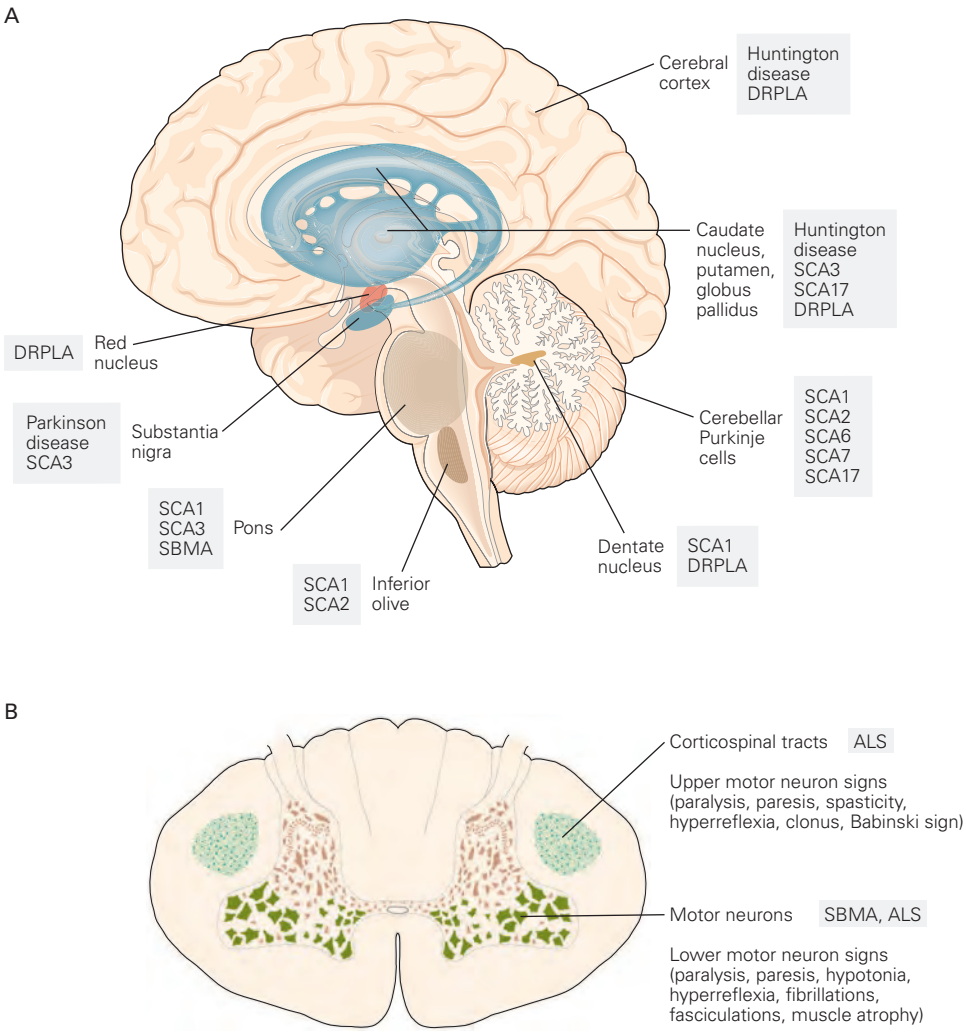

Figure 63–2 Neuronal selectivity illustrated by the primary sites of neuronal degeneration in the trinucleotide repeat diseases and Parkinson disease.

A. Brain regions most typically affected by adult-onset disease (see Table 63–1). (Abbreviations: **DRPLA**, dentatorubropallidoluysian atrophy; **SCA**, spinocerebellar ataxia.)

B. Comparison of neuropathology of amyotrophic lateral sclerosis (**ALS**) and spinobulbar muscular atrophy (**SBMA**).

characterized by extremely long repeats. Juvenile SCA1 can involve oculomotor abnormalities, for example, or cause dystonia, rigidity, and cognitive impairment, features that overlap with Huntington disease and DRPLA; death usually occurs within 4 to 8 years of symptom onset. Juvenile SCA7 patients can suffer seizures, delusions, and auditory hallucinations, and infantile disease also produces somatic features such as short stature and congestive heart failure. Infantile SCA7 causes progressive blindness by destroying both rods and cones; interestingly, infants with SCA2 can also suffer retinal degeneration. Such observations suggest that different cell types have different thresholds of vulnerability to toxic proteins with expanded glutamine tracts. Retinal cells, for example, seem more resistant to polyglutamine toxicity than cerebellar neurons, but more vulnerable than cardiac myocytes. Once the number of glutamines in the tract expands beyond a certain length—which varies from one protein to the next—no cell is safe.

Studies using mouse models suggest that protein misfolding is responsible for polyglutamine disorders. The longer the glutamine tract, the more severe the misfolding, and the more resistance there is to clearance; thus, the slow accumulation of higher-than-normal protein levels is a feature common to neurodegenerative diseases. As the tracts become very long, even cells with lower concentrations of disordered gene product