Where does Parkinson's disease pathology begin in the brain?

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Destruction and loss of dopaminergic neurons in the substantia nigra, pars compacta, together with the presence of α-synuclein-immunoreactive Lewy neurites and Lewy bodies in involved nerve cells there are pathognomonic for Parkinson's disease. Nonetheless, it has long been known that many extranigral sites become involved in the course of the disease process, and a recent post-mortem staging schema by Braak et al. (2003) confirms that the pathology is by no means confined to the dopaminergic system. In stage 1 cases, lesions are limited to the visceromotor cells of the dorsal vagal nucleus, to neurons of the superordinate autonomic center of the reticular formation – the intermediate reticular zone, and anterior olfactory structures (olfactory system). A third system becomes involved in stage 2: the gain or level setting system of the lower brain stem (including the serotonergic caudal raphe nuclei, gigantocellular nucleus of the reticular formation, and noradrenergic locus coeruleus). In stage 3, the pathology develops in the mesencephalic serotonergic raphe nuclei. Also affected are the autonomic central subnucleus of the amygdala, the mesencephalic cholinergic nucleus tegmentalis pedunculopontinus and dopaminergic pars compacta of the substantia nigra (both somatomotor centers), the cholinergic basal forebrain nuclei (medial septal nucleus, diagonal band nucleus, basal nucleus of Meynert), and the GABAergic hypothalamic tuberomamillary nucleus. In stage 4, the disease process reaches the cortex for first time (transentorhinal region, second sector of the Ammon's horn), the subnuclei of the thalamus with predominantly limbic influence, and the accessory subnucleus of the amygdala (olfactory system). Most individuals with Parkinson's disease probably display initial motor symptoms at stages 3-4. In the final stages 5-6, the pathology makes inroads into mesocortical autonomic and limbic centers but also into the extensive neocortical sensory association areas, prefrontal areas, premotor fields, and primary motor as well as primary sensory fields of the mature neocortex.

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