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Pathoanatomy of Parkinson's disease

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Abstract Parkinson's disease is a widespread degenerative illness affecting the human central, peripheral, and enteric nervous systems. The underlying pathological process progresses slowly but relentlessly and involves multiple neuronal systems. The disease is the consequence of changes in the neuronal cytoskeleton developing in only a few susceptible types of nerve cells. Afflicted neurons eventually produce Lewy bodies in their perikarya and Lewy neurites in their neuronal processes.

Immunoreactions against the presynaptic protein α-synuclein have revealed many kinds of inclusion bodies ranging from inconspicuous dot- or thread-like forms to particularly voluminous types. The selective vulnerability of nerve cells induces a distinctive distribution pattern of lesions which remains remarkably consistent across cases. Components of the limbic system and the motor system have been shown to be particularly vulnerable to severe destruction. Some subnuclei of the substantia nigra also undergo major changes. This damage is consistently accompanied by extranigral alterations, with predilection sites including the entorhinal region, the second sector of the Ammon's horn, and important subnuclei of the amygdala. In addition, the nucleus of the stria terminalis, components of the hypothalamus, all of the non-thalamic nuclei with diffuse projections to the cerebral cortex, and most of the centers regulating autonomic functions exhibit severe lesions.

Key Words Parkinson's disease · Cytoskeletal alterations · α-synuclein · Limbic system · Motor system

Introduction

Parkinson's disease is a fairly frequently occurring disorder, affecting the human central, peripheral, and enteric nervous systems. The underlying pathological process progresses slowly yet relentlessly and the disease manifests itself clinically, relatively late, after having reached an advanced phase [22, 33, 56]. Clinical diagnosis of Parkinson's disease is difficult and often deceptive despite the characteristic symptoms of the disease. In general, diagnosis requires post-mortem verification [40, 45].

Parkinson's disease is a disorder of the neuronal cytoskeleton affecting only a small number of neuronal types

Parkinson's disease is one of several degenerative disorders affecting the neuronal cytoskeleton. Within the central nervous system, only a select few of the many types of nerve cells develop these characteristic cytoskeletal abnormalities and, accordingly, neuronal damage does not occur randomly. Rather, the selective vulnerability of specific neuronal types induces a distinctive pattern of lesions which is essentially bilaterally symmetrical. Components of the limbic system and the motor system show particularly se-

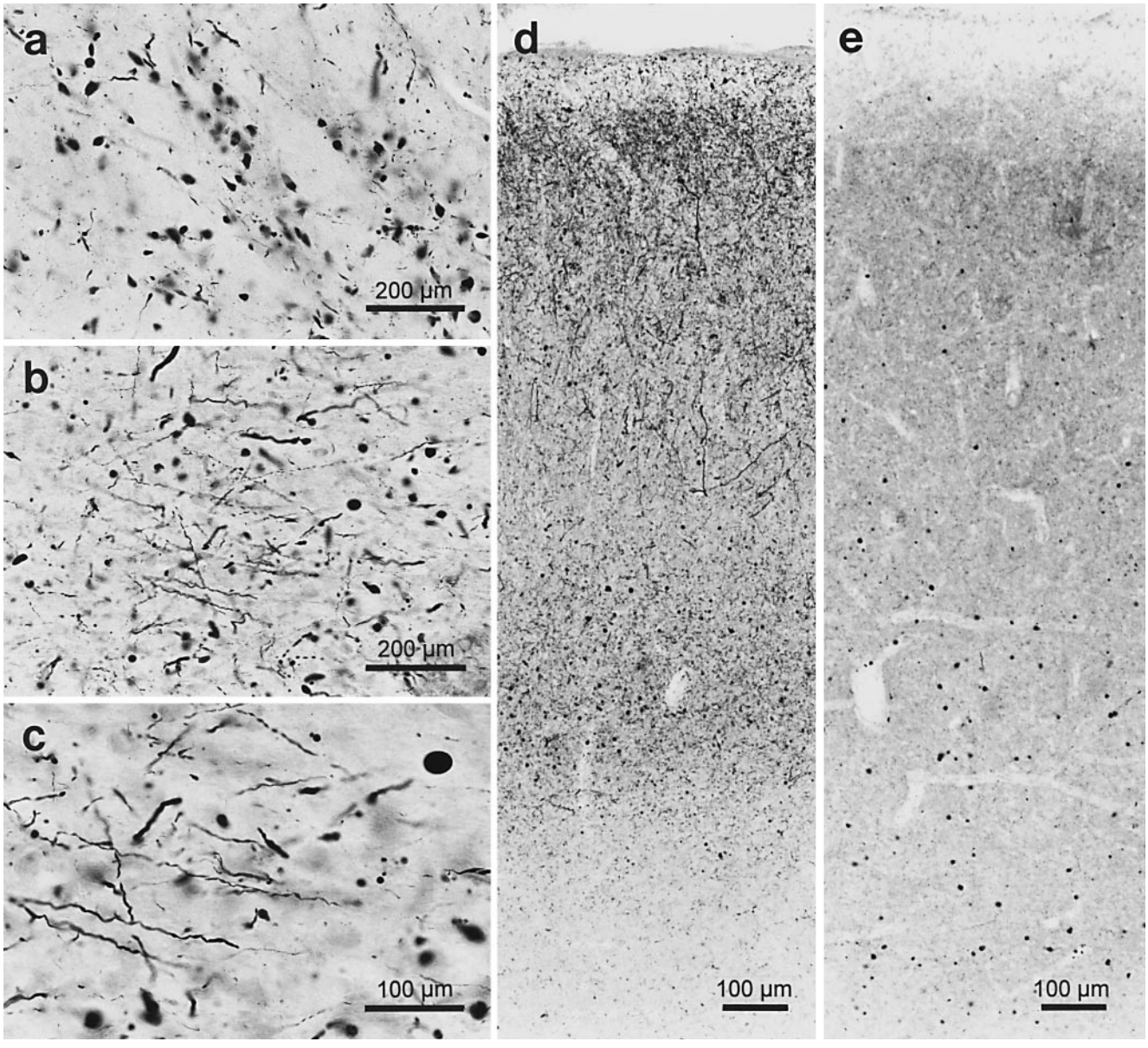


Fig. 1 a–e Parkinson's disease-related lesions as seen in immunoreactions against α-synuclein in both cortical (**d, e**) and subcortical (**a–c**) predilection sites (section thickness 100 µm). **a**) Healthy and diseased neuromelanin-containing projection cells in the pars compacta of the substantia nigra. Note the presence of globular Lewy bodies in the perikarya and elongated Lewy neurites in cellular processes of vulnerable nerve cells. **b and c**) The basal nucleus of Meynert is severely involved in Parkinson's disease and shows countless voluminous globular Lewy bodies and very long Lewy neurites (part of Fig. 1b is displayed in 1c at higher magnification). **d**) The transentorhinal region is stricken particularly badly by Parkinson's disease-associated pathological changes. Note the very dense network of Lewy neurites in the superficial layers of this cortical region, which serves as the most important gate of input for neocortical information into the limbic system. **e**) In cases of Parkinson's disease, anterior cingulate areas usually display numerous Lewy body-containing projection neurons in the deep layers of the cortex

vere destruction. The reasons for the marked vulnerability of some neuronal types and the decided resistance of others is unknown [10–12, 21, 43, 44, 49, 50].

As a result of the cytoskeletal changes, afflicted neurons develop Lewy bodies in the perikarya and Lewy neurites in the neuronal processes (Fig. 1a–c). Most of the Lewy neurites are presumably located in portions of the axon. At present, it is unclear whether Lewy neurites are capable of developing in dendrites as well. Glial cells and other cells of non-neuroectodermal origin do not display these cytoskeletal abnormalities.

The major components of Lewy bodies and Lewy neurites are abnormally phosphorylated neurofilaments, in other words, altered 'building blocks' of the cytoskeleton. Additional components include ubiquitin and a protein

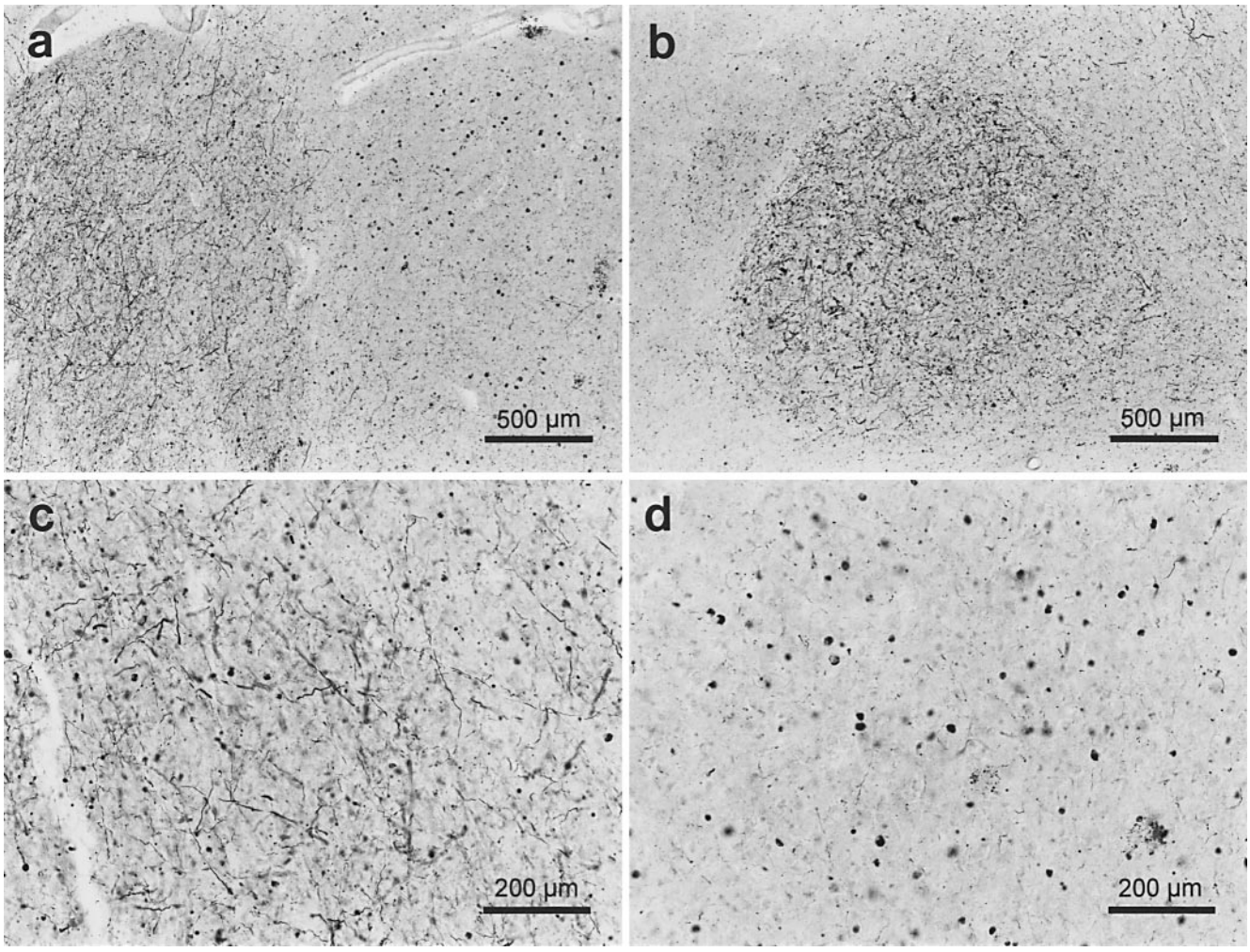


Fig. 2 a–d This illustration again displays the Parkinson's disease-associated cytoskeletal lesions as visualized in immunoreactions against α-synuclein in various subnuclei of the amygdala (section thickness 100 µm). **a**) Overview showing part of the lateral nucleus (left) and basal nucleus (right). Note the sharply drawn border between the two nuclei solely indicated by abrupt changes in the manner and degree of involvement. **b**) The severe affection of the central amygdalar nucleus can often be recognized by the naked eye. Numerous Lewy neurites and Lewy bodies of various diameters are evenly distributed throughout the nuclear grey. **c and d**) Part of the lateral (c) and the basal (d) nucleus at higher magnification. The lateral nucleus chiefly harbors a dense network of Lewy neurites while the basal nucleus contains many Lewy body-bearing projection cells

which normally occurs in the presynaptic membrane, α-synuclein. In spite of the damage, the neurons affected by cytoskeletal alterations are viable for a relatively long period of time. Nevertheless, they perish prematurely, having forfeited much of their functional integrity long before actual cell death occurs [3–6, 23, 24, 27, 28, 30, 41, 42, 47, 51, 61, 62, 64–67].

Parkinson's disease affects components of both the motor and the limbic systems

Parkinson's disease-related pathology is ostensibly focused on the substantia nigra, with a more or less severe loss of neuromelanin-laden dopaminergic projection cells in the pars compacta of this nuclear grey (Fig. 1a). In fact, some of the nigral subnuclei consistently reveal major changes. Others, however, remain more or less unscathed [8, 9, 20, 26, 29, 32, 35]. Similarly, many assemblies of dopaminergic nerve cells outside of the substantia nigra show no tendency to develop cytoskeletal abnormalities [37, 54]. There is currently no plausible explanation for the conspicuous resistance of these cell groups. The facile characterization of Parkinson's disease as a more or less isolated disorder of the dopaminergic system proves, upon nearer scrutiny, to be an unacceptable oversimplification of the pathology of the disease.

From the very outset of the disorder, damage to the substantia nigra is consistently accompanied by an impressive extranigral pathology (Figs. 1b–e, 2a–d). These

extranigral lesions result in considerable impairment of the limbic system, of telencephalic cortical functions, and of autonomic regulative mechanisms. Accordingly, it is by no means exclusively the dopaminergic neurons that display pathological changes. Rather, a significant number of other nerve cells, among them glutamatergic, cholinergic, tryptaminergic, GABAergic, noradrenergic, and adrenergic neurons, show grievous cytoskeletal damage [10–12, 15, 22, 44, 49]. Without exception, susceptible nerve cells belong to the group of projection neurons generating a lengthy axon, whereas local circuit neurons and short-axoned projection cells remain devoid of Parkinson's disease-related changes.

Organization of the motor system and the limbic system

The human cerebral cortex consists of an extensive neocortical territory and a small allocortical region. The allocortex essentially takes up the anteromedial portion of the temporal lobe and contains the higher centers of the limbic system. A partitioning into primary fields both for motor functions and for the initial processing of information coming from the sensory organs exists within the neocortex. Each of the primary sensory fields is surrounded by unimodal secondary areas connected to additional, unimodal as well as heteromodal association areas [7, 12, 68].

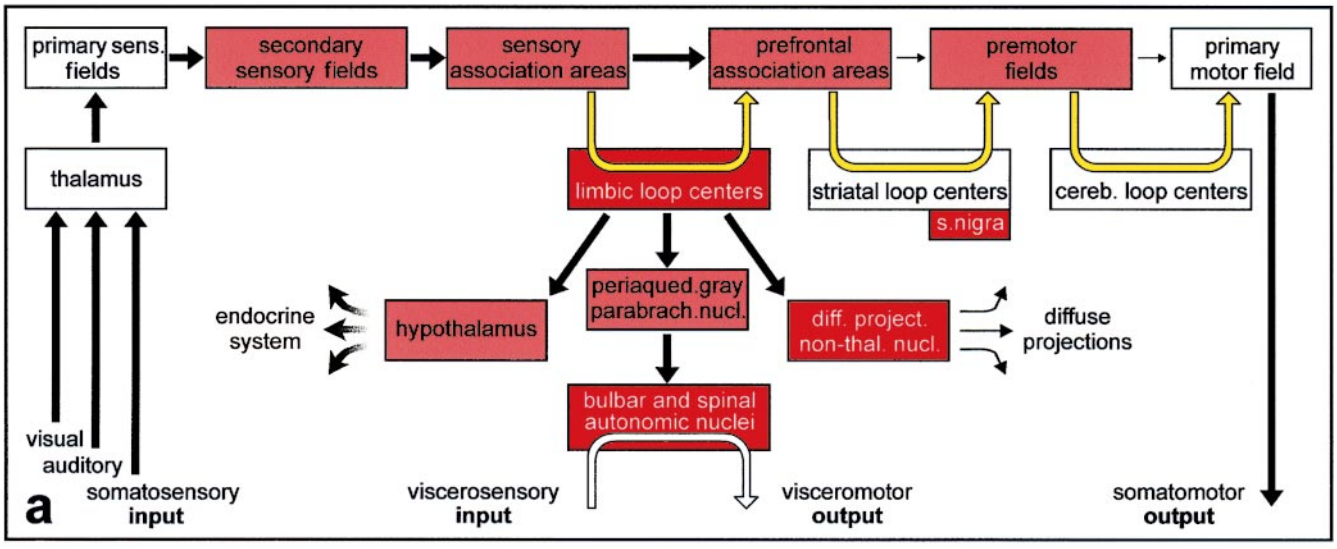
Somatosensory, auditory, and visual exteroceptive input reach, by way of the primary fields and secondary areas, a multiplicity of related association areas of the neocortex. From here, data are conveyed to the prefrontal cortex which is remarkably extensive in humans. Short pathways lead away from this highest deliberative instance in the human brain to subordinate fields – in the final analysis through premotor areas, to the primary motor field. The bulk of the information, however, traverses the striatal and cerebellar loops built into this pathway. In this manner, large portions of the basal ganglia, many nuclear greys of the lower brain stem, and the cerebellum participate in the regulation of cortical output (Fig. 3a).

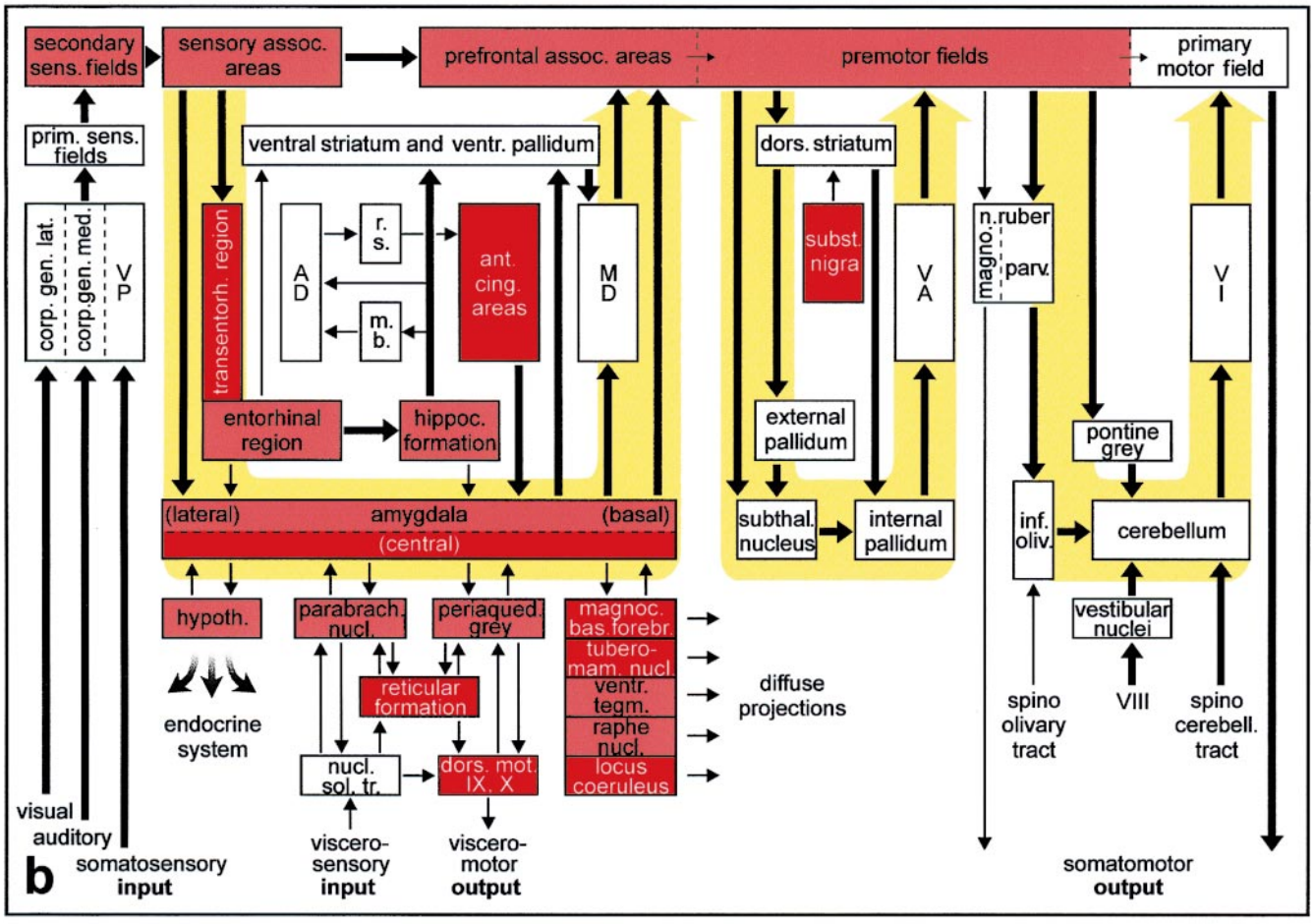
The neocortex is constantly inundated with an abundant stream of largely irrelevant exteroceptive stimuli and information. The data which are deemed important by the individual are filtered out of this stream and only these arrive, via many intermediate neocortial relay stations, at the gates of entrance to the limbic loop. Neocortical information is, thus, the dominant source of input to the human limbic system. The entorhinal territory and the lateral nucleus of the amygdala serve as gates of access for these highly processed data. The centers of the limbic loop subsequently dispatch their chief efferents in the direction of the neocortex, namely to the prefrontal areas [36, 38, 39, 55, 57, 58]. Thereby, they exert considerable influence on this crucial part of the neocortex which is simultaneously a constituent component of the motor system (Fig. 3a).

Three loops are depicted in greater detail in Fig. 3b. Proceeding from left to right, the limbic loop, striatal loop, and cerebellar loop can be identified and their recognition is facilitated by the broad yellow arrows. Schematic representation of these systems facilitates the perception of the intimate connections and tight relations between the limbic system, on one hand, and the motor system, on the other [1, 2, 36].

Fig. 3a, b Schematic representation of the limbic system and the motor system. The diagram appears in two forms, the first of which is extremely simplified for recognition of the most important connections (**a**), whereas the second is more complex (**b**). The summary diagrams depict the most important limbic and motor system centers. The damaged regions appear in red to illustrate the extent of the lesions which consistently develop in the brains of patients with Parkinson's disease. Both diagrams show the pathways by which sensory information normally proceeds through neocortical sensory areas and travels via long cortico–cortical projections to the prefrontal association areas. Short pathways lead away from the prefrontal cortex to the primary motor field. The major routes of transport for this information are provided by the striatal and cerebellar loops. Other pathways that convey information from the sensory neocortical association areas meet in the entorhinal region and amygdala, thereby establishing the afferent arm of the limbic loop. Projections from the entorhinal region, the amygdala, and the hippocampal formation contribute to the efferent arm of the limbic loop heading toward the prefrontal cortex. The amygdala integrates exteroceptive sensory data with interoceptive stimuli from autonomic centers. Many descending projections of amygdalar subnuclei terminate in nuclei regulating endocrine and autonomic functions. In addition, the amygdala sends efferent connections to all non-thalamic nuclei which in a non-specific manner project upon the cerebral cortex and other components of the central nervous system. Proceeding from left to right, the limbic loop, striatal loop, and cerebellar loop can be identified and their recognition facilitated by the broad yellow arrows. Note the Parkinson's disease-associated lesions in both the limbic and the motor systems. Damaged structures are marked in deep red (severe lesions) or light red (less severe lesions). The diagrams are intended to facilitate an understanding of the functional consequences of the lesions ▶

Abbreviations: *AD* anterodorsal nucleus of the thalamus, *ant. cing. areas* anterior cingulate areas, *cereb. loop centers* cerebellar loop centers, *corp. gen. lat.* corpus geniculatum laterale, *corp. gen. med.* corpus geniculatum mediale, *diff. project. non-thal. nucl.* diffusely projecting non-thalamic nuclei, *dors. mot. IX, X* dorsal motor area of the glossopharyngeal and vagal nerves, *dors. striatum* dorsal striatum, *hippoc. formation* hippocampal formation, *hypoth.* hypothalamus, *inf. oliv.* inferior olive, *m. b.* mamillary body, *magnoc. bas. forebr.* magnocellular nuclei of the basal forebrain, *MD* mediodorsal nuclei of the thalamus, *n. ruber magno.* magnocellular portion of the nucleus ruber, *n. ruber parv.* parvocellular portion of the nucleus ruber, *nucl. sol. tr.* nuclei of the solitary tract, *parabrach. nucl.* parabrachial nuclei, *periaqued. grey* periaqueductal gray, *prim.(ary) sens. fields*, primary sensory fields, *r.s.* retrosplenial region, *raphe nucl.* raphe nuclei, *s. nigra* substantia nigra, *secondary sens. fields* secondary sensory fields, *sensory assoc. areas* sensory association areas, *spinocerebell. tract* spinocerebellar tract, *subst. nigra* substantia nigra, *subthal. nucleus* subthalamic nucleus, *transentorh. region* transentorhinal region, *tuberomam. nucl.* tuberomamillary nucleus, *VA* ventral anterior nuclei of the thalamus, *ventr. pallidum* ventral pallidum, *ventr. tegm.* ventral tegmentum, *VI* ventral intermediate nuclei of the thalamus, *VP* ventral posterior complex of the thalamus, *VIII* vestibular nerve


primary sens. fields
secondary sensory fields
sensory association areas
prefrontal association areas
premotor fields
primary motor field
thalamus
limbic loop centers
striatal loop centers
s.nigra
cereb. loop centers
endocrine system
hypothalamus
periaqued.gray parabrach.nucl.
diff. project. non-thal. nucl.
diffuse projections
bulbar and spinal autonomic nuclei
visual
auditory
somatosensory input
viscerosensory input
visceromotor output
somatomotor output
a


secondary sens. fields
sensory assoc. areas
prefrontal assoc. areas
premotor fields
primary motor field
prim. sens. fields
ventral striatum and ventr. pallidum
dors. striatum
corp. gen. lat.
corp.gen. med.
VP
transentorh. region
AD
r. s.
m. b.
ant. cing. areas
MD
subst. nigra
VA
n.ruber magno. parv.
VI
entorhinal region
hippoc. formation
external pallidum
pontine grey
(lateral)
amygdala
(basal)
(central)
subthal. nucleus
internal pallidum
inf. oliv.
cerebellum
hypoth.
parabrach. nucl.
periaqued. grey
magnoc. bas.forebr.
tubero-mam. nucl.
ventr. tegm.
raphe nucl.
locus coeruleus
reticular formation
diffuse projections
vestibular nuclei
endocrine system
spino olivary tract
VIII
spino cerebell. tract
nucl. sol. tr.
dors. mot. IX, X
visceromotor output
viscerosensory input
visual
auditory
somatosensory input
somatomotor output
b

In essence, three centers comprise the pre-eminent structures of the limbic system: the entorhinal region and the hippocampal formation, both belonging to the allocortex, and the neighboring subcortical amygdala. All three centers are intricately interlinked (Fig. 3b). The limbic loop plays an integral role in the maintenance of emotional equilibrium, learning ability, and memory functions. At the same time, it affects motor activity and, in fact, the influence of the limbic system on the prefrontal cortex explains why an individual's motor activity reflects his or her emotional state. Remarkably, it is precisely the components of the limbic loop that undergo major pathological changes in Parkinson's disease.

Parkinson's disease – related alterations to the motor and limbic systems

In parkinsonian patients, all three higher order centers of the limbic loop become affected and many of the cortical fields, as well as subcortical nuclei which are connected with them, suffer serious damage (Fig. 3b). An immunoreaction for α-synuclein displays the previously neglected very severe affliction of the entorhinal territory (Fig. 1d). The micrograph shows the transentorhinal region which directly abuts upon the proper entorhinal region and represents the first and most important port of entry for highly processed data coming from the neocortex (Fig. 2b). Numerous Lewy neurites extend throughout the superficial layers of the cortex, whereas the deep layers primarily harbor Lewy body-bearing projection neurons. Such a degree of devastation is perfectly capable of interrupting the exchange of vital data between the neocortex and the higher order centers of the limbic system, as well as hampering their influence on the prefrontal cortex (Fig. 2b). Such lesions pave the way for a decline of intellectual faculties [15, 48]. The lesions of the transentorhinal region are much more severe than those of the anterior cingulate cortex for example (Fig. 1e). Anterior cingulate areas belong to the typical predilection sites of cortical involvement in cases of Parkinson's disease.

The lesions developing in the hippocampal formation can often be detected in immunostained sections by the naked eye. A dense network of extended Lewy neurites develops in the second sector of the Ammon's horn [17, 18]. Such a pathological cortical network always evolves in the course of the disease and is so typical that, on the basis of its appearance alone, one could mount a case for the neuropathological diagnosis of Parkinson's disease [12].

The severe deterioration within the reaches of the amygdala is pivotal to an understanding of the disease-related destruction [10]. Figures 2a and c show the second port of entry for neocortical data into the limbic loop: the lateral nucleus of the amygdala. This grey is seriously ravaged and contains a dense and twisted network of Lewy neurites (Fig. 2c). The areas with major efferents heading toward the ventral striatum, ventral pallidum, mediodorsal thalamus, and prefrontal cortex, such as the basal nucleus of the amygdala for instance, reveal numerous Lewy bodies in their projection neurons (right half of Fig. 2a and Fig. 2d).

The central amygdalar nucleus is an area of serious cytoskeletal damage and displays numerous Lewy neurites and Lewy bodies of various diameters (Fig. 2b). Many of them belong to the inconspicuous drop- or thread-like forms and require immunostaining for α-synuclein for more obvious detection [13, 62]. The central nucleus of the amygdala and the bed nucleus of the stria terminalis normally exert important influence on the autonomic and neurosecretory nuclei of the hypothalamus, thereby attaining directive functions over large segments of the endocrine system (Figs. 3a and b). The severe pathology found in the central amygdalar nucleus is certainly detrimental to these important functions.

Beyond these tasks, the central nucleus of the amygdala also serves as the steering center for processing viscerosensory data and for control of all visceromotor areas of the brainstem and spinal cord. All of the limbic and autonomic centers bidirectionally connected with the amygdala display intense Parkinson's disease-specific devastation [12, 14, 16, 19, 25, 31, 34, 46, 49, 52, 53, 59, 60, 63]. These structures are the periaqueductal grey, the parabrachial region, the gigantocellular nucleus of the reticular formation, the intermediate reticular zone, and the dorsal vagal area, together with the centers for regulation of the digestive tract, respiratory organs, and cardiovascular system.

Finally, the central nucleus of the amygdala exerts important influence on all non-thalamic nuclei with diffuse connecting projections to the cerebral cortex and many other structures of the central nervous system. Severe Parkinson's disease-related pathological changes also develop in these diffusely projecting nuclei, that is the cholinergic magnocellular nuclei of the basal forebrain, the GABAergic tuberomamillary nucleus of the hypothalamus, the serotonergic raphe nuclei, the dopaminergic nuclei of the ventral tegmentum, and the noradrenergic locus coeruleus. The rampant destruction of both the central nucleus of the amygdala and the nuclei with diffuse projections greatly reduces the general input to the cerebral cortex.

Concluding remarks

The summary diagrams displaying the most important centers of both the limbic system and the motor system show the damaged regions in red, thereby illustrating the extent of the lesions which consistently develop in the brains of patients with Parkinson's disease (Fig. 3).

In light of the findings presented, Parkinson's disease appears to be a chronic, progressive cytoskeletal disorder involving specific types of projection neurons. The illness devastates specific regions of the motor, limbic, and auto-

nomic systems, progressing slowly and unremittingly. The lesions engulf not only cortical and subcortical components of the central nervous system but large portions of the peripheral and enteric nervous systems as well.

The success of the valuable yet symptomatic therapy with levodopa, which is applicable only for a limited period of time and fails to address the root of the illness, occasionally leads to an oversimplified conception of Parkinson's disease. It is misleading to reduce Parkinson's disease to a malady of the substantia nigra. Previously suggested animal paradigms, focusing essentially on the demise of nigral dopaminergic neurons, are inadequate models for this disease. A renewed study of the healthy and diseased human nervous system, especially of the aberrations of the cytoskeleton of susceptible nerve cell types, is a prerequisite for the ongoing development of therapeutic strategies aimed at finding an effective and causal treatment of this devastating disease.

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