidal) motor pathways was independently taking shape in the mind of clinicians,[3] Prus' findings exerted little initial appeal to physiologists and clinicians (Louis, 1993). Only in 1912 did the term extrapyramidal come back to the clinical literature, this time to stay. Without mentioning Prus' work, Wilson (1912) applied the concept to either a class of motor symptoms or an anatomical construct. On the former, he stated:

> It may be remarked in this connexion [*sic*] that two of my own cases were at one time thought to be hysterical, and treated accordingly. Our ignorance of the symptomatology of extrapyramidal motor affections, I believe, is the explanation of mistakes of this sort. (p. 311)

Later on, Wilson averred that "a lesion of the pyramidal system is not by itself sufficient to produce involuntary movements" (p. 467) and embraced the "strong assumption" that "other, extrapyramidal, paths must be injured" for involuntary movements to occur at all. These pathways, he argued, made up a long afferent-efferent loop whose operation was relatively independent from the cerebral cortex (p. 467):

> The former [afferent] 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 [efferent] is the lenticulo-rubrospinal system, which is perhaps less well known. The nucleus lentiformis is practically independent of the cortex, but has important descending connexions, via the ansa lenticularis, with the regio subthalamica, the corpus Luysii, and the nucleus ruber. From the latter the path is continued as the rubrospinal

[3] As early as in 1901, Collier and Buzzard stated that "Monakow's bundle, the ponto-spinal tract, and vestibulo-spinal tracts, and some fibres of the dorsal and ventral longitudinal bundle may be considered together as constituting a system descending from various lower levels of the brain and probably constituting an alternative path by which motor impulses reach the spinal cord, the other path being the pyramidal system" (p. 212).

> tract of Monakow, to the anterior horns of the spinal cord. To lesions of this system I attribute very important symptoms, as will duly appear. It is to be noted that there is a kind of "shortcircuit" between the corpus striatum and the optic thalamus.

The Irresistible Chant of Phylogenesis

Beyond the claim that "very important symptoms" (those of progressive hepatolenticular degeneration) resulted from "lesions of this system" (i.e., the extrapyramidal system), two implicit assumptions in Wilson's writings betray the edge and bias of contemporary anatomical knowledge, which was largely driven by the allure that phylogenetic thinking exerted on scholars and lay public alike (Hodos & Campbell, 1969). *The Origin of Species by Means of Natural Selection* had been published only 42 years earlier, bolstered by the burgeoning science of geology, "which investigates the successive changes that have taken place in the organic and inorganic kingdoms of nature; it inquires into the causes of these changes, and the influence which they have exerted in modifying the surface and external structure of our planet" (Lyell, 1830, p. 1).

The geological model implied that the Earth had a history, a history that was recorded in layers. As long as fossils became progressively more ancient as deeper layers were probed, geology opened the way to Darwin's ideas that life on Earth had a history as well (Lyell, 1847):

> In that case one new layer of matter may be superimposed upon another for a thickness of many thousand feet, and the fossils of the inferior beds may differ greatly from those entombed in the uppermost, yet every intermediate gradation may be indicated in the passage from an older to a newer assemblage of species. (p. 184)

We concur with Magoun (1958) that the geological model exerted a pervasive influence on the earliest scientific attempts to make sense out of the complexity of the human nervous system in health and disease. The idea of cortico-striato-pallido-thalamo-cortical loops, a truism to modern neuroscientists (Cummings, 1993), would probably be felt as quite odd by a *Belle Époque* neurologist used to seeing the mammalian nervous system as a layered structure in which, much like the Earth, newer layers were superimposed upon phylogenetically older ones following a rigid hierarchical organization (Jackson, 1887):

> It is not possible at this stage to do more than state [. . .] the evolutionary hierarchy of the nervous centres. . . . The periphery is the real lowest level; but we shall speak of three levels of central evolution. (1) The lowest level consists of anterior and posterior horns of the spinal cord, and of Clarke's (visceral) column, and Stillings nucleus and of the homologues of these parts higher up. It represents all parts of the body most nearly directly. . . . (2) The middle level consists of Ferrier's motor region, with the ganglia of the corpus striatum, and also of his sensory region. It represents all parts of the body doubly indirectly. (3) The highest level consists of highest motor centres (præ-frontal lobes), and of highest sensory centres (occipital lobes). They represent all parts of the body triply indirectly. These highest sensori-motor centres make up the "organ of mind" or physical basis of consciousness; they are evolved out of the middle,

> as the middle are out of the lowest, and as the lowest are out of the periphery; thus the highest centres re-re-represent the body—that is, represent it triply indirectly. (pp. 29–30)

Soon after Wilson advanced his model, Hunt (1917a, 1917b) proposed that the *globus pallidus* was the "essential" efferent motor nucleus of the *corpus striatum*, exercising "a controlling influence on automatic and associated movements through the medium of the extra-pyramidal motor tracts" (1917a, p. 116). In subsequent publications, Hunt (1918) elaborated on the idea of two distinct motor systems—the "paleokinetic system," which was phylogenetically old and responsible for the execution of automatic and associated movements, and the "neokinetic system," which subserved isolated synergic movements of cortical origin, such as those of hands and fingers. Hunt postulated that the anatomical substrate of the paleokinetic system was a "striospinal" collection of basal nuclei and related projections that ran in parallel with the pyramidal tracts to the motor neurons of the spinal cord (p. 309).

Besides explaining the automatic-voluntary dissociations observed in the clinic (e.g., Foix, Chavany, & Marie, 1926), the view that certain subcortical nuclei established afferent-efferent loops with considerable functional autonomy from the cerebral cortex concurred with the belief that, as in other mammals, automatic movements in humans were primarily organized at subcortical levels (de Oliveira-Souza, Moll, & Graman, 2011).

Truly, the cortical independence of the thalamo-striatal circuit might promptly have been falsified had the real nature of Muratoff's subcallosal fasciculus been duly appreciated. Unfortunately, the status of the subcallosal fasciculus as a prominent corticostriatal projection fiber system was established beyond doubt only much later (Schmahmann & Pandya, 2007b). Moreover, notwithstanding the fact that functionally relevant projections reach the striatum from discrete thalamic nuclei, particularly the centromedian (McLardy, 1948), only in the second half of the twentieth century were the predominant direction of projections from the lenticular nucleus to the thalamus emphasized (Parent & Hazrati, 1995), thus bringing Forel's (1877) work back to the center stage of basal ganglia hodology, but inverting the direction of the neural conduction that prevailed in the models espoused by Wilson, Jakob, and Hunt.

Extrapyramidal as a Short Label for Syndromes Of Nonparalytic Abnormal Involuntary Movements and Postures

Despite contrary evidence on the prominence of the extrapyramidal nuclei and tracts in humans (Gee & Tooth, 1898; Marie & Guillain, 1903; Thomas, 1903; Long & Roussy, 1908; Weisschedel, 1937), the anatomical speculations advanced by Wilson and Hunt were quickly taken for granted by the medical and scientific community (see Figure 1). The extrapyramidal concept increasingly appeared in scientific journals and textbooks, in a clear indication that the ill-defined brainstem pathways envisaged by Prus had blossomed into an intricate collection of nuclei and fiber pathways seated at the base of the cerebral hemispheres. The misleading assumption that the basal ganglia massively projected to the brainstem extrapyramidal nuclei was instrumental in shifting the focus from Prus' brainstem tracts to the basal ganglia:

> Although [the term, extrapyramidal system] can be interpreted literally as denoting all of the brain's effector mechanisms that do not involve the

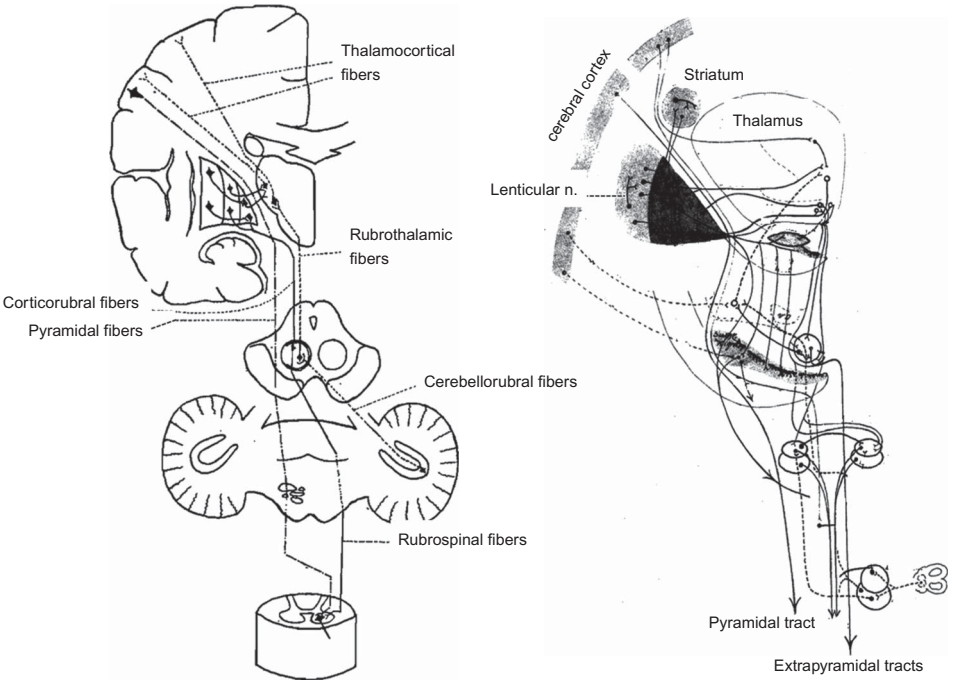

Figure 1. Prevailing early-twentieth-century conceptions of the extrapyramidal system (modified from Wilson [on the reader's left] and Jakob). Note the increase in the complexity of the extrapyramidal nuclei and pathways and the emphasis on parallel descending motor pathways. Surprisingly, the extrapyramidal pathways in both diagrams were wholly hypothetical and for the most part refuted by contemporaneous (Gee & Tooth, 1898; Marie & Guillain, 1903; Long & Roussy, 1908) and later clinico-anatomic evidence (Sie, 1956; Nathan, Smith, & Deacon, 1996). Subsequent observations showed that the pyramidal tracts are the critical structures through which abnormal basal ganglia activity finds expression as AIMP, the extrapyramidal fiber systems being actually irrelevant for this purpose.

> pyramidal tract, convention over the years has made the term very nearly synonymous with the basal ganglia and their efferent connections. (Nauta & Domesick, 1984 p. 3)

In this regard, a fundamental distinction pervades the pyramidal and extrapyramidal concepts. Whereas the former had its origins in human pathology (Schmahmann & Pandya, 2007a), the latter began as an anatomical postulate that fulfilled the need to explain certain experimental findings on dogs (Prus, 1898, as translated by Willner & Kennard, 1948). By the end of the 1880s, when the syndrome of cerebral hemiplegia had unequivocally been related to the degeneration of the pyramidal tracts (Thomas, 1910), the nonparalytic AIMP were just beginning to be parceled into discrete syndromes that were hesitantly related to discrete lesions of striopallido-thalamic sectors (Barbeau, 1958). The relative uniformity of spastic hemiplegia and the pyramidal tracts stood in sharp contrast with the difficulty in finding order within the chaos of torsions, shakings, clasps, jumps, grimaces, and howls, and tentatively relating these to the intricate anatomy of the basal ganglia and their fiber

connections (Finger, 1994). The anatomy and physiology of the extrapyramidal system were inextricably tied to the refinement of the phenomenology of AIMP (Jakob, 1925):

> The entire gray substance in this anatomic region [*striatum*, *pallidum*, *substantia nigra* and the subthalamic and red nuclei] is designated the extrapyramidal system, and the motor disturbances due to disease of these centers are called extrapyramidal motor disturbances. (p. 597)

Two Parallel Motor Systems

A final leap was the proposal that the extrapyramidal system was extensively represented in the cortex of the dorsolateral (Brodmann's area [BA] 6 and 8) and medial frontal (medial BA 6), parietal (BA 5 and 7), and temporal (BA 22) lobes. This rostral addition was again physiological because extrapyramidal was defined as the cortex that on direct stimulation gave rise to slow contraversive synergies of eyes, head, and trunk and flexion and extension of the ipsilateral limbs (Foerster, 1936). Conversely, damage or experimental ablation of the same areas caused a contralateral hemiplegic attitude and a proclivity to rotate the head to the side of the lesion—provided the precentral-pyramidal projection system was intact (Denny-Brown, 1966). The inclusion of the cerebral cortex in the extrapyramidal system compounded the view, supported by experiments on primates, that the human extrapyramidal system was organized from the cerebral cortex to spinal cord in parallel with the pyramidal tracts. This vertical formulation eventually superseded the layered geological model and introduced considerable order into the extrapyramidal concept because it allowed for a cortical control over the basal ganglia and related nuclei:

> Our own approach to these problems begins with the conception of the extrapyramidal system as a continuous latticework of motor organization extending from cerebral cortex to the reticular formation of the mesencephalon and lateral pons, and thence to spinal segments via the reticulospinal tracts. This is the primitive motor organization of the vertebrate nervous system, integrity of which is necessary for the special motor adjustments peculiar to the pyramidal system. (Denny-Brown, 1968, p. 134)
>
> The cerebral cortex, through its extrapyramidal connections with the basal ganglia, can restrict the response to one limb, contralateral to the hemisphere concerned. In addition, each hemisphere can effect postural adjustments on both sides, through the bilateral connections on the central tegmental tract, decussating in the pons. Each area 6 of Brodmann also appears to have a direct control over the extrapyramidal effects of both hemispheres through a pathway that also crosses in the pons. (Denny-Brown, 1967, pp. 440–441)

An Unanticipated Paradox: The Pyramidal Syndrome Turns Extrapyramidal

Since the latter half of the nineteenth century, the syndrome of hemiplegia, spasticity, hyperactive phasic muscular reflexes, and the sign of Babinski had been established as a reliable predictor of injury (Bouchard, 1866a, 1866b; Babinski, 1898), immaturity (Babinski, 1898), or dysfunction (Elliott & Walshe, 1925) of the pyramidal tracts. A major consequence of the success of the extrapyramidal concept was the unanticipated influence that it exerted on the pyramidal concept itself, which was thereafter increasingly

disputed. Compelling arguments imported from experimental physiology extended the extrapyramidal concept from animals to humans (Fulton & Viets, 1935):

> It is therefore proposed in the present paper to interpret the upper motor neuron syndromes of clinical neurology in the light of recent neurophysiologic investigations on monkeys and the higher apes, the terms of clinical literature being used for descriptive purposes. (p. 358)

Another leading researcher of the time was no less persuasive:

> What [. . .] recent experimental work has demonstrated is that too great a responsibility has been placed upon the pyramidal system. A large proportion of signs attributed to its damage are in fact due to nonpyramidal interference at both cortical and subcortical levels. (Mettler, 1948, pp. 196–197)

One extreme view was put forth by Tower based on her experiments on monkeys:

> Thus the one unique function of the pyramidal tracts—their minute control of the skeletal musculature—appears in default as the one reliable sign of pyramidal lesion. (Tower, 1940, p. 86)

The interpretations of experimental physiologists were seemingly bolstered by the overall good results of surgical excisions of cortical and subcortical targets for the treatment of epilepsy or AIMP. The famous neurosurgeon Paul Bucy (1978), for example, claimed that "the destruction of the pyramidal tract does not lead to permanent and complete paralysis; it does not result in spasticity, increased tendon reflexes, or the abolition of superficial reflexes (abdominal and cremasteric). The only part of the so-called 'pyramidal syndrome' that does result from destruction of the pyramidal tract is the development of the sign of Babinski" (p. 144). Less polarized views were advocated by equally prominent clinicians, who claimed that injuries confined to the pyramidal tracts gave rise to a hypotonic (i.e., nonspastic) paresis of the voluntary movements of digits and toes with concurrent impairment of skilled movements of hands and feet (Wiesendanger, 1984).

The Rise and Fall of the Extrapyramidal Concept

Like the pyramidal concept, the extrapyramidal system enjoyed a relatively short time of glory. One of the earliest arguments against its validity was raised on purely epistemological grounds (Meyers, 1953):

> The extrapyramidal system and, for that matter, the pyramidal system, are not demonstrated facts [. . .], but man-made concepts, i.e., verbal maps, intended to describe and account for certain empirically observable aspects of the structure and function of the nervous system. (p. 630)
>
> The pyramidal tract [. . .] seemingly includes a number of elements which cannot properly be considered parts of the pyramidal system. For this and other reasons already mentioned, the pyramidal system appears to be an uncertain concept. By the same token, the extrapyramidal system, which by definition depends for its claim to anatomic and physiologic discreteness

> upon being non-pyramidal, appears similarly uncertain, if not largely fanciful. Of even greater significance is the fact that clinicopathologic and experimental evidence cannot readily be reconciled with current anatomic and functional concepts of the so-called pyramidal and extrapyramidal motor systems. This may mean that the extrapyramidal concept is but a term for a high-order abstraction, referents for which are not demonstrable in the phenomenal world. (p. 649)

Doubts on the anatomical and physiological validity of the extrapyramidal *and* the pyramidal concepts were also proffered by outstanding anatomists, who wrote on the futility of both (A. Brodal, 1963):

> We are at present familiar with the fact that the classical notion of the pyramidal tract has to be discarded. (p. 19)
>
> It follows from the above that the term "extrapyramidal", referring to (motor) structures and functions "other than pyramidal" becomes meaningless. (p. 20)
>
> It is no longer possible to consider a "pyramidal system" as separate from an "extrapyramidal system". This is clearly shown by anatomical studies which demonstrate [. . .] that corticospinal fibres as well as corticofugal fibres to nuclei classified as belonging to the so-called "extrapyramidal system" arise from the same cortical regions (largely from the precentral cortex). (p. 33)

A view that has not substantially changed ever since (P. Brodal, 2010):

> The nuclei giving origin to these other tracts (often included in the "extrapyramidal system") are located in the brainstem, but several of them receive afferents from the cerebral cortex—in particular, from the motor cortex. . . . Thus, several indirect pathways—synaptically interrupted in the brainstem—transmit signals from the cortex to the motoneurons. In addition, some other brainstem nuclei with descending connections to motoneurons do not receive fibers from the motor cortex. The latter nuclei are primarily involved in control of highly automatic muscle contractions, such as those aiming at maintaining body balance and the movements of respiration. (p. 308)

As the preceding paragraphs show and summarized in the "Introduction," the extrapyramidal concept has survived the harsh attacks of twentieth-century science as an amalgam of loosely related ideas that fulfilled the descriptive needs of different authors in particular settings and epochs. This obvious want of internal coherence may be responsible for the fact that the contemporary use of the extrapyramidal concept has largely been sidelined or even abandoned by eminent authors (Lanska, 2010).

Out of the disparate and conflicting proposals discussed above, a body of anatomical observations remains that may ultimately rescue the extrapyramidal concept from certain oblivion and bring it back to its deserved rank in the pantheon of neurology. Maybe somewhat unexpectedly, this fund of knowledge directly springs from Prus' original formulation, the only one that has stood the tests of parsimony, utility, and consistency over time.

Conclusion

The main conclusion that naturally springs from this review is that somehow the extrapyramidal concept has stubbornly survived its detractors, a phenomenon not alien to neuroscience (Heimer, 2008). This is so because the extrapyramidal concept reflects a specific anatomic entity, namely, the collection of brainstem motor nuclei and their projections (e.g., reticulospinal) to the motor pools of the spinal cord.[4] Because this ensemble of nuclei and fascicles constitutes an undisputable *anatomical fact* shared by all vertebrates (Nudo & Masterton, 1988), including man (Nathan & Smith, 1982; Nathan, Smith, & Deacon, 1996), extrapyramidal remains a suitable and valid term to refer to this *anatomic* system as long as it does not conceal any physiological or clinical implications. Thus defined, the human extrapyramidal system is composed of six widespread collections of axons better identified by their brainstem nuclei of origin and spinal cord destinations than by the term "fascicles," which presupposes at least some degree of spatial closeness that is definitely not the case. These ensembles of axons comprise the reticulospinal (medial and lateral), the vestibulospinal (medial and lateral), the rubrospinal (lateral only), and the tectospinal (medial only) groups/ensembles.[5]

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[4]The emphasis on the motor nature of the extrapyramidal system excludes several descending tegmentospinal fiber systems that pertain to the visceral nervous system and are note, by definition, extrapyramidal.

[5]A detailed account of the anatomy and physiology of the extrapyramidal system is beyond the scope of this article. The interested reader may find precious information in clinicoanatomic publications dealing specifically with the human extrapyramidal system (Gee & Tooth, 1898; Thomas, 1903; Long & Roussy, 1908; Marie & Guillain, 1903; Weisschedel, 1937; Sie, 1956; Nathan & Smith, 1982; Nathan, Smith, & Deacon, 1996).

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