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Parkinson's disease: affection of brain stem nuclei controlling premotor and motor neurons of the somatomotor system

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Abstract Pathological changes which consistently develop in the lower brain stem of patients suffering from Parkinson's disease are described against the background of the internal organization and interconnections of the involved nuclei, i.e., the gigantocellular reticular nucleus, bulbar raphe nuclei, and coeruleus-subcoeruleus area. Immunoreactions against the presynaptic protein α-synuclein reveal not only the voluminous forms of Lewy bodies and Lewy neurites but also the otherwise inconspicuous dot- or thread-like types. These lesions develop solely in specific neuronal types. Lipofuscin- or neuromelanin-laden projection cells which at the same time generate a long, unmyelinated or sparsely myelinated axon are particularly susceptible to developing the changes. The bulbar nuclei under consideration receive strong input from supramedullary sources, above all from higher order centers of the limbic system such as the central amygdalar nucleus, periaqueductal gray, and parabrachial nuclei. In turn, they generate descending projections to premotor and motor neurons of the somatomotor system. The disease-related deterioration of both the supramedullary limbic centers and the bulbar brain stem nuclei reduces the limbic influence and markedly impairs the control of premotor and motor neurons. This functional deficit most probably contributes to the overall dysfunction of the motor system typically evolving in the course of Parkinson's disease.

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Introduction

The deterioration of the brain stem which occurs in the course of Parkinson's disease (PD) is not random. Specific gray matter nuclei and select neuronal types give rise to the development of Lewy bodies (LBs) and Lewy neurites (LNs), whereas others remain intact. The involvement of dopaminergic projection neurons of the substantia nigra significantly contributes to the manifestation of motor dysfunction and has received particular attention during the past decades [4, 11–14, 18]. Nevertheless, substantial PD-related damage consistently evolves outside of the substantia nigra as well [2, 6, 7, 21, 22]. This study is aimed at drawing attention to a severe PD-related involvement of the gigantocellular reticular nucleus. Similar changes occur in the nearby bulbar raphe nuclei and coeruleus-subcoeruleus area [15, 16, 28]. All three nuclei receive heavy input from supramedullary limbic centers and, in turn, generate important descending projections which control the level of excitability of bulbar and spinal premotor and motor neurons of the somatomotor system [19, 20, 27].

The present report is based upon evaluation of uninterrupted series of 100-µm-thick sections cut perpendicular to Meynert's brain stem axis. Advanced silver techniques and immunoreactions for α-synuclein have been applied to demonstrate all types of LBs/LNs [31]. The study also provides an architectonic delineation of the lower brain stem nuclei involved in PD supplemented by diagrams for easy recognition of the most important afferent and efferent connections of the affected nuclei. These diagrams take into account the known supramedullary lesions, thereby facilitating an understanding of the functional consequences which possibly result from the PD-associated affection of the bulbar nuclei under consideration.

Materials and methods

Brains from 12 individuals with clinically documented and neuropathologically confirmed PD (6 females, 6 males, aged 70.5±6.6 years, Hoehn and Yahr stages III–V, concomitant Alzheimer's disease-related neurofibrillary changes less than stage III) were studied, and 3 additional brains from patients lacking a history of neurological disorders were used for control and comparison (1 female, 2 males, aged 67.0 ± 10.4 years, devoid of concomitant Alzheimer's disease-related neurofibrillary changes). The brains were fixed by immersion in a 4% buffered solution of formaldehyde. The brain stems were embedded in polyethylene glycol (PEG 1000) and cut perpendicular to the Meynert's axis into an uninterrupted series of 100-µm sections.

Four sets of free-floating sections, each cut serially 1 mm equidistant from the other, were treated with four different staining procedures as follows: (1) aldehydefuchsin-Darrow red for both lipofuscin pigmentation and Nissl substance for purposes of topographical orientation, (2) α-synuclein antiserum (1 : 2,000–1 : 4,000) for immunocytochemical detection of LBs and LNs. The antiserum was generated by one of the authors (W. P. Gai) in sheep using a peptide corresponding to the amino acid residues 116–131 of the human α-synuclein. The immunoreactions were performed with a peroxidase-linked secondary antibody and diaminobenzidine [31]. (3) An advanced silver-staining technique was applied for demonstration of LBs and LNs [2, 6, 8].

For each PD and control case, an uninterrupted series of sections through one entire hemisphere was processed as described above and used for assessing the supramedullary lesions to gain a better understanding of the functional consequences of the disease-related involvement of the lower brain stem nuclei studied.

Results

Sections processed with immunoreactions for α-synuclein reliably demonstrate all types of LBs and LNs including the slender and otherwise inconspicuous subtle forms. In the material examined the distribution pattern of brain stem LBs and LNs is bilaterally symmetric. This study focuses on the PD-related affection of the reticular formation, bulbar raphe nuclei, and coeruleus-subcoeruleus area. The gigantocellular reticular nucleus bears the brunt of the cytoskeletal pathology occurring within the reticular formation.

The gigantocellular reticular nucleus

Drawings of a few sections cut perpendicular to Meynert's brain stem axis are presented in Fig. 1. At the junction of the medulla oblongata and the pontine tegmentum, the gigantocellular reticular nucleus represents the preeminent component of the reticular formation. Its oral portion extends into the caudal third of the pontine tegmentum, whereas its caudal extremity imperceptibly blends into the central nucleus of the medulla. The nucleus is bounded ventromedially by the medial lemniscus and the dorsal accessory olive. Dorsolaterally, it abuts on the intermediate reticular zone and the parvicellular reticular nucleus.

Two types of large multipolar neurons and a heterogeneous population of small nerve cells form the nuclear gray matter [24, 30]. In the adult brain, the predominate type among the large neurons contains a capacious and relatively sharply delineated deposit of tightly packed lipofuscin pigment granules often extending into the broad cone-shaped stem of one of the major dendrites. Intensely stained clusters of Nissl substance occupy the peripheral portion of the cell body and areas close to the deep invaginations of the nuclear membrane facing the pigment accumulation. The second, less frequently occurring type among the large cells bears a certain resemblance to a motor neuron. It displays a multipolar soma with a centrally located nucleus and a wealth of distinct, intensely basophilic Nissl bodies evenly dispersed throughout the perikaryon and even reaching into the proximal dendrites. These cells either contain fine dust-like lipofuscin granules or remain devoid of pigment. The group of the small nerve cells comprises many different types of neurons based on varying patterns of pigmentation and the nature of the basophilic material.

The brunt of the PD-associated pathology is borne by the large pigment-laden nerve cells. In the pathological material studied, both the non-pigmented large neurons and the heterogeneous group of small neurons remain exempt from the formation of PD-related cytoskeletal abnormalities.

The bulbar raphe nuclei

A predilection site which exhibits high densities of PD-related lesions is the complex of the bulbar raphe nuclei. The dominating component is the nucleus raphes magnus which is supplemented by two caudally extending satellites, the nucleus raphes obscurus and nucleus raphes pallidus [3, 30]. The nucleus raphes magnus extends caudally from the level of the facial motor nucleus and the superior olive, slightly exceeding the level of the pontomedullary sulcus. Cross sections display the nucleus as a spindle-shaped accumulation of medium-sized nerve cells. Laterally, the cell density decreases gradually without a sharp boundary towards the adjoining reticular formation. The nucleus raphes obscurus consists of two narrow, perpendicularly arranged frond-like lamellae located on both sides of the midline and extending between the motor nucleus of the hypoglossal nerve and the interolivary stratum. The nucleus raphes pallidus likewise starts from the nucleus raphes magnus as a caudally running extension located close to the median fissure and occupying the narrow spaces between the medial lemniscus and the pyramidal tract (Fig. 1).

The constituent neuronal type of the bulbar raphe nuclei is a triangular or spindle-shaped multipolar cell harboring a centrally located nucleus and a wealth of densely packed coarse lipofuscin granules [3, 29]. The pigment often extends into the proximal dendrites. A few scattered spindle-shaped and sparsely pigmented nerve cells occur sporadically within the reaches of the raphe nuclei. They most probably represent displaced neurons belonging to precerebellar nuclei in the immediate neighborhood such as the dorsal paramedian nucleus or the arcuate nucleus (Fig. 1).

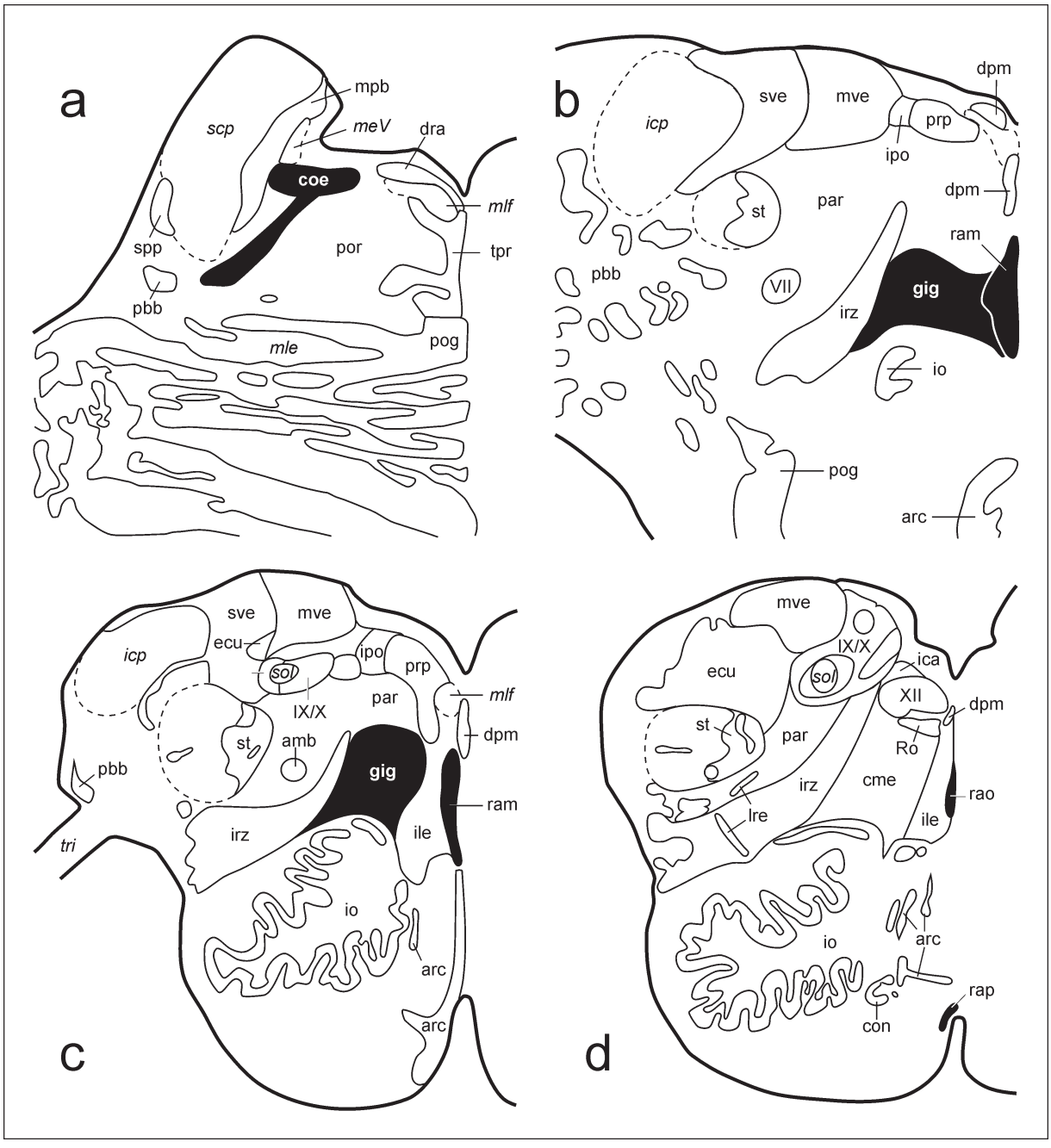


Fig. 1 Pathoarchitectonic pattern of Parkinson's disease-specific lesions in lower brain stem nuclei as seen in sections cut perpendicular to Meynert's axis. The gigantocellular reticular nucleus, the bulbar raphe nuclei, and the coeruleus-subcoeruleus area are marked in *black* (*VII* motor nucleus of the facial nerve, *IX*/X dorsal glossopharyngeal and vagal area, *XII* motor nucleus of the hypoglossal nerve, *amb* ambiguus nucleus, *arc* arcuate nucleus, *cme* central medullary nucleus, *coe* coeruleus-subcoeruleus area, *con* conterminal nucleus, *dpm* dorsal paramedian nucleus, *dra* dorsal raphe nucleus, *ecu* external cuneate nucleus, *gig* gigantocellular reticular nucleus, *ica* intercalated nucleus, *icp* inferior cerebellar peduncle, *ile* intralemniscal nucleus, *io* inferior olive, *ipo* interpositus nucleus, *irz* intermediate reticular zone, *lre* lateral reticular nucleus, *meV* mesencephalic trigeminal tract, *mle* medial lemniscus, *mlf* medial longitudinal fascicle, *mpb* medial parabrachial nucleus, *mve* medial vestibular nucleus, *par* parvicellular reticular nucleus, *pbb* pontobulbar body, *pog* pontine gray, *por* pontine reticular nucleus, *prp* prepositus hypoglossal nucleus, *ram* nucleus raphes magnus, *rao* nucleus raphes obscurus, *rap* nucleus raphes pallidus, *Ro* nucleus of Roller, *scp* superior cerebellar peduncle, *sol* solitary tract, *spp* subpeduncular pigmented nucleus, *st* spinal trigeminal nucleus, *sve* spinal vestibular nucleus, *tpr* tegmentopontine reticular nucleus (Bechterew), *tri* trigeminal nerve)

The PD-related pathology in the material examined evolves exclusively within the pigment-laden neurons of the raphe nuclei. All of the neurons encountered therein, but showing morphological characteristics different from those of the pigment-laden cells, remain devoid of PD-related cytoskeletal abnormalities. In comparison with controls, the number of pigment-laden neurons appears to be reduced.

The coeruleus-subcoeruleus area

The noradrenergic neuromelanin-laden neurons of the coeruleus-subcoeruleus area are located at the lateral edge of the pontine tegmentum close to the aqueduct and to the mesencephalic tract of the Vth cranial nerve. From an ill-defined anterior pole commencing at about the level of the decussation of the IVth cranial nerve, the coeruleus-subcoeruleus area extends in a caudal direction to the level of the VIIth cranial nerve (Fig. 1). The predominating neuromelanin-laden neurons contain a small eccentrically placed nucleus and coarse peripherally located Nissl bodies which rarely extend into the dendrites. A pale central region of the soma appears almost devoid of Nissl material or pigment granules. The portion of the cell nucleus facing the pale area shows numerous and deep invaginations.

The PD-related pathology chiefly affects the neuromelanin-laden neurons. Small nerve cells found within the nuclear gray matter displaying features different from those of the neuromelanin-laden neurons remain exempt from the formation of LBs and LNs. Comparison with control cases reveals a marked loss of melanoneurons. In the PD cases the neuromelanin granules usually are smaller and less densely packed together than in the melanoneurons of the controls. Small particles immunoreactive for α-synuclein appear exclusively within the accumulations of neuromelanin. Larger deposits of the pathological material display a pallid center. Not infrequently, three to five solid LBs occur within a single perikaryon.

Discussion

Selective vulnerability of specific neuronal types

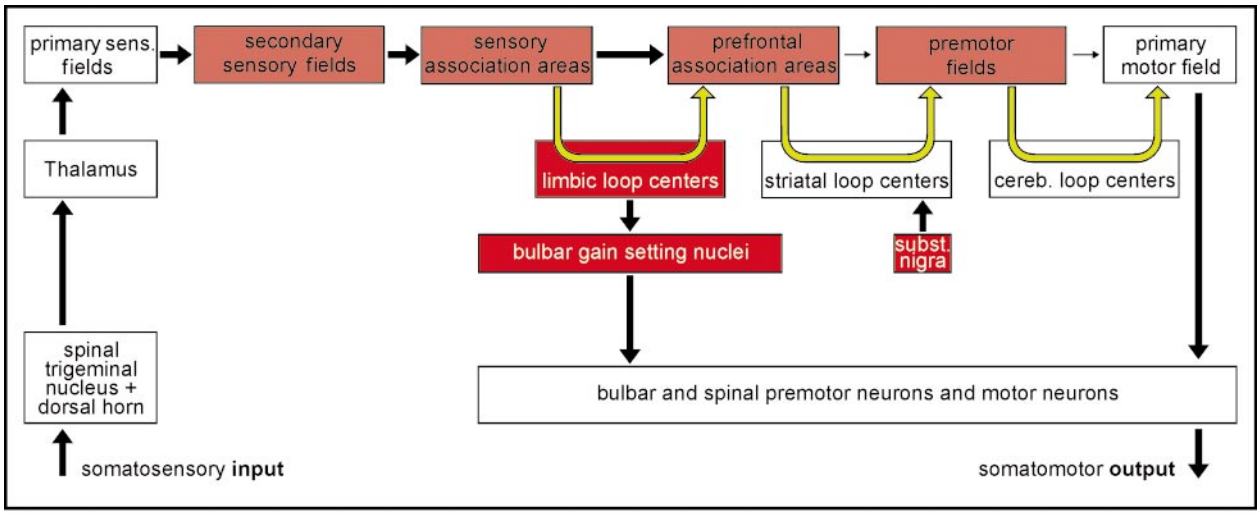
The PD-related cytoskeletal pathology evolving in the gigantocellular reticular nucleus, bulbar raphe nuclei, and coeruleus-subcoeruleus area targets only nerve cells belonging to the class of projection neurons. More exactly, all of the affected cells belong to a subclass of projection neurons giving rise to a conspicuously lengthy axon which attains only a small diameter and either remains unmyelinated or exhibits a particularly thin myelin sheath [27]. The same features are common to most of the neuronal types within the central nervous system which exhibit a propensity for developing LBs/LNs [8]. Interestingly, all of the neuronal types generating a particularly short axon or a voluminous long axon enclosed in a thick myelin sheath remain protected from the development of LBs and LNs.

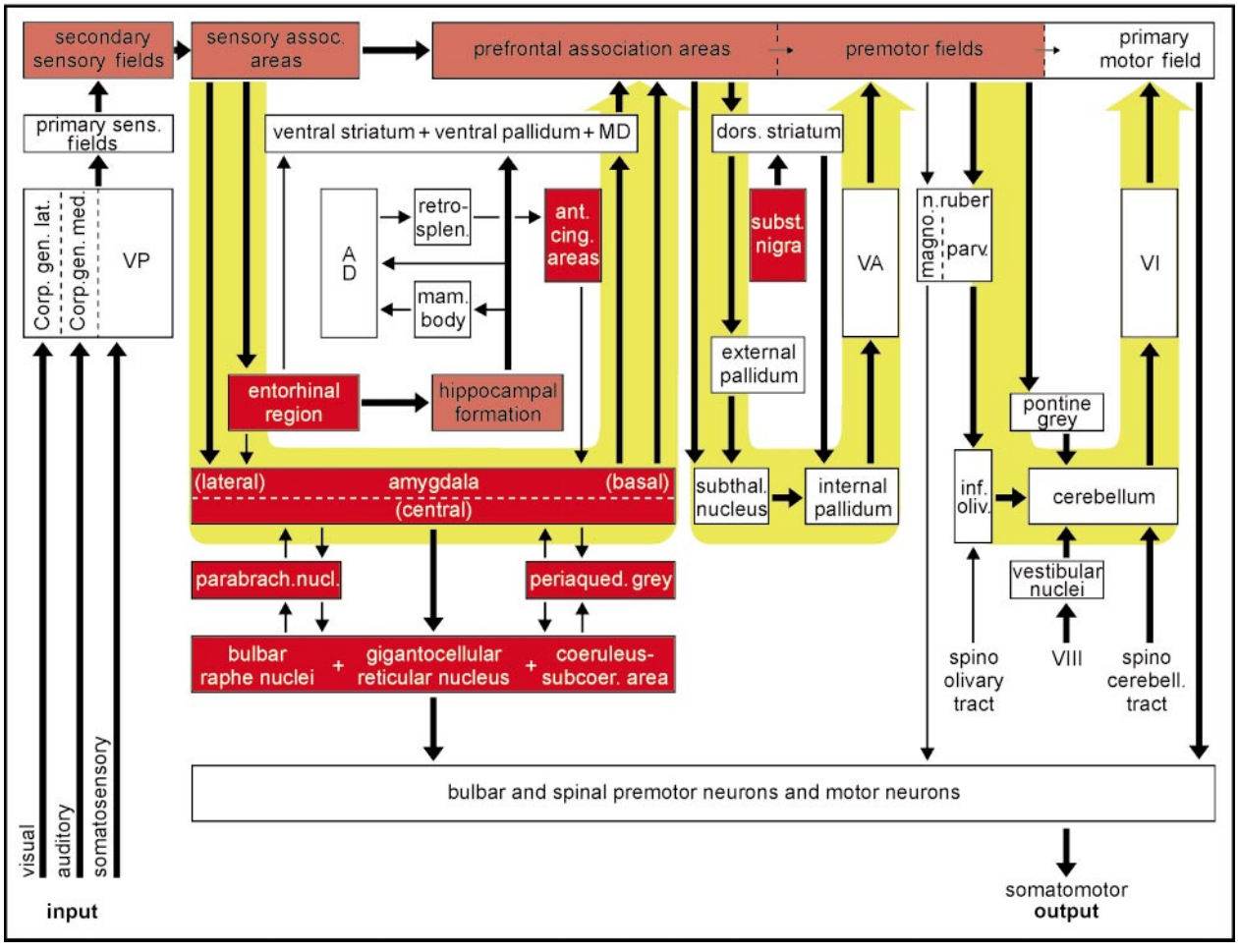
In all of the lower brain stem nuclei and in all of the PD cases studied, disease-related intracytoplasmic inclusions evolve exclusively in the lipofuscin- and/or neuromelanin-laden neurons. Susceptibility to development of LBs/LNs thus appears to be greater in pigment-laden nerve cells than in sparsely pigmented or unpigmented ones. Our observation that in lower brain stem nuclei the most subtle alterations, probably the initial ones, are confined solely to the aggregations of the lipofuscin- or neuromelanin granules likewise points in this direction. This prompts speculation to the effect that the somatic compartment harboring the pigment granules is somehow essential for the formation of the abnormal material and its gradual transformation into intracytoplasmic inclusions which subsequently cannot be degraded by the parent cell.

Distribution pattern of the lesions and possible functional consequences of selective destruction

The lower brain stem is inserted between the higher order centers of the tel-, di-, and mesencephalon on the one

Fig. 2 Schematic representation of supramedullary limbic input to ▶ the gigantocellular reticular nucleus, the bulbar raphe nuclei, and the coeruleus-subcoeruleus area, together with major descending output projections of these lower brain stem nuclei which exert an important influence upon bulbar and spinal components of the somatomotor system. The diagram appears in two forms, the first of which is extremely simplified for easy recognition of the most important connections, whereas the second is more complex. The known Parkinson's disease-associated supramedullary lesions of both the limbic and the motor systems are marked in *red* (severe lesions) or *pink* (less severe lesions) to facilitate an understanding of the functional consequences of the lesions. Both diagrams show the pathways by which sensory information normally proceeds through neocortical sensory areas and then travels to the prefrontal cortex. Centers of the striatal and cerebellar loops lead away from the prefrontal cortex to the primary motor area. Other pathways convey information from sensory neocortical association areas to the centers of the limbic loop, which in turn exert considerable influence upon the prefrontal cortex. Descending projections of limbic loop centers steer the bulbar nuclei under consideration which control the level of excitability of both bulbar and spinal relay stations of the somatomotor system. The *yellow arrows* are thought to facilitate recognition of the limbic, striatal, and cerebellar loops (*AD* anterodorsal nucleus of the thalamus, *ant. cing. areas* anterior cingulate areas, *cereb. loop centers* cerebellar loop centers, *coeruleus-subcoer. area* coeruleus-subcoeruleus area, *Corp. gen. lat.* Corpus geniculatum laterale, *Corp. gen. med*. Corpus geniculatum mediale, *dors. striatum* dorsal striatum, *grac*.gracile nucleus, *inf. oliv*. inferior olive, *mam. body* mamillary body, *MD* mediodorsal nucleus of the thalamus, *n. ruber magno*. magnocellular portion of the nucleus ruber, *n. ruber parv*. parvicellular portion of the nucleus ruber, *parabrach. nucl*. parabrachial nuclei, *periaqued. gray* periaqueductal gray, *primary sens. fields* primary sensory fields, *retrosplen.* retrosplenial region, *sensory assoc. areas* sensory association areas, *spinocerebell. tract* spinocerebellar tract, *subst. nigra* substantia nigra, *subthal. nucleus* subthalamic nucleus, *VA* ventral anterior nuclei of the thalamus, *VI* ventral intermediate nuclei of the thalamus, *VP* ventral posterior complex of the thalamus, *VIII* vestibular nerve)





hand and the spinal cord on the other. Most of its nuclei promote control and modification of data exchanged between the supramedullary and inframedullary components of the central nervous system [19, 20, 24, 27]. On this account, further speculation regarding the significance of the PD-related lesions evolving in the lower brain stem only makes sense within the larger discussion of the most important afferent and efferent connections of the affected nuclei. Diagrams taking into account the most important pathways of both the limbic and the motor systems are presented to facilitate understanding of the damage within the framework of this larger context (Fig. 2).

The human cerebral cortex consists of an extensive neocortex and a small allocortex. The latter includes limbic system centers such as the hippocampal formation and the entorhinal region. The amygdala is connected closely

with the allocortex. Auditory, visual, and somatosensory data pass through primary, secondary, and higher order processing areas of the neocortex en route to the prefrontal association cortex. Short efferent pathways lead from the prefrontal areas to premotor fields and the primary motor area. The bulk of the data, however, traverse the striatal and cerebellar loops which are built into these return pathways [5, 8]. The limbic system participates in this flow of information at that point where data are transferred from the sensory association areas to the prefrontal cortex. Some of the information converges via numerous cortical relay stations upon centers of the limbic loop, i.e., amygdala, entorhinal region, and hippocampal formation. Important efferents from these centers arrive (partially via ventral striatum, ventral pallidum, and mediodorsal thalamic nucleus) at the prefrontal cortex [17, 26]. The limbic loop is an integral player in the maintenance of emotional equilibrium and memory functions [25]. At the same time, it receives crucial viscerosensory input, influences nuclei regulating endocrine and autonomic functions, and affects motor activity [19, 20, 24, 27].

The gigantocellular reticular nucleus, the bulbar raphe nuclei, and the coeruleus-subcoeruleus area receive major input from higher order components of the limbic loop, such as the central amygdalar nucleus, and from subordinate structures, such as the periaqueductal gray and parabrachial nuclei. In turn, they generate descending projections to the premotor and motor neurons of the somatomotor system (Fig. 2). Via these projections, the three nuclei normally control the susceptibility of premotor and motor neurons for excitatory input received from the neocortex, the magnocellular portion of the red nucleus, and other supramedullary sources [19, 20, 24, 27].

Grievous PD-related lesions are known to occur in many supramedullary centers of the limbic system [6–8]. The control over the bulbar relay nuclei under consideration is impaired greatly by this pathology (Fig. 2, affected areas are marked in pink or in red). Among the most important cortical sites are the anterior cingulate and basal insular areas, the temporal proneocortex, the transentorhinal and entorhinal regions, and the CA2 sector of the hippocampal formation. Severely affected subcortical nuclei include the central amygdalar nucleus, the nucleus of the stria terminalis, the limbic system-associated nuclei of the thalamus, the periaqueductal gray, and the parabrachial nuclei (Fig. 2).

The severe cytoskeletal lesions in the gigantocellular reticular nucleus, bulbar raphe nuclei, and coeruleus-subcoeruleus area considerably aggravate the situation and further reduce the functional capacities of the three nuclei [10, 23]. Normally, the target neurons of these nuclei are capable of switching back and forth from a lower to a higher level of excitability and, apparently, an individual's emotional status determines the appropriate level in any given situation [19]. A widely intact limbic system is a *sine qua non* for the maintenance of this adaptive behavior. Patients suffering from PD characteristically exhibit a marked dissociation between the voluntary and emotional motor systems. Much effort has been expended to date in studying the devastating impairments of somatomotor functions which result from the destruction of dopaminergic nerve cells in the substantia nigra [1, 9]. The present study is intended to point to the severe involvement of limbic system-moderated lower brain stem nuclei, the impairment of which leads to an altered motor neuron responsiveness and thereby significantly contributes to the PD-related dysfunction of the motor system.

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