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REVIEW

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Stages in the development of Parkinson's disease-related pathology

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Abstract The synucleinopathy, idiopathic Parkinson's disease, is a multisystem disorder that involves only a few predisposed nerve cell types in specific regions of the human nervous system. The intracerebral formation of abnormal proteinaceous Lewy bodies and Lewy neurites begins at defined induction sites and advances in a topographically predictable sequence. As the disease progresses, components of the autonomic, limbic, and somatomotor systems become particularly badly damaged. During presymptomatic stages 1–2, inclusion body pathology is confined to the medulla oblongata/pontine tegmentum and olfactory bulb/anterior olfactory nucleus. In stages 3–4, the substantia nigra and other nuclear grays of the midbrain and forebrain become the focus of initially slight and, then, severe pathological changes. At this point, most individuals probably cross the threshold to the symptomatic phase of the illness. In the end-stages 5–6, the process enters the mature neocortex, and the disease manifests itself in all of its clinical dimensions.

Keywords Alpha-synuclein · Lewy bodies · Lewy neurites · Parkinson's disease · Pathoarchitectonics · Staging

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Introduction

The pathological process underlying Parkinson's disease (PD) requires years to reach its full extent in the human nervous system. The disease relentlessly progresses to the full-blown clinical syndrome, providing that it is not interrupted by the death of the individual. During its course, the intraneuronal lesions increase steadily in severity, and predictable changes occur in their distribution pattern. The alterations develop, to some degree, even in the brains of persons whose clinical protocols make no mention of disease-associated motor dysfunctions, and therefore, the course of the disease can be subdivided into presymptomatic and symptomatic phases (Fig. 1A; Wolters et al. 2000; Del Tredici et al. 2002; Braak et al. 2003a). At present, only the late phase of the degenerative process can be assessed clinically.

PD progresses in six neuropathological stages (Fig. 1A, B), each of which is marked by the continual development of distinctive inclusion bodies that present in the form of spindle-like or thread-like and, in part, branching Lewy neurites (LNs) within cellular processes and as granular aggregations and spherical pale bodies and/or Lewy bodies (LBs) in the somata of the involved nerve cells (see Fig. 6; Lowe 1994; Braak et al. 1998; Takahashi and Wakabayashi 2001; Apaydin et al. 2002; Jellinger and Mizuno 2003). All of the affected neurons eventually develop LNs and LBs, and, despite the presence of these inclusion bodies, some neurons survive for a long period of time, although LB/LN-bearing cells probably cease functioning long before they die.

The inclusion bodies in PD can readily be distinguished from those associated with other neurodegenerative diseases. Furthermore, the combination of specific vulnerable neuronal types and susceptible brain regions is peculiar to PD and makes its differential diagnosis from other disorders possible. Even in the complete absence of detectable clinical symptoms, LNs/LBs are not innocuous changes that accompany "healthy" aging. Instead, these inclusion bodies are the hallmarks of early presymptom-

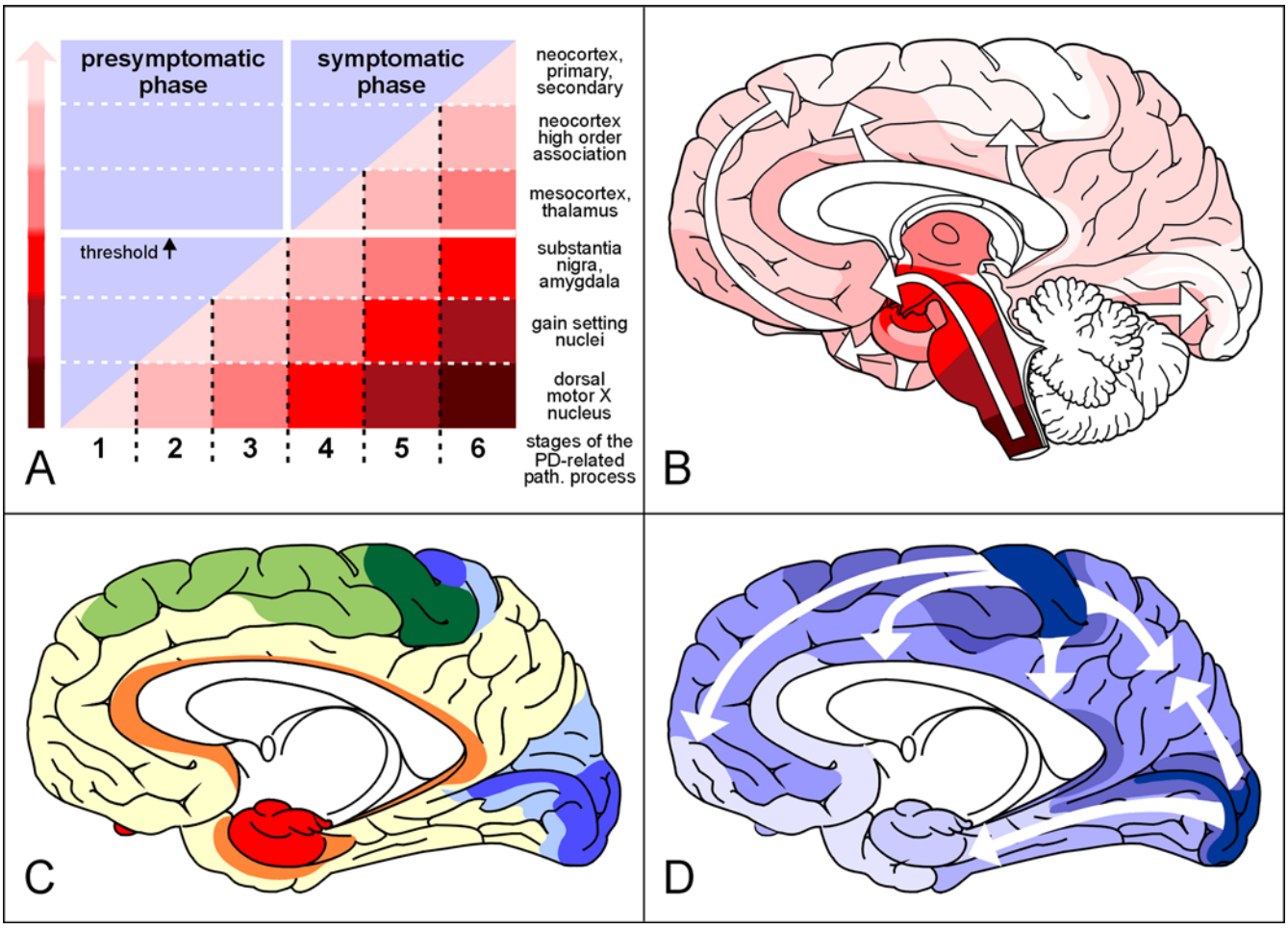


Fig. 1A, B PD presymptomatic and symptomatic phases. **A** The presymptomatic phase is marked by the appearance of Lewy neurites/bodies in the brains of asymptomatic persons. In the symptomatic phase, the individual neuropathological threshold is exceeded (*black arrow*). The increasing slope and intensity of the *colored areas below the diagonal* indicate the growing severity of the pathology in vulnerable brain regions (*right*). The severity of the pathology is indicated by *darker degrees of shading* in the *colored arrow left*. **B** Diagram showing the ascending pathological process (*white arrows*). The *shading intensity* of the *colored areas* corresponds to that in **A** (and in Fig. 4). **C** Composition of the human cerebral cortex. The allocortex (*red*) consists of the olfactory bulb, entorhinal region, and hippocampal formation. The extensive neocortex with its parietal, temporal, and occipital lobes consists of primary sensory fields (*dark blue*), first order sensory association areas (*light blue*), and the related high-order sensory association areas (*orange*). Similarly, the frontal neocortex consists of a primary motor field (*dark green*), premotor areas (*olive*), and prefrontal areas (*yellow*). **D** Neocortical myelination begins in the primary sensory and primary motor fields (*dark blue*) and progresses (*white arrows*) via first order sensory association areas and premotor areas (*medium blue*) to the related high-order association and prefrontal areas (*light blue*). This produces densely myelinated primary sensory and primary motor fields in the human adult. With increasing distance from the primary fields, the average myelin content gradually lessens and is minimal in the anterior portions of the mesocortex (shown by differences in shading). The myelination process proceeds in the opposite direction to the destruction of less densely and relatively late myelinating portions of the neocortex; this occurs in the later stages (see **A**, **B**)

atic disease-related PD stages (Braak et al. 1995; Dickson 1998; Thal et al. 2004).

The intraneuronal inclusion bodies consist mainly of aggregations of a misfolded protein, α-synuclein (Wakabayashi et al. 1992; Spillantini et al. 1997; Dickson 1999; Duda et al. 2000; Giasson et al. 2000; Galvin et al. 2001; Goedert 2001; Jensen and Gai 2001), which is mostly located in both the axon and its terminal presynaptic boutons. The protein is soluble in cytosol but usually binds with high affinity to the membranes of synaptic vesicles or to membranes rich in acidic phospholipids (Perrin et al. 2000; Jensen and Gai 2001). This small, hydrophilic, natively unfolded, 140-amino-acid-containing protein exists in many, but not all, nerve cells of the human nervous system and, thus, in order to become involved in PD, vulnerable neurons require sufficient amounts of normal α-synuclein (Braak et al. 2001).

Under certain conditions, which remain the subject of intense research, α-synuclein in a few predisposed neuronal types shows a marked tendency to give up its membrane-binding capacity. Following a conformational change, it takes on a β-sheet structure and, in this altered form, tends to self-aggregate with other similarly pathologically misfolded α-synuclein molecules and with additional proteins, including synphilin-1, phosphorylated neurofilaments, and ubiquitin. This pathological shift is

central to the disease process because it initiates the development of PD. The reason that the involved nerve cells are not able rapidly to eliminate the abnormal protein via ubiquitination and proteasomal recycling is still unclear (Trojanowski and Lee 2000; Chung et al. 2001; Ding and Keller 2001; McNaught and Jenner 2001; Walker and LeVine 2001).

Vulnerability of select neuronal types

Only a few of the many nerve cell types within the human nervous system are prone to develop the abnormal proteinaceous aggregations. Other neuronal types, even when they are located directly next to involved nerve cells, maintain their morphological and functional integrity. This means that neuronal damage in the brain during PD is not random but obeys certain rules, thereby leaving a distinctive lesional distribution pattern in its wake (Braak et al. 1998, 2003a). The reasons for the marked vulnerability of some neuronal types and the decided resistance of others are still not adequately understood.

PD displays a pronounced affinity for select nuclear grays and cortical areas. All somatosensory or viscerosensory relay centers of the brain remain, for the most part, intact except for olfactory structures. The neuronal damage and loss thus revolve almost completely around areas related to motor functions, particularly the superordinate centers of the somatomotor, visceromotor, and limbic systems.

The susceptible cell types share two common properties. First, they are all projection neurons with axons that are disproportionately long and thin in relation to the size of their somata (Fig. 2C). In contrast to these cells, short-axoned local circuit neurons and projection cells with short axons (e.g., the small pyramidal cells of neocortical layers II and IV, the granule cells of the fascia dentata, and the neurons of the presubicular parvocellular layer) are resistant (Fig. 2A).

The endangered nerve cell types all display a second feature that, although necessary, does not suffice to explain the formation of the intraneuronal aggregates: their long thin-caliber axons are unmyelinated or poorly myelinated (Figs. 1D, 2C; Braak et al. 2003a, 2003b; Braak and Del Tredici 2004). The counter-test is also true. All nerve cells with long robust axons insulated by thick-caliber myelin sheaths are protected against the formation of LNs and LBs during the entire course of PD (Fig. 2B; Braak et al. 2003a, 2003b; Del Tredici and Braak 2004).

What potentially neuroprotective properties are attributable to a sturdy myelin sheath? To begin with, the speed of axonal conduction grows with increasing thickness of the myelin sheath. In addition, far less energy for the

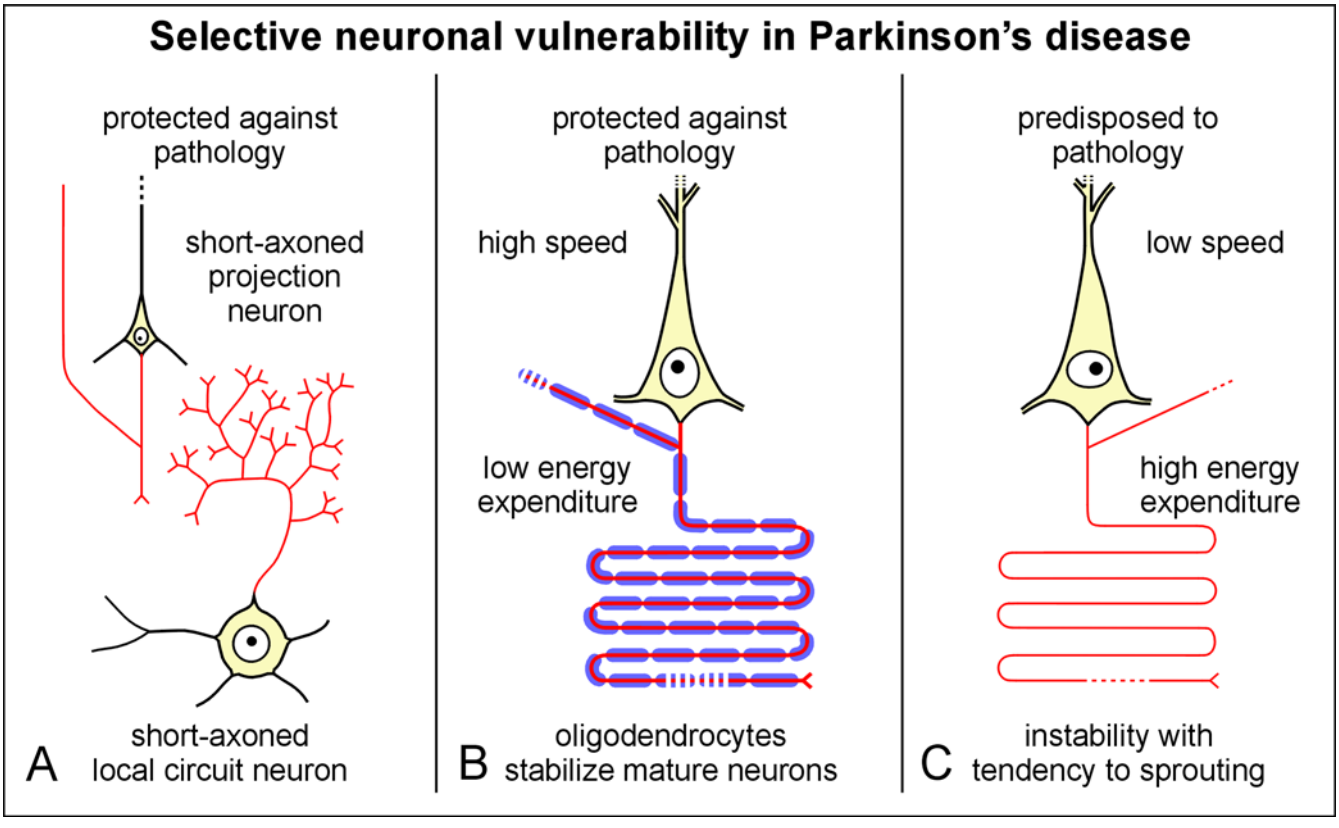


Fig. 2A–C Selective neuronal resistance and vulnerability to PD. **A** Projection cells and local circuit neurons with short axons are resistant. **B** Heavy axonal myelination offers the following advantages: high conductivity, low energy output, and superior stability of the parent neuron against axonal sprouting. Long-axoned, sturdily myelinated projection neurons are resistant to PD. **C** Projection cells that generate long, thin, poorly myelinated or unmyelinated axons are among the most vulnerable nerve cell types

transmission of impulses is needed by a neuron with a solidly myelinated axon (Nieuwenhuys 1999).

Furthermore, the parent neuron is more stable and less susceptible to pathological sprouting because of the interaction of the axon with the oligodendroglial cells that generate and sustain the myelin sheath (Kapfhammer and Schwab 1994). All three properties are all the more pronounced the earlier axonal myelination begins and the thicker the myelin sheath becomes during this process of maturation and differentiation. This explains why all of the vulnerable cells in PD belong to the group of projection neurons with long, thin-caliber, poorly myelinated or even unmyelinated axons.

Anatomical background

PD chiefly involves centers of the limbic, visceromotor, and somatomotor systems (Braak et al. 2003a, 2003b). Recognition of the non-random lesional pattern and multisystem aspects of the pathological process is made possible in diagrams showing the superordinate centers of each of these systems (Fig. 4). The normal functioning of all three systems depends heavily on the activity and efficiency of the cerebral cortex. Expansive portions of the cerebral cortex are late-developing structures, both phylogenetically and ontogenetically.

Considerable architectonic differences exist between the small allocortex and the far-reaching neocortical brain regions (Fig. 1C; Braak 1980; Zilles 2004). Briefly, the neocortex is chiefly responsible for relationships to the world beyond the individual. It receives abundant somatosensory, auditory, and visual input, while concommitantly regulating somatomotor activity that impinges on the organism's environment (Fig. 3B).

The allocortex includes the olfactory bulb and related areas and superordinate centers of the limbic system, such as the entorhinal region and hippocampal formation, which are important for learning and memory functions (Fig. 4; Braak and Braak 1992; Insausti and Amaral 2004). The subnuclei of the amygdala are closely interconnected with the allocortex (Amaral et al. 1987; Sims and Williams 1990). Allocortex and amygdala not only receive data from the internal organs but also influence endocrine and visceromotor functions (Fig. 3B).

Transitional zones between the mature neocortex and the allocortex proper comprise a unique architectonic entity, the mesocortex. Its anteromedial temporal portion is remarkably well developed only among higher primates and above all in humans (Figs. 1C, 4; Braak 1980).

The neocortex is fundamentally divided into highly refined primary fields that are responsible for motor activity and for the initial processing of incoming data from the sensory organs via specific thalamo-cortical projections (Figs 1C, 4). Each of the primary fields is flanked by less highly differentiated first order sensory association areas and premotor fields. These fields, in turn, are interconnected with extensive but simply organized high-order sensory association areas and prefrontal fields (Figs. 1C, 4; Pandya and Yeterian 1990; Mesulam 1998).

Visual, auditory, and somatosensory input arrives at the respective primary sensory field and reaches, by way of the first order association areas, the high-order processing areas. The exteroceptive data then proceeds via long and

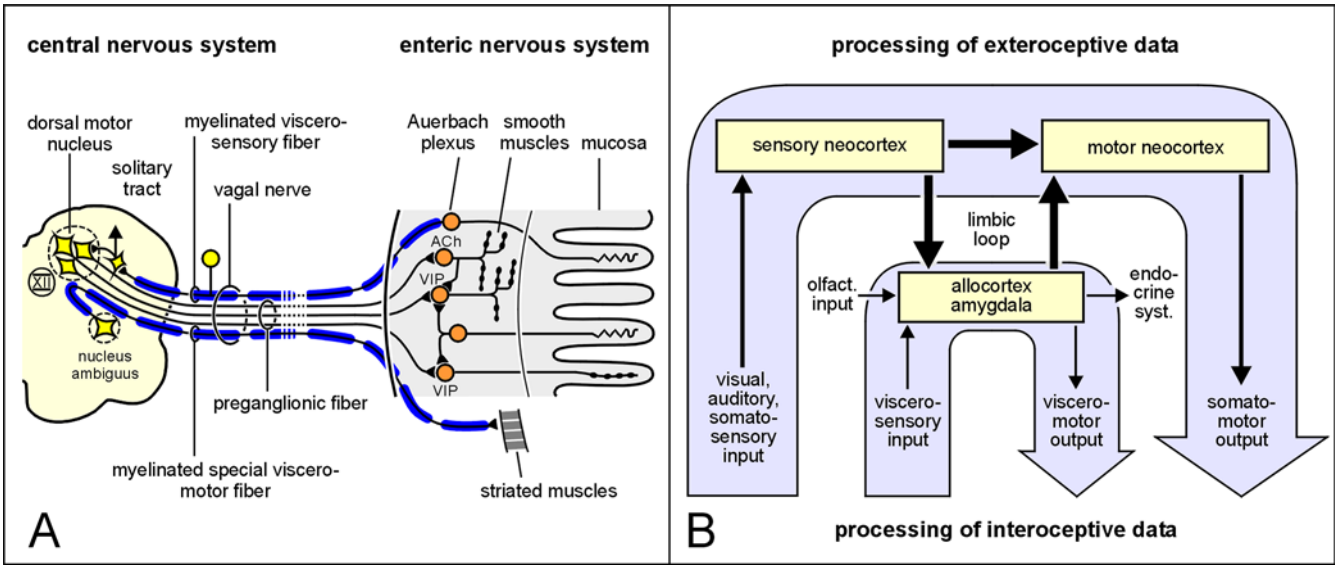


Fig. 3 **A** The enteric and central nervous systems are connected via the vagal nerve. Unmyelinated preganglionic fibers from the dorsal motor nucleus of the vagal nerve contact ganglion cells of Auerbach's plexus. This fiber pathway is susceptible to PD-related lesions. Myelinated viscerosensory fibers terminate in the small-celled nuclei surrounding the solitary tract, and myelinated motor fibers from the ambiguous nucleus innervate striated muscles of the upper esophagus. Both of these pathways resist PD pathology (*ACh* acetylcholine-positive cells, *VIP* vasoactive intestinal polypeptide cells). **B** The neocortex (*outer blue arrow*) processes mainly exteroceptive data. It receives somatosensory, visual, and auditory input and regulates somatomotor output. The superordinate centers of the limbic system (*inner blue arrow*) receive viscerosensory input and regulate the endocrine system and visceromotor output (*thick black arrows* afferent and efferent trunks of the limbic loop that interconnect the neocortex with the amygdala and allocortex)

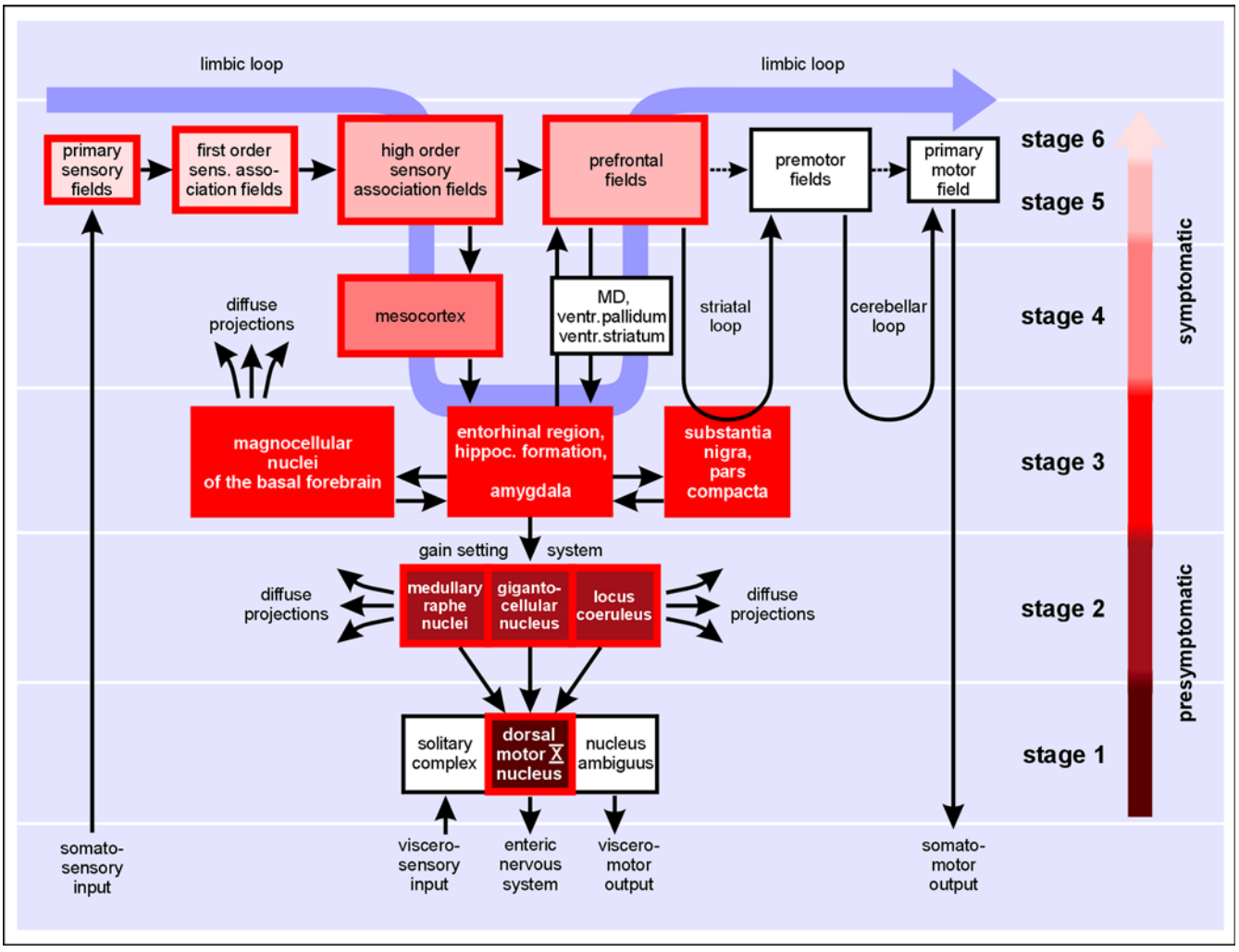
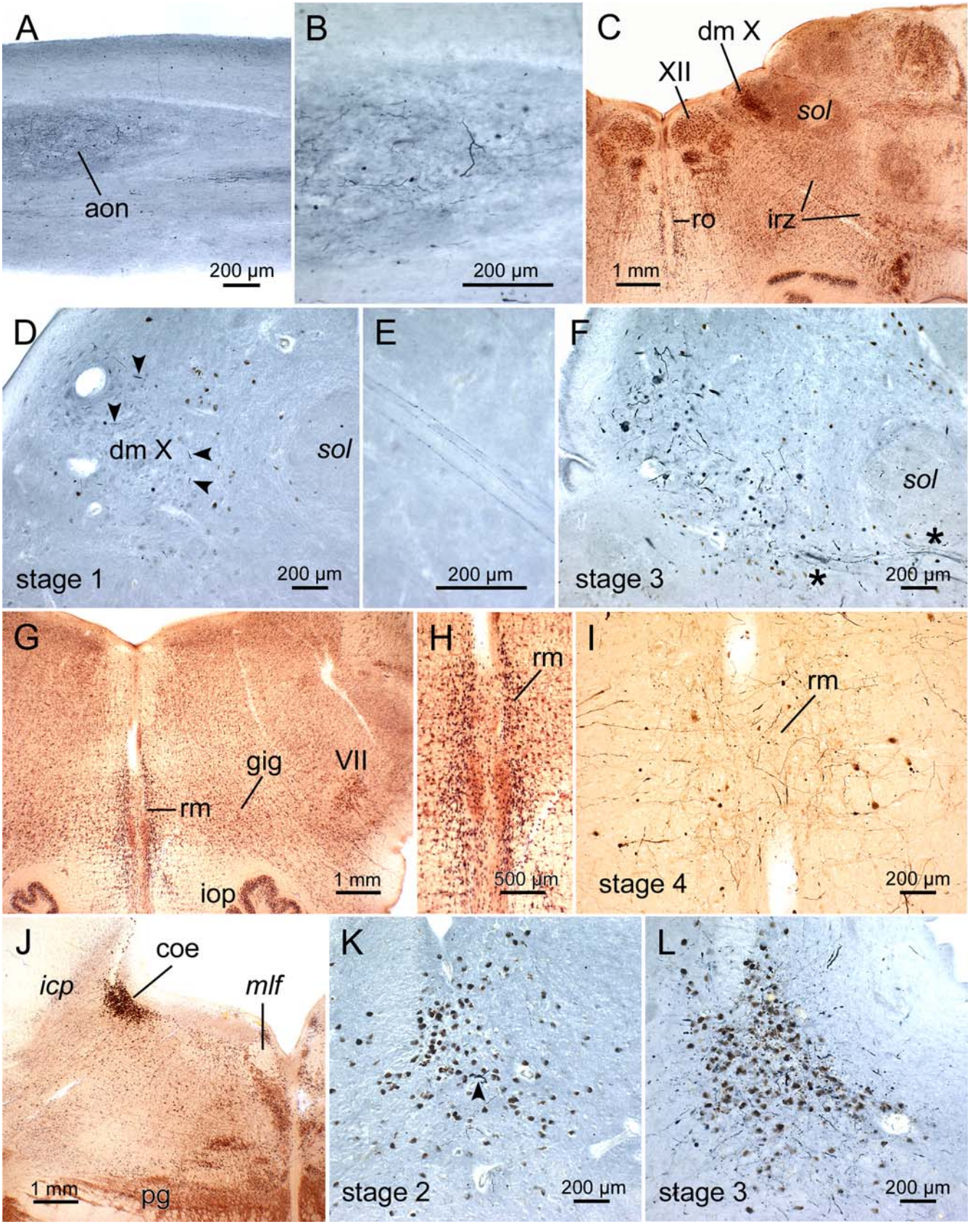


Fig. 4 Diagram of the chief subdivisions of the neocortex and major limbic loop components (entorhinal region, hippocampal formation, amygdala). *Shading intensity* and *color-coding* correspond to those in Fig. 1A, B. Uninvolved areas appear in *white*. *Black arrows* indicate the chief anatomical connections and facilitate recognition of the principal pathways. The limbic loop occupies a strategic position between neocortical high-order association areas and the prefrontal neocortex (*blue arrow*). The afferent trunk of the limbic loop includes the temporal mesocortex, which is exceptionally well developed in the human brain. Normal limbic loop functions depend on the structural integrity of the temporal mesocortex. The efferent trunk chiefly includes the ventral striatum, ventral pallidum, and mediodorsal thalamus, which channel data toward prefrontal fields. The superordinate centers of the limbic and striatal loops suffer the worst neuronal damage. Severe involvement of the temporal mesocortex leads to reduced data transfer from the sensory neocortex via the entorhinal region, hippocampal formation, and amygdala to the prefrontal cortex. The decline of cortically controlled intellectual capabilities supplements dysfunctions of the visceromotor and somatomotor systems (*dorsal motor X nucleus* dorsal motor nucleus of the vagal nerve, *first order sens.* association field first order sensory association fields, *hippoc. formation* hippocampal formation, *MD* mediodorsal nuclei of the thalamus, *ventral pallid.* ventral pallidum, *ventral striat.* ventral striatum)

sparsely myelinated cortico-cortical projections to the prefrontal association cortex (Fig. 4). These connections terminate in layer IV of the target fields (Rockland and Pandya 1979). Minor pathways that lead away from the prefrontal cortex are provided by cortico-cortical backward projections that end in layer I of their target areas (Fig. 4) and transmit the data via premotor areas to the primary motor field. The striatal and the cerebellar loops, however, serve as the main routes for this return pathway and integrate the basal ganglia, the many lower brain stem nuclear grays, and the cerebellum into the regulation of cortical output (Fig. 4; Alheid et al. 1990; Heimer et al. 1991; Albin et al. 1995; Parent and Hazrati 1995; Haber and Gdowski 2004; Petrides and Pandya 2004).

The superordinate centers of the limbic system are also involved in data transfer and do so at the nodal point at which information is conveyed from high-order sensory association areas to the prefrontal cortex. Some of this information, after leaving the mainstream, proceeds through multiple neocortical relay stations and the anteromedial temporal mesocortex until it converges on the entorhinal region and amygdala, thus making the neocortex the major source of input to the human limbic system (see the afferent trunk of the limbic loop in Fig. 4).

During the evolutional transition from macrosomatic mammals to microsomatic higher primates, including humans, the neocortex underwent not only a remarkable degree of expansion but also a thoroughgoing internal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◀ **Fig. 5A–L** Topographic anatomy (staining for lipofuscin pigment and Nissl material in 100 μm-thick polyethylene glycol sections) and PD inclusion body pathology (100 μm-thick polyethylene glycol sections with immunoreactions for α-synuclein) in anterior olfactory structures, the dorsal motor nucleus of the vagal nerve, and nuclei of the gain setting system (*aon* anterior olfactory nucleus, *coe* coeruleus-subcoeruleus complex, *dm X* dorsal motor nucleus of the vagal nerve, *gig* gigantocellular reticular nucleus, *iop* inferior olive, principal nucleus, *icp* inferior cerebellar peduncle, *irz* intermediate reticular zone, *mlf* medial longitudinal fascicle, *pg* pontine gray, *rm* nucleus raphes magnus, *ro* nucleus raphes obscurus, *sol* solitary tract, *VII* motor nucleus of the facial nerve, *XII* motor nucleus of the hypoglossal nerve). **A** Olfactory bulb pathology in the anterior olfactory nucleus in stage 1. **B** Higher magnification of **A** showing LNs/LBs in greater detail. **C–F** Dorsal motor nucleus of the vagal nerve in the medulla oblongata. **C** Overview of the dorsal motor vagal area from a control case for orientation. **D** Isolated LNs (*arrowheads*) at stage 1. **E** α-synuclein positivity in preganglionic axons of the vagal nerve en route through the medulla oblongata at stage 1. **F** LNs/LBs in a case at stage 3 (*asterisks* vagal axonal α-synuclein aggregates). **G–L** Nuclear grays of the gain setting system. **G** Overview of the nucleus raphes magnus and gigantocellular reticular nucleus from a control case at the level of the motor nucleus of the facial nerve (VII). **H** Higher magnification of **G** with the nucleus raphes magnus and, immediately medial from it, the dorsal paramedian nucleus. **I** Affection of the nucleus raphes magnus extends at stage 4 beyond the midline. **J** Overview of the pontine tegmentum, including the gain setting coeruleus-subcoeruleus complex, from the same control case as in **C** and **G** for orientation. **K** LN in a case at stage 2 (*arrowhead*). **L** The lesions become more severe at stage 3

reorganization of its interconnectivities with centers of the limbic loop. In particular, there was a massive increase of those portions of limbic loop centers that received input from and generated output to the neocortex. These internal changes took place at the expense of the formerly predominant territories involved in the processing of olfactory data (Del Tredici and Braak 2004).

The entorhinal region, hippocampal formation, and amygdala are heavily interconnected and send important projections that terminate in the ventral striatum, which includes the accumbens nucleus and "limbic" subdivisions of the putamen.

From the ventral striatum, the data are conducted by way of the ventral pallidum and mediodorsal thalamus to medial and orbital portions of the prefrontal neocortex (Heimer et al. 1991). These projections bring "limbic" influence to bear on the prefrontal cortex (see the efferent trunk of the limbic loop in Fig. 4). In their role as custodians of memory and learning, limbic loop centers act as a neuronal bridge that links the external and internal worlds (Fig. 3B; Hyman et al. 1990; Mesulam 1998).

Stages 1–6 of PD

The intraneuronal lesions in PD evolve sequentially, beginning at definite predisposed sites and advancing from there in a predictable manner throughout the vulnerable regions of the gray matter (Fig. 1B). Within the central nervous system, the first lesions develop at two predilection sites simultaneously, namely, at the dorsal motor nucleus of the vagal nerve plus adjoining intermediate reticular zone and the olfactory bulb together with related portions of the anterior olfactory nucleus (Del Tredici et al. 2002; Braak et al. 2003a).

The olfactory pathology is seen chiefly in the cellular islands of the anterior olfactory nucleus; these islands are dispersed throughout the olfactory tract (Pearce et al. 1995; Mesholam et al. 1998; Hawkes et al. 1999; Doty 2001; Hawkes 2003; Price 2004). A network of tightly woven but thin long LNs rapidly develops in this nucleus (Figs. 5A, B). From stages 3–4 onward, the lesions extend into more remote olfactory sites without advancing into non-olfactory nuclear grays or cortical areas (Braak et al. 2003a; Del Tredici and Braak 2004). Thus, the disease process chiefly begins in the dorsal motor nucleus of the vagal nerve and, from then on, proceeds upward until it arrives at the cerebral cortex (Fig. 1B).

Stage 1

The dorsal motor nucleus of the vagal nerve (Fig. 5C) is always involved in stage 1 (Fig. 5D). The large projection cells of this nucleus generate long unmyelinated preganglionic fibers that connect the central nervous system with the postganglionic nerve cells of the enteric nervous system (Fig. 3A; Huang et al. 1993; Hopkins et al. 1996).

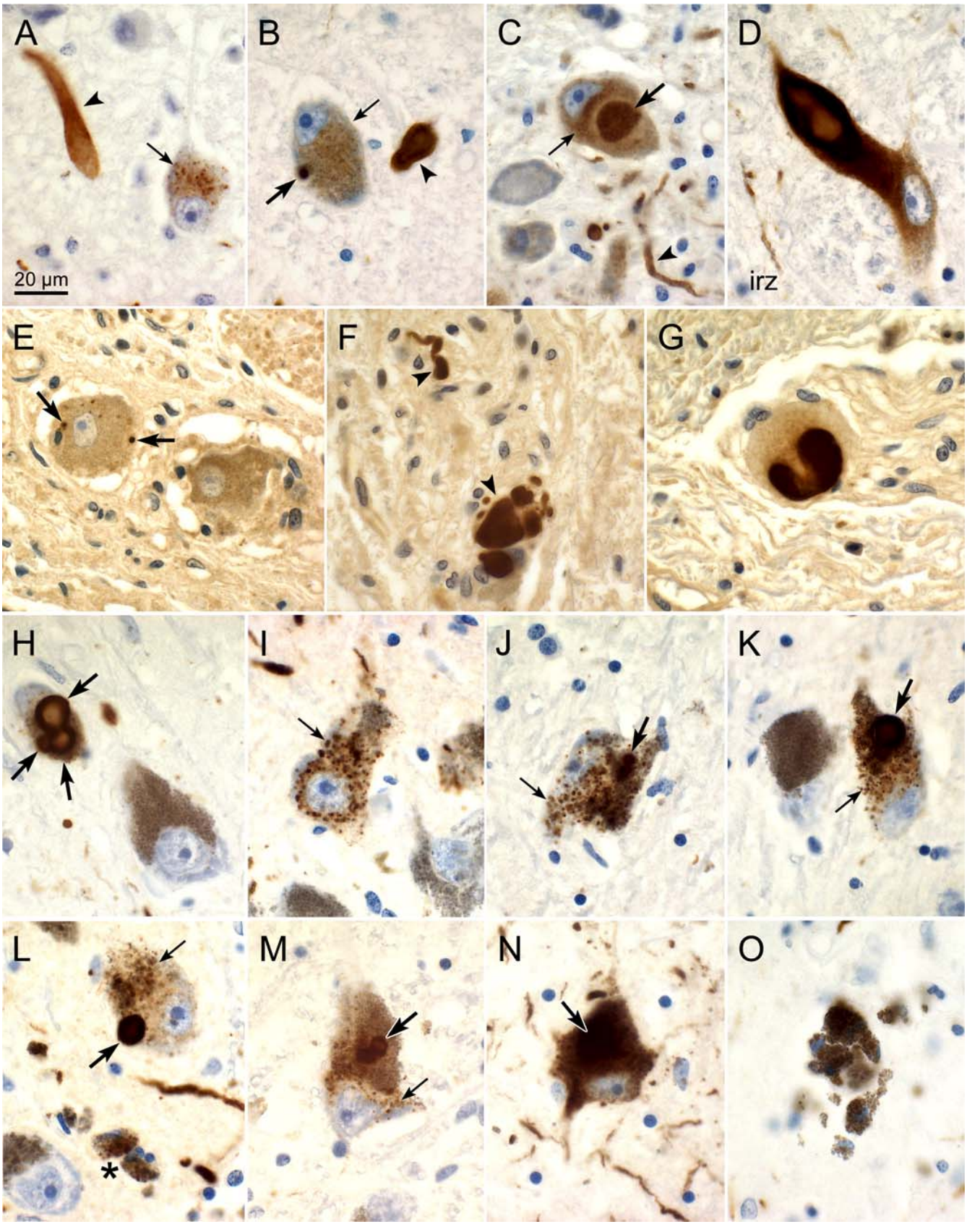
At first, stage 1 cases exhibit no more than a few isolated LNs in the dorsal motor nucleus and in the adjoining intermediate reticular zone (Figs. 5D, 6A–D). A few spindle-shaped LNs also may appear in the preganglionic axons of the vagal nerve (Fig. 5E; Saha et al. 2004), whereas the myelinated viscerosensory fibers terminating in small-celled grays surrounding the solitary tract and the special visceromotor projections originating from the ambiguus nucleus of the vagal nerve do not become involved at any point during the disease process (Fig. 3A; Braak et al. 2003a, 2003b).

The same forms of inclusion bodies as those found in the central nervous system occur in select neuronal types within the enteric nervous system (Figs. 3A, 6E–G), e.g., in vasoactive intestinal polypeptide (VIP) neurons of the Auerbach plexus (Wakabayashi et al. 1990, 1993; Iwanaga et al. 1999).

Stage 2

The pathology in the dorsal motor nucleus worsens in stage 2 and the following stages (Fig. 5F), with the damage spreading beyond the limits of this nuclear gray to include the lower raphe nuclei and magnocellular portions of the reticular formation, in particular the gigantocellular reticular nucleus (Figs. 5G–I). In addition, the first LNs also appear within the coeruleus–subcoeruleus complex (Figs. 5J, K; Saper 1987; Saper et al. 1991; Braak et al. 2003a).

All of the nuclei that first sustain damage in stage 2 function closely together as components of the so-called "gain setting" or "level setting" system. The sparingly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◀ **Fig. 6A–O** PD inclusion body pathology in selectively vulnerable cellular types of the lower brain stem (α-synuclein immunoreactions in 6 μm-thick paraffin sections). **A–C** LNs can be seen in cholinergic neurons of the motor nucleus of the vagal nerve (*arrowheads*). Maturing or mature intraneuronal LBs are found in cholinergic nerve cells (*large arrows*), whereas particulate α-synuclein occurs as aggregates (*smaller arrows*). The discrete particles aggregate to form LBs. **D** A large LN dwarfs a nerve cell in the intermediate reticular zone of a case at stage 5. **E–G** PD lesions in the Auerbach plexus of the enteric nervous system. Start of LB pathology (**E**, *large arrows*), mature LB (**G**), and LNs (**F**, *arrowheads*) in the esophagus. **H–O** Dopaminergic melanoneurons in the substantia nigra, pars compacta. **H** Multiple LBs (*arrows*) fill a nerve cell directly next to a healthy melanoneuron. **I–M** Particulate α-synuclein (*small arrows*) aggregates to form LBs (*larger arrows*). In **K**, compare the normal melanoneuron, without α-synuclein particles, to the one *right*. In **L**, two astrocytes have ingested α-synuclein-immunoreactive material plus neuromelanin (*asterisk*). The term "extraneuronal" neuromelanin can be applied to such material. **N** In this nerve cell, it is difficult to distinguish the LB (*arrow*) from the surrounding α-synuclein particles. **O** Here, a group of neuromelanin-containing macrophages mark the shape of the former nerve cell. *Bar* in **A** applies to **A–O**

myelinated descending tracts of the gain setting nuclei comprise a pain control system that partially inhibits the relay nuclei for somatosensory and viscerosensory input. In addition, they function as a motor control system by regulating the sensitivity and excitability levels of medullary and spinal premotor and motor neurons, possibly placing them in a heightened state of preparedness for action (Holstege 1996; Nieuwenhuys 1996; Braak et al. 2000; Holstege et al. 2004; Koutcherov et al. 2004).

The components of the cerebellar loop commence myelination relatively early and generally resist the development of PD-related lesions or show only minor changes in late stages of the disease.

It is important to bear in mind that during the first two stages, the pathology in non-olfactory sites is confined to the medulla oblongata and pontine tegmentum. Thus, the process that ultimately leads to the full clinical picture of PD does not have, as its point of departure, the substantia nigra (Figs. 1B, 4; Del Tredici et al. 2002). On the contrary, the involvement of the substantia nigra presupposes the existence of an obvious pathology in the medulla oblongata. Indeed, were it to become possible to diagnose PD in the presymptomatic stages 1 or 2, and were a causal therapy to become available, the subsequent neuronal loss in the substantia nigra could be entirely prevented (Braak et al. 2003a).

Stage 3

In stage 3, the upward-moving process crosses the upper limit of the pontine tegmentum and enters the basal portions of the midbrain and forebrain. More specifically, the very first solitary LNs can be seen to take shape in the pars compacta of the substantia nigra followed by the appearance of granular aggregations, pale bodies, and LBs within its melanized projection neurons, all of which generate thin and sparsely myelinated axons (Figs. 6H–O, 7A–C). Since the actual loss of the melanoneurons takes place in subsequent disease stages, the substantia nigra is macroscopically intact. However, even microscopically, there are no visible signs of neuronal loss in stage 3 cases (Figs. 7B, C).

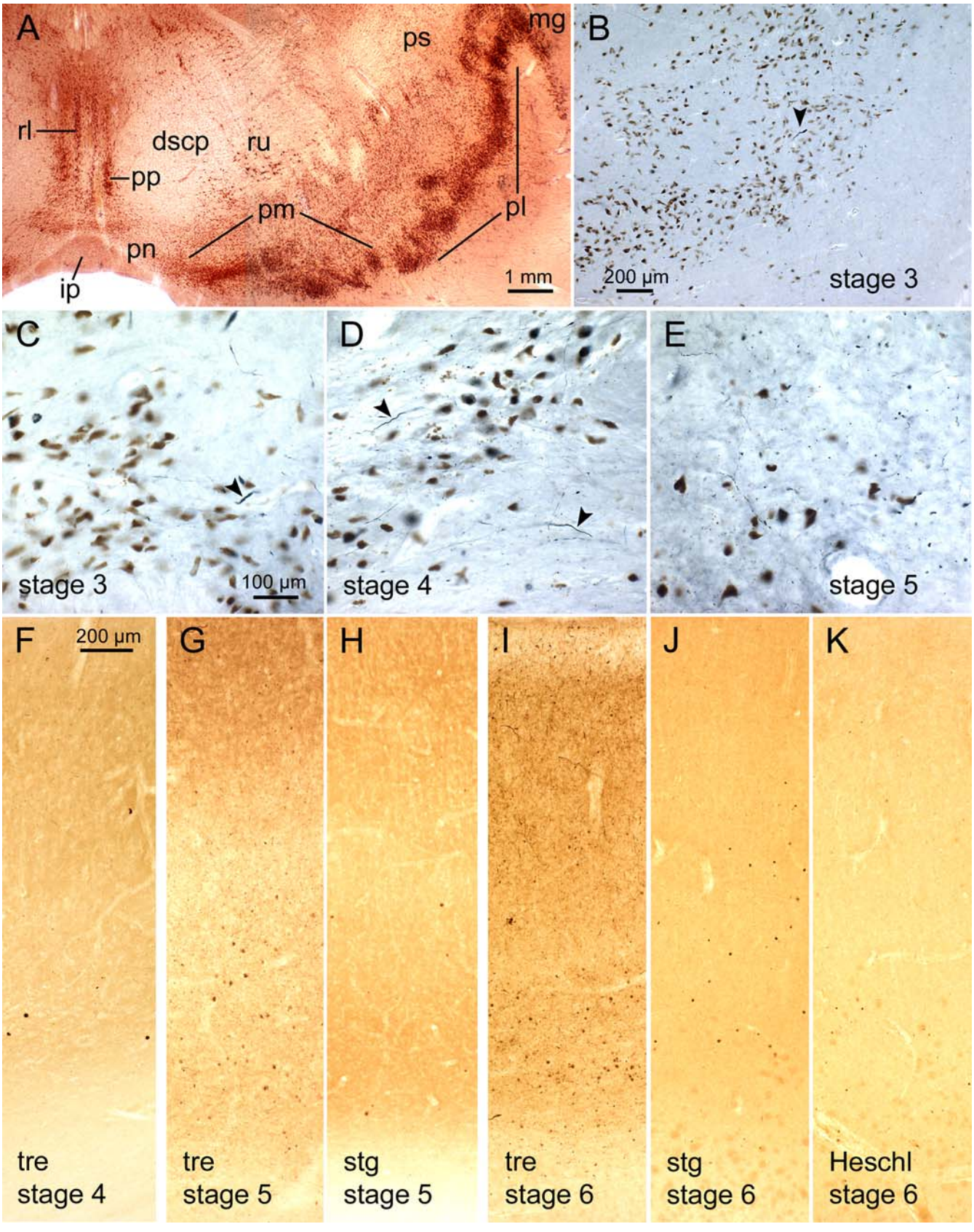
As a rule, the nigral pathology begins in the posterolateral subnucleus of the pars compacta (Fig. 7A; Braak and Braak 1986; Gibb and Lees 1991) and goes on to affect the posterosuperior and posteromedial subnuclei, either bypassing the magnocellular and anterior subnuclei of the substantia nigra or leaving behind only mild lesions there (Braak et al. 2003a).

The severity of the pathology in involved nuclear grays from earlier stages becomes exacerbated (Figs. 5F, L). At the same time, the disease process encroaches on the central subnucleus of the amygdala and from there extends into the basolateral nuclei. A distinctive network of LNs gradually fills the central subnucleus and distinguishes it off from the surrounding structures. The central subnucleus sends a major descending and poorly myelinated fiber tract both to the nuclei of the gain setting system and the dorsal motor nucleus of the vagal nerve; in so doing, it exerts a superordinate "limbic" influence on both of these modulatory lower brain stem regions and regulates them (Fig. 4; Amaral et al. 1987; Sims and Williams 1990; Braak et al. 1994; Bohus et al. 1996). Additional brain regions that become involved in stage 3 include the cholinergic tegmental pedunculopontine nucleus (Garcia-Rill 1991; Inglis and Winn 1995; Rye 1997; Pahapill and Lozano 2000), the oral raphe nuclei, the cholinergic magnocellular nuclei of the basal forebrain (Candy et al. 1983; Whitehouse et al. 1983; Mesulam et al. 1992), and the hypothalamic tuberomamillary nucleus (Del Tredici and Braak 2004). Except for the substantia nigra and the tegmental pedunculopontine nucleus, all of the striatal loop centers commence myelination early and resist developing the pathological changes.

Stage 4

In stage 4, a specific portion of the cerebral cortex, namely a portion of the transition zone between the allocortex and neocortex (i.e., the poorly myelinated temporal mesocortex, including the transentorhinal region) is drawn into the disease process for the first time (Braak et al. 2003a). A thick network of LNs emerges in the superficial layers of this phylogenetically late-appearing and ontogenetically late-maturing region, and many of the small projection neurons located in its deep layers display LBs (Fig. 7F). The anteromedial temporal mesocortex sends bidirectional projections to the entorhinal region, hippocampal formation, and amygdala (Fig. 4), the last-mentioned of which also becomes affected just prior to the anteromedial temporal mesocortex (Del Tredici and Braak 2004).

A plexus of LNs in the second sector of Ammon's horn (Dickson et al. 1994) starts to develop during this stage and makes inroads into the adjoining first and third sectors in stages 5 and 6. This feature is so characteristic of the late stages 4–6 that, even when sections through the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◀ **Fig. 7A–K** Topographic anatomy and PD inclusion body pathology (100 μm-thick polyethylene glycol sections stained for lipofuscin pigment and Nissl material or with immunoreactions for α-synuclein) in the midbrain, mesocortex, and neocortex. **A** Overview of the substantia nigra from a control case with posterior subnuclei of the pars compacta for orientation (*dscp* decussation of the superior cerebellar peduncle, *ip* interpeduncular nucleus, *mg* magnocellular subnucleus, *pl* posterolateral subnucleus, *pm* posteromedial subnucleus, *pn* paranigral nucleus, *pp* parabrachial pigmented nucleus, *ps* posterosuperior subnucleus, *rl* linear nucleus of the raphe, *ru* red nucleus, magnocellular part). **B** In stage 3, the pathology reaches the midbrain substantia nigra for the first time (*arrowhead* a lone LN). **C** A stage 3 case displays incipient nigral pathology (*arrowhead*) but practically no neuronal loss. **D**, **E** In subsequent stages, the lesions in the pars compacta (**D**, *arrowheads* thin elongated LNs) are attended by increasing and more drastic thinning of the melanoneurons (**E**). **F–K** Involvement of the cerebral cortex between stages 4 and 6 (*Heschl* gyrus of Heschl, *stg* superior temporal gyrus, *tre* transentorhinal region). **F** Typical of stage 4 is the progression into the cerebral cortex, for the first time, by the disease process at a circumscribed region: the temporal mesocortex, particularly the transentorhinal periallocortex (the "eye of the needle") within the afferent trunk of the limbic loop (see also Fig. 4). LBs appear in the projection neurons of the deep cortical layers V–VI. **G–K** In stages 5 and 6, the pathology in the transentorhinal region steadily worsens (see also the LNs in layers II–III in **I**) and advances from the mesocortex into the mature neocortex, first making inroads into the extended prefrontal and high-order sensory association areas (**H**, **J**), followed by incursions into premotor and first order sensory association areas, and eventually, the primary fields (**K**). In the neocortex, LBs continue to appear in the deep layers V–VI, whereas there are fewer or no LNs in cortical layers II–III

substantia nigra are unavailable to the neuropathologist, the diagnosis of PD can be made based on the presence of the Ammon's horn lesions alone (Del Tredici and Braak 2004).

It is highly likely that at some point during the intermediate stages 3–4 the presymptomatic phase gradually gives way to the clinically manifest phase of PD (Braak et al. 2003a; Thal et al. 2004). To understand the functional consequences of the increasingly severe lesions in the anteromedial temporal mesocortex, it should be emphasized that this region is involved in the transfer of data from the high-order sensory association areas to the prefrontal cortex by way of the superordinate centers of the limbic system (Fig. 4). Limbic loop centers are constantly informed about neocortical processes, and projections from limbic loop components influence the prefrontal cortex. In Fig. 4, the blue arrow emphasizes the strategic intermediary position of the limbic loop between the high-order sensory association areas of the neocortex, on the one hand, and the prefrontal neocortex, on the other.

In the healthy human brain, limbic loop components and the neocortex always function hand-in-hand. The neocortex specializes in the precise and initially unfiltered analysis of extrinsic sensory information arriving from the eyes, ears, and skin. Should it prove necessary, however, for the organism to retain an item in its memory or to categorize it as important, that single item has to be selected from the barrage of extrinsic data. Co-operation between the neocortex and limbic loop centers makes this selective data processing possible.

As though passing through the eye of a needle, all of the vital information coming from neocortical high-order sensory association areas is siphoned through the temporal mesocortex to the amygdala, entorhinal region, and hippocampal formation and goes on from there to the prefrontal cortex. Bilateral impairment of this data stream opens the way for memory dysfunctions and cognitive decline (Zola-Morgan and Squire 1993; Dubois and Pillon 1997). Furthermore, diminution of the limbic system input to the prefrontal cortex can lead to the loss of personal initiative and other forms of hypofrontality.

Stages 5 and 6

In the final stages 5 and 6, the neurodegenerative process attains its greatest topographic extent (Figs. 1B, 4). The vulnerable portions of the substantia nigra appear nearly denuded of melanoneurons and are unmistakably pale upon macroscopic inspection (Fig. 7E). With the temporal mesocortex as its starting point, the inclusion body pathology gradually overruns the entire neocortex (Figs. 4, 7G–K). Inclusion bodies appear first in the prefrontal and high-order sensory association areas of the neocortex (stage 5; Fig. 7H), then in the premotor and first order sensory association areas, and, finally, in some instances, even in the primary fields (stage 6; Fig. 7K; Braak et al. 2003a; Del Tredici and Braak 2004).

In these stages, patients manifest the full range of PD-associated clinical symptoms. Severe damage to the autonomic, limbic, and somatomotor systems that began in the presymptomatic phase can become compounded by supervening functional deficits on the part of the cerebral cortex (Azuma et al. 2003).

Progression of the cortical pathology during PD stages 4–6 recapitulates the process of cortical myelination in reverse order

The remarkably consistent topographic expansion of the pathology in PD remains enigmatic. One key to its decipherment may be the observation that the sequential appearance of inclusion bodies in the neocortex and the process of neocortical myelination are mirror images: the progression is the same, but the order is reversed (compare Fig. 1B with Fig. 1D; Braak et al. 2003a). Mesocortical and neocortical areas that undergo late myelination develop lesions earlier in the disease process and at higher densities than those that begin to myelinate early (Bartzokis 2004; Braak and Del Tredici 2004). Furthermore, regressive brain changes tend to repeat the maturation process but in reverse order (Bachevalier and Mishkin 1992; Reisberg et al. 1992, 1999; Braak and Braak 1996).

Myelination is the final step in brain maturation, and functional maturity of projection neurons is achieved after axonal myelination has been completed (van der Knaap et al. 1991). Myelination of the human neocortex is a late-

onset event, and the prolonged process follows a predetermined sequence (Yakovlev and Lecours 1967; Hasegawa et al. 1992; Nieuwenhuys 1999). It begins in the primary fields of the neocortex and slowly proceeds via the first order sensory association areas and premotor fields into high-order sensory association areas and prefrontal fields until it reaches the mesocortex (Fig. 1D).

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