Chapter 18

Progressive Supranuclear Palsy and Related Parkinsonian Disorders

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INTRODUCTION

Parkinsonism refers to a complex of neurological symptoms including tremor, rigidity, bradykinesia, and postural instability. Neurodegenerative syndromes that involve parkinsonism are united by progressive damage to the nigrostriatal dopamine system. Historically the parkinsonian disorders have been divided into (typical) Parkinson disease (PD) on the one hand and atypical parkinsonian or "Parkinson plus" disorders on the other. This distinction helped identify patients whose parkinsonism was more or less likely to respond to levodopa therapy. Increasingly, however, these terms are being abandoned as our understanding of the "atypical" disorders matures. The non-PD parkinsonian disorders have been recognized as clinically and conceptually important in their own right, no longer requiring that they simply be differentiated from PD.

Parkinsonian disorders less prevalent than PD include the tauopathies, progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD), and the other synucleinopathies, diffuse Lewy body disease (LBD) and multiple system atrophy (MSA). In this chapter, we focus on the tauopathies (Table 18.1). PSP and CBD are neurodegenerative four-repeat tauopathies, which differentiates them from disorders in which predominantly three-repeat tau aggregates are seen (Pick's disease) and those in which inclusions are composed of both three-repeat and four-repeat tau (Alzheimer disease ad some inherited tauopathies). PSP and CBD begin to produce symptoms around the same age as PD but typically lead to a more rapid progression.

When discussing the parkinsonian disorders or any neurodegenerative disease, it is critical to disambiguate clinical from pathological terms. PSP and CBD refer to histopathological entities. PSP syndrome (PSP-S) (also known as Richardson syndrome) and corticobasal syndrome (CBS), on the other hand, are terms that refer to specific symptom-deficit profiles. These terms arose to separate the syndromes from their most common underlying pathological causes and allow for the observation that both PSP-S and CBS are associated with a pathological differential diagnosis. Owing to prominent substantia nigra (SN) degeneration, PSP-S and CBS both involve extrapyramidal motor impairments, as seen in PD, but there are important differences in the affected motor and extramotor domains, as described subsequently. Whereas PSP-S is a falling disease with prominent oculomotor dysfunction, CBS is an asymmetric akinetic-rigid syndrome with progressive loss of limb control (Table 18.1).

Anatomically, typical PD can be distinguished from PSP and CBD based on the specific sites of anatomical involvement. PD onset typically occurs in the lower brain stem. PSP, in contrast, most likely begins in the upper brain stem, subthalamic nucleus, and pallidum, whereas in CBD the early targets include perirolandic cortex and striatum. This distinction in the pathological epicenter for each disease will help define the each disease's primary network target.

The goal of this chapter is to provide a modern synthetic view of PSP-S and CBS from a network-based perspective. To set the stage, we will introduce intrinsic connectivity networks (ICNs) as defined by task-free functional MRI (fMRI). This information will provide background for the recurring theme of this chapter, that each of these parkinsonian neurodegenerative syndromes targets a specific large-scale network. In the second section, we will briefly summarize typical

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TABLE 18.1 Similarities and Difference Between Parkinson Disease (PD), Progressive Supranuclear Palsy Syndrome (PSP-S), and Corticobasal Syndrome (CBS)

Syndrome	Path DDX	Major Disease Protein in Most Common Path DDX	Dominant Symptom in Typical Patient	Core Affected Anatomy	Genes
PD	**LBD** MSA **PSP** **CBD**	Alpha synuclein	Tremor/bradykinesia	**Substantia nigra**, globus pallidus, subthalamic nucleus	SNCA,* LRRK2,* PARK2,* PINK1*
PSP-S	**PSP** **CBD** **PiD**	**Four-repeat tau**	Falls	Rostral midbrain tegmentum, tectum, dentate nucleus, globus pallidus, subthalamic nucleus **substantia nigra**	**MAPT,*** STX6, EIF2AK3, **MOBP**
CBS	**CBD** AD **PSP** TDP-A **PiD** **(LBD)** (CJD)	**Four-repeat tau**	Progressive loss of limb controls	Perirolandic cortex, striatum, **substantia nigra**	**MAPT*,** **MOBP,** lnc-KIF13B-1, SOS1

Items in bold are common to more than one of the three syndromes listed. Genes with asterisks are rare monogenic causes; the remainder are risk genes. Path DDXs in parentheses are rare diagnoses. *DDX,* disease diagnosis; *TDP-A,* TDP type A; *CJD,* Creutzfeldt–Jacob disease; *LBD,* Lewy body disease; *MSA,* multiple system atrophy; *PiD,* Pick disease; *AD,* Alzheimer disease.

idiopathic PD. We will then introduce the diagnostic criteria for PSP-S and CBS and more deeply characterize these syndromes. Next, we will describe the underlying ICNs that mirror the patterns of gross atrophy in PSP-S, CBS, and related syndromes. In the third section we will expand on a model of transneuronal spread from a disease "epicenter," describing evidence that these diseases progress from a selectively vulnerable brain region in a manner that can be predicted by that brain region's structural and functional intrinsic connections. We will then examine the clinicopathological correlations, including the proteinopathies that cause PSP-S and CBS and the diversity of syndromes that result from PSP and CBD pathology. Finally, we will review genetic causes and risk factors in PSP and CBD.

EACH NEURODEGENERATIVE SYNDROME REFLECTS A NETWORK

Class-Wide Principles of Network-Based Neurodegeneration

That neurodegenerative diseases represent organized network degenerations has long been postulated (Braak & Braak, 1991; Pearson, Esiri, Hiorns, Wilcock, & Powell, 1985; Saper, Wainer, & German, 1987). Advances in human network mapping techniques have enabled researchers to clarify the network architecture of the human brain and use this information to deepen our understanding of the spatial patterning of neurodegenerative disease. Novel network imaging methods include fMRI-based functional intrinsic connectivity mapping and diffusion tractography, among others. Studies to date have shown that anatomically distinct ICNs, defined by task-free fMRI, span the same distributed set of brain regions that undergo atrophy in Alzheimer disease and the frontotemporal dementias (Buckner et al., 2009; Seeley, Crawford, Zhou, Miller, & Greicius, 2009; Zhou, Gennatas, Kramer, Miller, & Seeley, 2012). Convergent findings have been derived from diffusion tensor imaging (Raj, Kuceyeski, & Weiner, 2012), which suggests that both functional and structural connections may predict vulnerability and spread (Raj et al., 2015). The network-based model of regional vulnerability has been further refined by identifying a focal "epicenter" for each syndrome, defined as the brain region or regions whose intrinsic connectivity pattern in healthy individuals best matches the spatial pattern of disease-related atrophy. The intrinsic functional connections among all regions within a given ICN can be determined to derive an intranetwork graph. As predicted by the network spread model, in all frontotemporal dementia (FTD) syndromes investigated to date, more severe atrophy is seen in nodes with shorter network path lengths to the syndrome-specific epicenter. In addition to intranetwork disease spread from an epicenter, evidence suggests that these diseases can spread between ICNs in a process of transnetwork spread (Zhou et al., 2012). Thus a given disease is not confined to a specific set of regions within a

single ICN. Instead, there appear to be "target" (or "core") and "off-target" (or "periphery") networks with predictable gradations in vulnerability based on the sites of regional onset.

To understand the regional vulnerability landscape for each syndrome, it is useful to define the extent of the major ICNs and their place within the whole-brain network. A whole-brain graph of connections within and between ICNs in the healthy brain has been described by several groups. The modular composition of one such network (Power et al., 2011) is shown in Fig. 18.1. This network was determined by using task-free fMRI data from a large set of healthy adults and calculating functional connectivity between 264 nodes in the cortex, basal ganglia, thalamus, midbrain, and cerebellum. A modularity analysis of this whole-brain network revealed approximately 10 intrinsic connectivity networks (Fig. 18.1): default mode, frontoparietal task control, dorsal attention, ventral attention (bearing some similarity to the salience network, as previously described) (Seeley et al., 2007), cingulo-opercular, sensory-somatomotor, visual, subcortical, and anterior temporal. The cognitive and behavioral processes supported by these different networks in health translate directly into the cardinal symptoms of specific neurodegenerative syndromes. Superimposed on this graph in Fig. 18.1 are boxes indicating the affected networks of regions showing most substantial atrophy and dysconnectivity in PSP-S (dotted squares—edged box), CBS (solid-edged box), and bvFTD (dotted circles—edged box), the most common FTD syndrome; we will return to the discussion of these boxes in section "Clinicopathological Correlation in Progressive Supranuclear Palsy and Corticobasal Degeneration." The sensory-somatomotor network includes primary cortices for processing sensory input and motor output, particularly along the dorsal/medial surface of the brain where the body and hands are represented. The cingulo-opercular network covering the posterior medial frontal cortex, anterior cingulate, frontal operculum, and dorsal anterior insula defines the task control system, which maintains the appropriate mental set during goal-directed behavior (Dosenbach et al., 2007). The salience network integrates interoceptive input from sensory, visceral, and autonomic streams in the ventral anterior insula to represent subjective feeling states, which can then mobilize appropriate emotional, cognitive, and behavioral responses via the dorsal anterior cingulate (Zhou & Seeley, 2014). The frontoparietal network spanning the dorsolateral prefrontal cortex and intraparietal sulcus is part of an executive control network involved in prioritizing and maintaining set during goal-directed thinking or behavior (Dosenbach et al., 2006; Seeley et al., 2007).

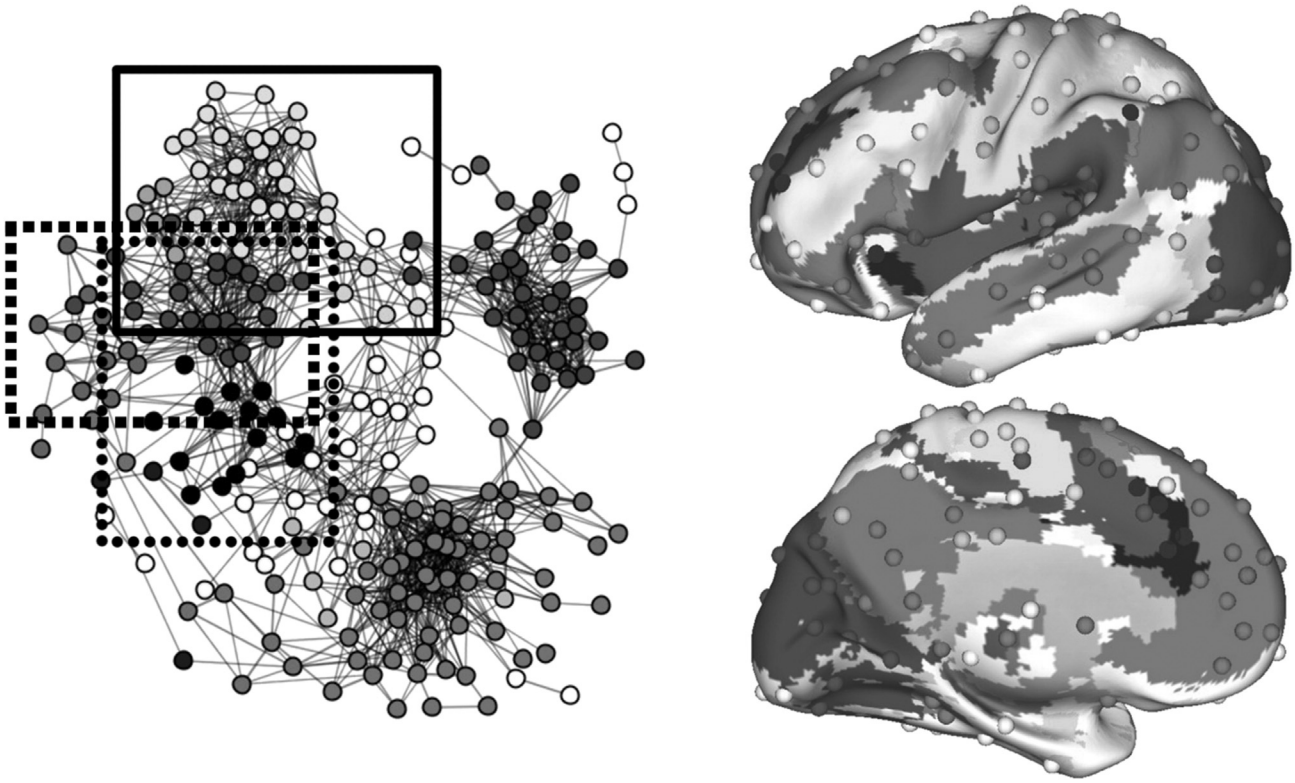

FIGURE 18.1 Functional network graph with boxes covering regions exhibiting atrophy in PSP-S (*dotted squares—edged box*), CBS (*solid-edged box*), and bvFTD (*dotted circles—edged box*). *Modified from Power, J.D., Cohen, A.L., Nelson, S.M., Wig, G.S., Barnes, K.A., Church, J.A., … Petersen, S.E. (2011). Functional network organization of the human brain.* Neuron*, 72(4), 665—678. http://doi.org/10.1016/j.neuron.2011.09.006.*

The dorsal attention network encompasses the secondary sensory and motor association cortices, which support top-down selection of stimuli and responses (Corbetta & Shulman, 2002). The basal ganglia, thalamus, brain stem, and cerebellum are sparsely represented in this cortico-centric analysis, although in many parkinsonian syndromes the disease epicenter is a subcortical nucleus and spreads to the cortex later in the disease process.

PARKINSONIAN SYNDROMES: PARKINSON DISEASE AND OTHERS

Parkinson Disease: Clinical and Anatomical Features

Clinical PD is a sporadic movement disorder syndrome with a mean age at onset of 62 years. In addition to the hallmark parkinsonian features, there are a host of nonmotor features in PD including anosmia, constipation and other forms of autonomic dysfunction, sleep disturbances (particularly excessive daytime sleepiness and rapid eye movement sleep behavior disorder), depression, anxiety, and frontal/executive dysfunction. Presenting symptoms typically involve unilateral parkinsonism, including tremor. PD results from a progressive neurodegenerative process that ascends from the peripheral enteric, autonomic, and olfactory nervous systems before gaining entry to the central nervous system via the dorsal motor nucleus of the vagus or the olfactory apparatus. The ascent continues to involve the major aminergic nuclei in the brain stem, with prominent SN involvement, the basal ganglia, and eventually the limbic system and cerebral cortex (Fig. 18.2). Most patients experience a dramatic clinical benefit from levodopa, which increases dopaminergic neurotransmission at nigrostriatal projection terminals. The underlying pathology for the PD syndrome is usually LBD, recognized by characteristic neuronal inclusions containing misfolded alpha-synuclein. Aggregates appear as neuronal cytoplasmic and neuritic inclusions, known respectively as Lewy bodies and Lewy neurites. Braak and colleagues proposed a staging scheme for LBD that identifies alpha-synuclein deposits in six sets of brain areas (Heiko Braak et al., 2003): (1) the anterior olfactory nucleus and dorsal motor nucleus of vagus; (2) pontine tegmentum; (3) SN pars compacta and pedunculopontine nucleus; (4) hypothalamus, thalamus, and anterior medial temporal cortex; (5) high-order association cortex; and (6) first-order association and primary cortices. The cardinal neuroanatomical feature of PD is loss of dopaminergic neurons in the SN. The resultant disruption of functional motor circuitry is well characterized. Loss of SN inputs from these dopaminergic neurons has two major consequences. In the direct pathway, decreased excitation of D1 dopamine receptor-expressing neurons in the putamen causes diminished inhibition of the globus pallidus interna (GPi), releasing the GPi to overinhibit the thalamus, reducing excitation of the motor cortex. In the indirect pathway, decreased inhibition of D2 neurons in the putamen causes overinhibition of the globus pallidus externa, disinhibiting the subthalamic nucleus (STN) and releasing the GPi, which in turn suppresses the thalamus, again resulting in underexcitation of the cortex (Albin, Young, & Penney, 1989; Alexander, DeLong, & Strick, 1986; Blandini, Nappi, Tassorelli, & Martignoni, 2000). Whole-brain functional MRI findings echo these circuit disruptions. Hacker and colleagues found connectivity deficits in PD among the striatum, thalamus, and midbrain (Hacker, Perlmutter, Criswell, Ances, & Snyder, 2012). This work pinpointed the lower brain stem as the epicenter of PD onset and attributed the predominant loss of posterior putamen connectivity among striatal regions to its tighter integration with lower brain stem structures in a healthy functional network. Other studies have highlighted fMRI hyperconnectivity in patients with PD, both in cortical-STN motor circuits (Baudrexel et al., 2011) and prefrontal-premotor action selection circuits (Rowe, Hughes, Barker, & Owen, 2010). Structural MRI studies in PD have revealed relatively spared subcortical areas and more substantial atrophy in prefrontal,

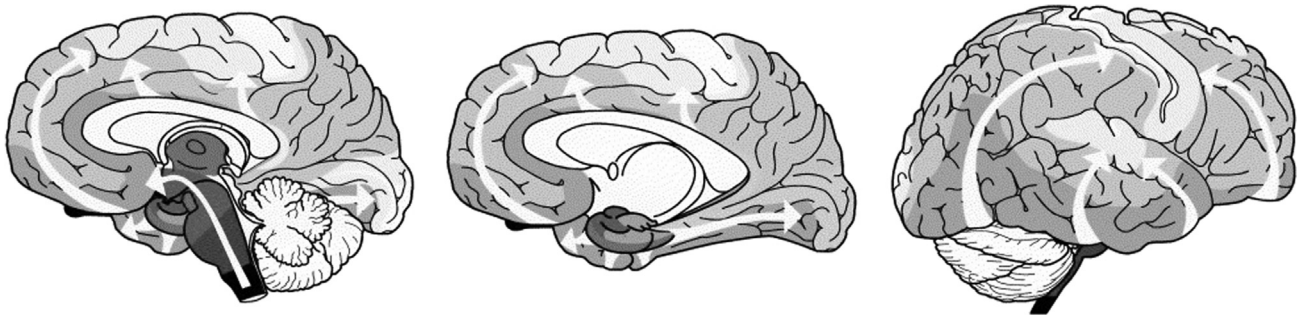

FIGURE 18.2 Braak staging of PD suggests ascent from the caudal medulla (*along white arrows*), from areas of early involvement (*darker*) to those in which inclusions are seen at later stages (in order of increasing lightness) (Heiko Braak et al., 2003). Although the scheme is based on cross-sectional data, it predicts pathways of disease spread between interconnected brain structures.

parietal, and occipital cortices (Weintraub et al., 2011), although these findings could relate to a lesser methodological sensitivity to atrophy in small deep brain structures or the occurrence of comorbid Alzheimer disease in some patients.

Although PD is most commonly sporadic, 10% of familial cases of PD have been linked to a single monogenic mutation (Trinh & Farrer, 2013). One Mendelian form of the disease relates to mutations in *SNCA* (encoding alpha-synuclein), which confirms the genotype−phenotype link between SNCA and alpha-synuclein. Other Mendelian disease-causing genes are *LRRK2*, *PARK2* (encoding parkin), *PINK1*, *PARK7* (encoding DJ-1), and *ATP13A2* (Satake et al., 2009; Simón-Sánchez et al., 2009). The genetic diversity present in PD suggests that the disease may be differentiated into specific subtypes based on the specific pathogenic pathways involved; however, all of them converge on the PD-related anatomy.

Progressive Supranuclear Palsy Syndrome: Clinical Features

PSP was originally characterized as a distinct clinicopathological entity (Steele, Richardson, & Olszewski, 1964). The authors described a progressive syndrome that often began with subtle executive functioning and personality changes followed by vertical gaze slowing, postural instability, pseudobulbar palsy, and rigidity of the neck and upper trunk. Observed damage to nuclei of the upper midbrain, rostral to the oculomotor nucleus (superior colliculus and pretectum), combined with the resultant ophthalmoparesis, warranted the description of the syndrome as a "supranuclear palsy." The age of onset in these patients was the fifth and sixth decades and the disease had a course of 5 to 7 years before death. At autopsy, nerve cell death was apparent in the brain stem, basal ganglia, and cerebellum. The most apparent histopathological changes were neurofibrillary tangles, loss of nerve cells, granulovacuolar degeneration, and gliosis.

A half-century later, we now know that patients with typical PSP-S develop a mild neuropsychiatric/executive prodrome; apathy, mental rigidity, and multitasking problems are the most common. Shortly thereafter, disabling motor symptoms emerge. Early falls occur during ambitious tasks such as changing light bulbs on a ladder or descending stairs while carrying objects. The gait is stiff owing to axial rigidity and toppling, with severe retropulsive and at times propulsive instability. Bradykinesia and especially tremor are less common at onset than in PD. Falls are exacerbated by poor judgment, impulsivity, and the signature gaze abnormalities, which follow a predictable progression from square wave jerks to slowed vertical worse than horizontal saccades, to a full-blown supranuclear gaze palsy. Vestibulo-ocular reflexes remain intact, demonstrating the supranuclear nature of the ophthalmoparesis. Spastic dysarthria and dysphagia, pseudobulbar affect, and a fixed stare are all common features. These clinical deficits are accompanied by magnetic resonance−detectable atrophy in the midbrain, superior cerebellar peduncles, and posterior medial frontal cortex (Fig. 18.3). Disease progression is rapid, with survival time from symptom onset averaging 7 years (Golbe & Ohman-Strickland, 2007). Response to levodopa is typically lacking (Tsai & Boxer, 2014). Although selected patients may

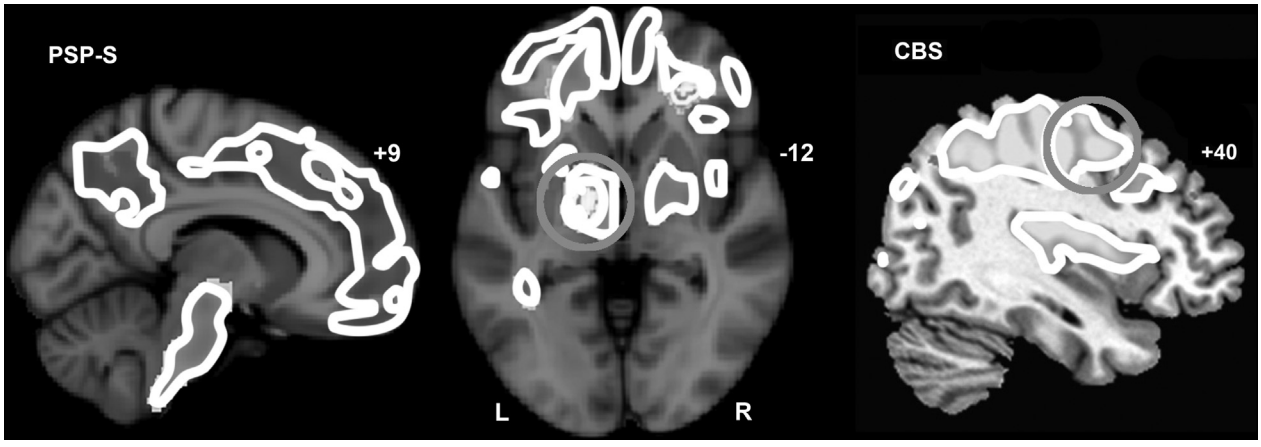

FIGURE 18.3 Patterns of atrophy in patients with PSP-S and CBS. In PSP-S, strongest atrophy is apparent in the midbrain, pallidum, SMA, preSMA, medial prefrontal cortex, and precuneus. Results are shown as white outlines around areas of high and moderate statistical significance for white matter (high: $P < 0.05$, familywise error rate corrected; moderate, $P < 0.01$ cluster corrected) and gray matter. The atrophy peak was in the mesothalamic junction and pallidum (*circled*). Results are from an unpublished analysis of 12 PSP-S patients and 20 healthy control subjects. For CBS, atrophy is apparent in the dorsal frontoparietal sensorimotor association areas, primary motor and sensory cortices, and dorsal insula. In this sample the atrophy peak was in the right premotor cortex (*circled*). *From Seeley, W.W., Crawford, R.K., Zhou, J., Miller, B.L., Greicius, M.D. (2009). Neurodegenerative diseases target large-scale human brain networks.* Neuron, *62(1), 42−52. http://doi.org/10.1016/j.neuron.2009.03.024.*

experience a partial response at higher doses, limited data are available to predict this response or about neuropathological diagnoses made in levodopa responders.

In 1996, Litvan and colleagues defined the National Institute for Neurological Disorders and Stroke-Society for Progressive Supranuclear Palsy Criteria (Litvan et al., 1996). The diagnostic criteria for "PSP probable" include age over 40 years at onset, vertical gaze palsy, slowing of vertical saccades, prominent postural and gait instability, and falls within the first year since onset (Litvan et al., 1996). The disorder must be gradually progressive and occur in the absence of other diseases or conditions that may cause the symptoms. A "PSP possible" diagnosis extends to patients who have vertical gaze palsy or a combination of slowing of vertical saccades and postural instability with falls in the first year of symptoms. Definite PSP requires a history of probable or possible PSP and histopathological confirmation of PSP at autopsy. In 2007, Golbe and Ohman-Strickland published a clinical rating scale for PSP (PSP-RS) that assesses symptom severity in six domains and provides predictive information about subsequent survival (Golbe & Ohman-Strickland, 2007). The scale is based on a 10-minute interview and examination conducted by a neurologist that measures impairment in six domains: daily activities (as measured by patient history), behavior, bulbar, oculomotor, limb motor, and gait/midline. The scale yields a score between 0 and 100. In the original publication, the observed rate of increase in PSP-RS was roughly linear at 10 points per year, which would extrapolate to a PSP-RS change from 0 to 70 between the time of symptom onset to death.

Numerous neuroimaging correlates of PSP-RS have been reported, including functional connectivity strength of the rostral midbrain (Gardner et al., 2013) (see section: Network Architecture of Neurodegenerative Parkinsonian Syndromes), longitudinal atrophy of the frontal lobe and midbrain (Josephs et al., 2013), and white matter integrity in the superior cerebellar peduncle (Whitwell, Master, et al., 2011). Specific motor and nonmotor symptoms tend to be associated with specific alterations in corresponding brain systems. Atrophy rates in the midbrain are correlated with worsening motor deficits (Josephs et al., 2013; Paviour, Price, Jahanshahi, Lees, & Fox, 2006), whereas eye movement abnormalities have been linked to lower fractional anisotropy of the superior longitudinal fasciculus (Whitwell, Master, et al, 2011). Cognitive and behavioral deficits in PSP are predominantly related to frontal processes. Apathy and impulsivity are hallmark symptoms, both of which are routinely measured using the Neuropsychiatric Inventory (Cummings et al., 1994). Patients have executive dysfunctions including set shifting difficulty, mental inflexibility, reduced processing speed (bradyphrenia), impaired verbal fluency, and difficulty with planning (Burrell, Hodges, & Rowe, 2014). Many of these deficits are likely to result from atrophy and dysfunction in the supplementary and presupplementary motor areas, dorsolateral prefrontal cortex (superior and middle frontal gyri), frontal and central operculum, and medial frontal cortex (Gardner et al., 2013; Josephs et al., 2013; Paviour et al., 2006; Whitwell, Master, et al., 2011). Social cognition is also impaired in PSP, negatively affecting emotion recognition and Theory of Mind, and has been shown to correlate with atrophy in this same distributed set of frontal regions (Ghosh et al., 2012).

PSP-S strongly predicts underlying tau pathology (Table 18.1). The large majority are 4R tauopathies, primarily PSP and less frequently CBD. In a meta-analysis of PSP-S, 13% of patients were found to have an underlying CBD pathology (Wadia & Lang, 2007).

Corticobasal Syndrome: Clinical Features

CBS is the term used for the clinical disorder originally described in 1968 by Rebeiz and colleagues, who reported three patients with progressive asymmetric rigidity and apraxia (Rebeiz, Kolodny, Richardson, 1968). They labeled the disorder "corticodentatonigral degeneration with neuronal achromasia" in reference to cortical atrophy and the loss of pigmentation in neurons from the cortex and substantia nigra. In the 1990s the disorder came to be known as "corticobasal degeneration," a term recognizing both the cortical symptoms of the disease (asymmetrical rigidity, apraxia, alien limb phenomenon, cortical sensory loss, myoclonus, and speech deficits) as well as its basal ganglia–related motor symptoms (bradykinesia, limb dystonia, action tremor, postural instability, and gait disturbance). In 2003, Boeve and colleagues clarified the distinction between this cluster of symptoms, which they called CBS, and the most common underlying pathology, for which the term CBD was reserved.

CBS typically begins as an akinetic-rigid syndrome that asymmetrically affects one hand or foot before progressing up the onset limb, into whichever of the two ipsilateral limbs was not affected at first, and ultimately into the orobuccal apparatus and contralateral limbs. Dystonia, myoclonus (which may be stimulus-sensitive), and alien limb phenomenon may accompany the core problem. Cognitive and behavioral symptoms in CBS primarily result from damage to frontal lobe-anchored networks. Patients have shown deficits in attention and concentration, processing speed, executive functioning, verbal fluency, language, and visuospatial function (Pillon et al., 1995; VanVoorst et al., 2008). A research diagnosis of probable CBS requires asymmetric presentation of at least two symptoms of limb rigidity or akinesia, dystonia, and myoclonus plus at least two symptoms of orobuccal or limb apraxia, cortical sensory deficit, and alien limb

phenomenon (Armstrong et al., 2013). A possible CBS diagnosis allows for symptoms to be symmetric if patients have at least one symptom in each of the two core symptom clusters. Criteria for a diagnosis of probable CBS resulting from CBD include insidious onset and gradual progression for 1 year, age 50 years or greater at onset, no family history of disease or known mutations in tau, and a clinical phenotype of probable CBS, but expert clinicians recognize that patients with non-CBD underlying pathological diagnoses often meet all of these criteria.

In patients with CBS, as in PSP, it is critical to recognize that a number of different proteinopathies can infiltrate the CBS-vulnerable network and result in a similar set of symptoms (Table 18.1). Whereas CBD is most common, there are cases of underlying PSP with a clinical presentation of CBS (Josephs, Katsuse, et al., 2006; Tsuboi et al., 2005). A subtle distinction can be made between brain atrophy patterns in pathology-proven CBD cases versus cases of CBS in which the underlying pathology is unknown (Lee et al., 2011). Neuroimaging studies of patients with CBS with unknown underlying pathology, in whom the two candidates are 4R tau and TDP-43 (TAR DNA-binding protein 43), have consistently reported a mixture of atrophy in frontal and parietal sensorimotor association areas, primary sensory and motor areas in perirolandic cortex, and dorsal insula (Fig. 18.3, right) (Boxer et al., 2006; Seeley et al., 2009; Zhou et al., 2012). In two similar studies published in 2010 and 2011, patients with CBS resulting from CBD were found to have predominant atrophy in the frontal lobe and striatum although the parietal lobe was largely spared (Lee et al., 2011; Whitwell et al., 2010). Imaging studies of patients with CBS caused by frontotemporal lobar dementia with TAR DNA-binding protein 43 (FTLD-TDP) show preferential atrophy in the inferior frontal gyrus and insula aligned with the perisylvian component of the cingulo-opercular network (Whitwell et al., 2010), whereas CBS caused by Alzheimer disease shows great parietal atrophy (Lee et al., 2011).

NETWORK ARCHITECTURE OF NEURODEGENERATIVE PARKINSONIAN SYNDROMES

The network model of neurodegenerative disease vulnerability provides a parsimonious explanation for the progression of a diverse set of syndromes. In addition, the model offers two potential clinical-translational advances. First, a network model can aid in earlier diagnosis by helping to pinpoint an epicenter where the disease originates. Second, the model can enable more precise monitoring of the disease progression, either its natural history or during treatment, by predicting where the disease is most likely to arise next.

Network Architecture of Progressive Supranuclear Palsy Syndrome

Building on previous studies linking each major neurodegenerative dementia syndrome to a specific ICN, Gardner et al., mapped the brain regions with intrinsic connectivity to the rostral midbrain tegmentum (rMT), identified in previous studies as an epicenter of PSP-S atrophy (Boxer et al., 2006). The rMT-anchored ICN topology in healthy control subjects (Fig. 18.4) included cortical, subcortical, brain stem, and cerebellar regions with known vulnerability in PSP-S (Gardner et al., 2013) and canvassed portions of the cingulo-opercular, frontoparietal, default mode, and salience networks. Patients with probable PSP-S showed widespread functional connectivity disruptions throughout this network, both in edgewise connectivity strength (Fig. 18.4, bottom left) and in nodewise weighted degree, the sum of connection strengths to a given node (Fig. 18.4, bottom right). Among the most severely impacted nodes were the mesothalamic junction (MTJ) (the node encompassing the rMT epicenter) and the presupplementary motor area (preSMA). Importantly, greater functional connectivity reductions in this network predicted greater clinical impairment on the Clinical Dementia Rating sum of boxes scale and the PSP-RS, as well as slower downward saccade velocity. An examination of the relative effect size of rMT-ICN impairment versus structural atrophy found that many areas showed PSP-related reductions in functional connectivity despite no atrophy, which suggested that fMRI ICN analysis may be more sensitive to early-stage system-level dysfunction that precedes eventual regional atrophy. Intrinsic connectivity deficits have been reported in a thalamocortical network, suggestive of degeneration of the dentatorubrothalamic tract (Whitwell, Avula, et al., 2011). Ongoing longitudinal studies should help determine the efficacy of rMT ICN strength and related measures as biomarkers for disease monitoring.

A critical test of the transneuronal spread model is to assess how well postmortem neuropathology follows the same network trajectory seen for antemortem structural atrophy and ICN disruption. An important study (Fig. 18.5) staged 33 cases of PSP into five levels of severity based on the extensiveness of tau inclusion pathology (Williams, Holton, Strand, Pittman, et al., 2007). The five stages were: (1) pallido-luyso (subthalamic nucleus)-nigral with sparse premotor cortex involvement; (2) moderate basal ganglia, pontine nuclei, dentate nucleus, and posterior frontal lobe, without parietal lobe; (3) severe basal ganglia and dentate nucleus, moderate frontal, and parietal lobe; (4) severe basal ganglia, pontine nuclei, and frontal and parietal lobe; and (5) severe subthalamic nucleus, substantia nigra, globus pallidus interna, pontine nuclei, cerebellar structures, and neocortex, with negligible pathology in caudate, putamen, and temporal lobe. The trajectory of this pathology would roughly affect subcortical and cingulo-opercular ICNs at stage 1, default mode,

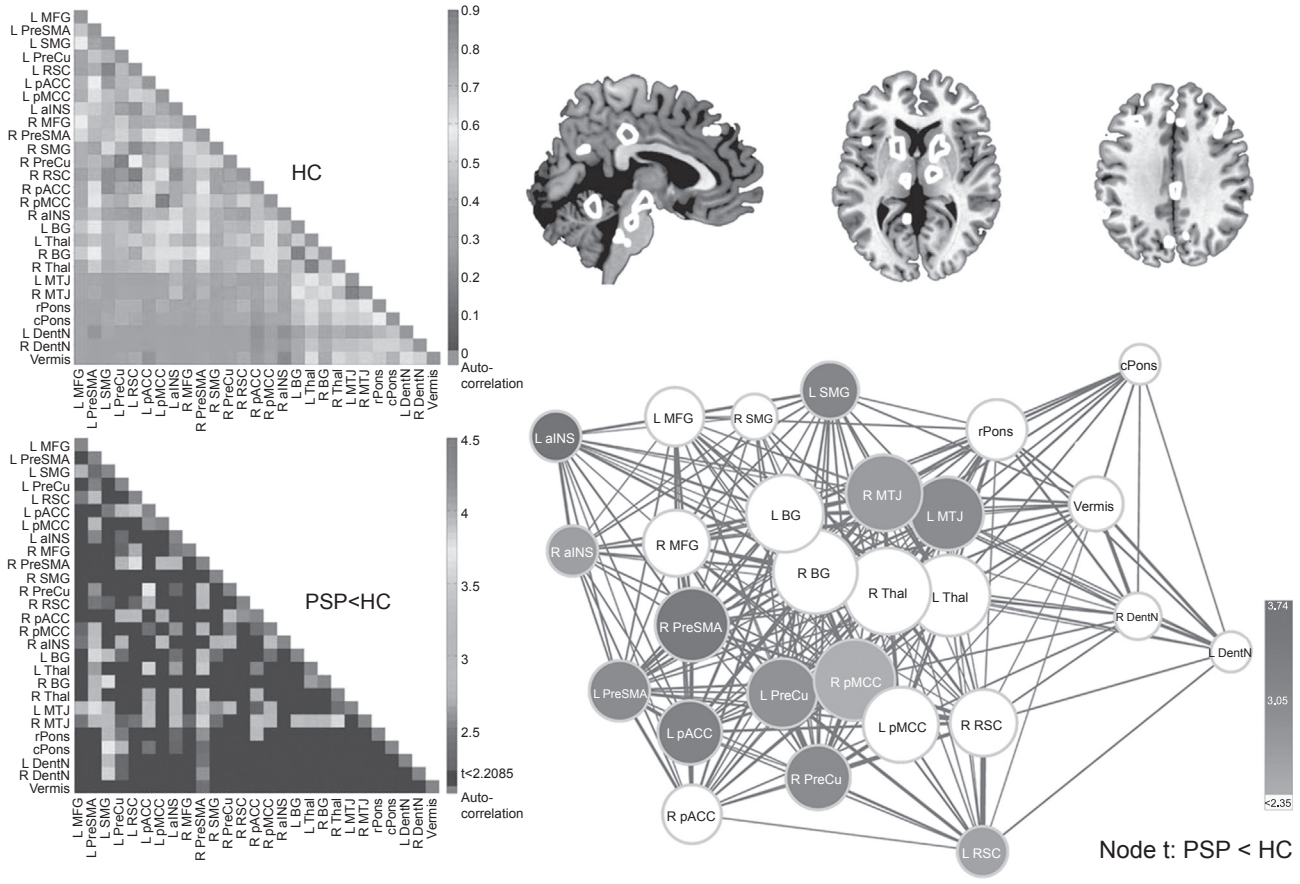

FIGURE 18.4 The rMT-anchored intrinsic connectivity network characterized in Gardner et al. (2013). The left panel shows the mean connectivity matrix representing the connections between the 27 nodes (*clusters shown at top right*) in the network in healthy controls and for connections significantly diminished in PSP-S. The bottom right shows the force-directed, spring-embedded network diagram for healthy control subjects with nodes showing significantly reduced total flow (mean connection strength) in black. *HC*, healthy controls; *aINS*, anterior insula; *BG*, basal ganglia; *DentN*, dentate nucleus; *L*, left; *MFG*, middle frontal gyrus; *MTJ*, mesothalamic junction; *pACC*, pregenual anterior cingulate cortex; *pMCC*, posterior midcingulate cortex; *PreCu*, precuneus; *PreSMA*, presupplementary motor area; *R*, right; *RSC*, retrosplenial cortex; *Thal*, thalamus.

sensory-somatomotor, and frontoparietal networks at stage 3, and worsening pathology in all nontemporal, nonoccipital ICNs at higher stages. This trajectory is extrapolate from the available data, based on a broad but incomplete subset of brain regions sampled. This observation of stages of increasingly widespread pathology, akin to the Braak staging of Alzheimer disease and PD, is consistent with a model of transsynaptic propagation of hyperphosphorylated tau fragments throughout the network. At subsequent stages the disease would radiate out further from the disease epicenter into neighboring ICNs, causing impairments in multiple domains and progressive structural atrophy (Josephs et al., 2013; Paviour et al., 2006; Sanders et al., 2014).

Network Architecture of Corticobasal Syndrome

Patients with CBS show atrophy involving epicenters of degeneration in the precentral and postcentral gyri (Fig. 18.3) (Seeley et al., 2009; Zhou et al., 2012). The intrinsic functional connectivity pattern in healthy individuals that best matches the CBS atrophy pattern spans the primary and secondary somatosensory cortex (Zhou et al., 2012, Fig. 18.6A). Nodes within this ICN were used to define the CBS vulnerable network (Fig. 18.6B) and determine the shortest path lengths for each node to the epicenters. Nodes with longer path lengths to the epicenter had less atrophy than those closer connected to the epicenter (Fig. 18.6C), which supports a "transneuronal spread" model of disease propagation. Critically, this correlation remained after controlling for the Euclidean distance between brain regions, indicating that network path length from the epicenter was the optimal model for predicting regional vulnerability.

The regions within the CBS-vulnerable network are circumscribed by the top box in Fig. 18.1 and largely cover five ICNs: sensory-somatomotor, dorsal attention, cingulo-opercular, subcortical, and frontoparietal task control. Overlap

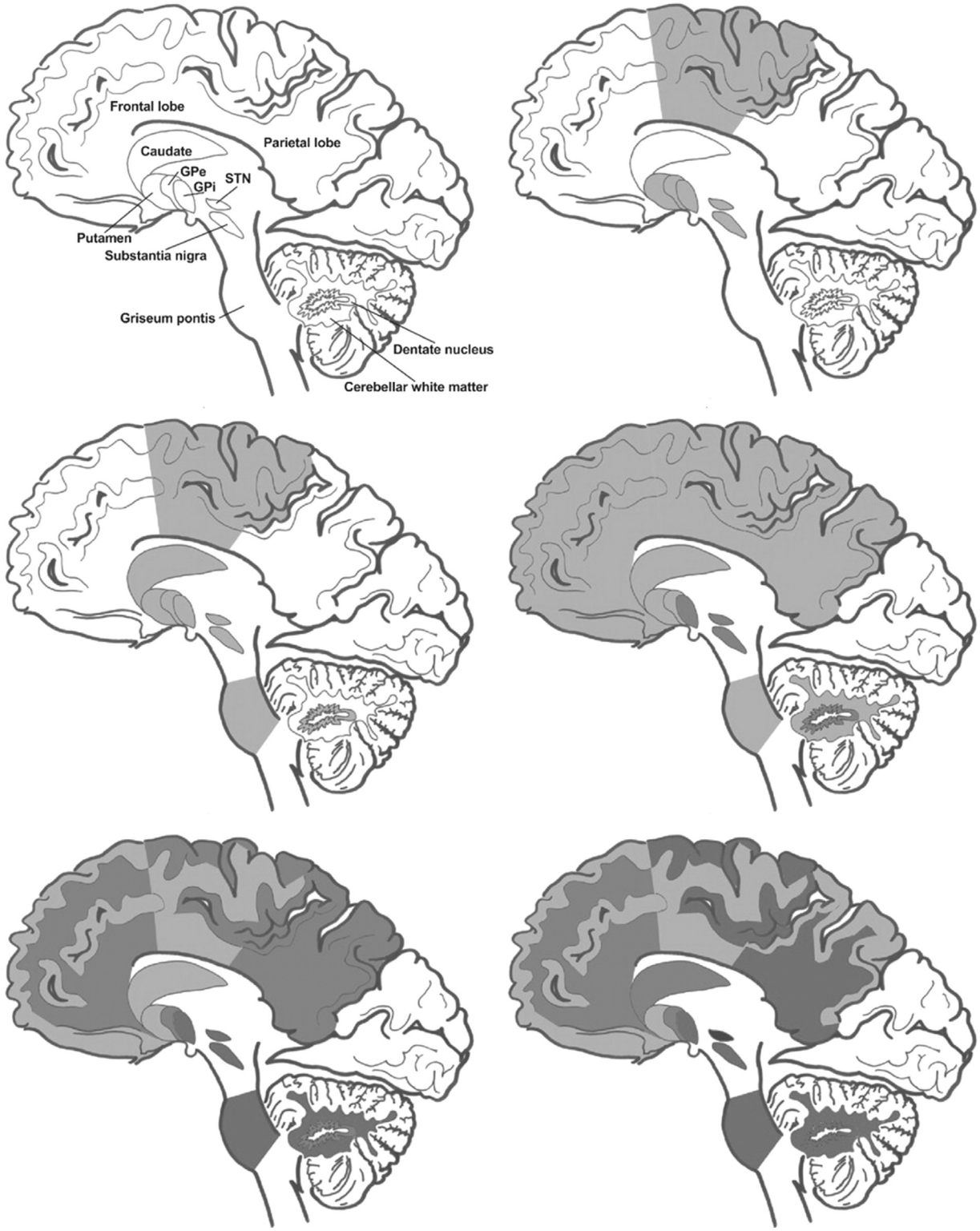

FIGURE 18.5 PSP stagewise regional distribution and progression of pathology. *From Williams, D. R., Holton, J. L., Strand, C., Pittman, A., de Silva, R., Lees, A. J., & Revesz, T. (2007). Pathological tau burden and distribution distinguishes progressive supranuclear palsy-parkinsonism from Richardson's syndrome.* Brain, 130*(6), 1566–1576. http://doi.org/10.1093/brain/awm104.*

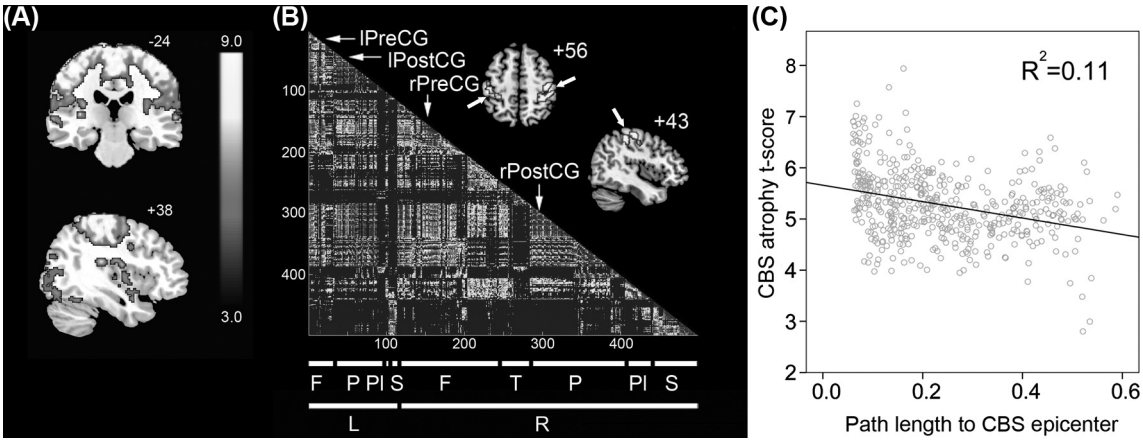

FIGURE 18.6 Intrinsic connectivity network correspondence with atrophy patterns in CBS. (A) The task-free functional MRI seed connectivity network (from $n = 16$ healthy subjects) whose spatial layout had the best goodness of fit to the gray matter atrophy pattern in CBS (from $n = 17$ patients) is a primary and secondary somatomotor network. (B) Functional connectivity matrix depicting the connectivity among all 499 regions canvassing the network shown in (A). The nodes defined as epicenters are located in the rolandic and perirolandic cortices indicated with arrows in the inset. (C) Correlation between path length from the CBS epicenter and CBS atrophy score. *F*, frontal; *T*, temporal; *P*, parietal; *PI*, paralimbic; *S*, subcortical; *L*, left hemisphere; *R*, right hemisphere; *PreCG*, precentral gyrus; *PostCG*, postcentral gyrus. *Modified from Zhou, J., Gennatas, E.D., Kramer, J.H., Miller, B.L., Seeley, W.W. (2012). Predicting regional neurodegeneration from the healthy brain functional connectome.* Neuron*, 73(6), 1216–1227. http://doi.org/10.1016/j.neuron.2012.03.004*.

between these regions and areas vulnerable in PSP-S and behavioral variant FTD (bvFTD) is most evident in the cingulo-opercular network. An important goal for future studies of CBS and related syndromes will be to elucidate the temporal sequence of fMRI connectivity disruption and structural atrophy during disease progression, in a manner comparable to the insights emerging for Alzheimer disease (Jack et al., 2013; Raj et al., 2015). A complementary aim will be to study how well characteristic profiles of functional connectivity alteration track along with subject-specific symptoms or, better yet, anticipate them.

CLINICOPATHOLOGICAL CORRELATION IN PROGRESSIVE SUPRANUCLEAR PALSY AND CORTICOBASAL DEGENERATION

Multiple Proteinopathies Can Cause Progressive Supranuclear Palsy Syndrome and Corticobasal Syndrome

The most important concept for understanding neurodegenerative disease diagnosis is that each syndrome reflects where the disease is present (ie, which network), not which disease is present (ie, which proteinopathy). A patient with typical PSP-S (also known as Richardson syndrome) most likely has PSP as the underlying pathology (Dickson, Rademakers, & Hutton, 2007), but exceptions occur. In contrast, the link between CBS and CBD is more tenuous (Armstrong et al., 2013; Boeve, Lang, & Litvan, 2003; Lee et al., 2011). In this section, we focus on the pathological differential diagnoses for PSP-S and CBS. Changing viewpoints, we next discuss the spectrum of clinical syndromes beyond PSP-S and CBS associated with a pathological diagnosis of PSP or CBD.

Pathological Causes of Progressive Supranuclear Palsy Syndrome

PSP-S can be caused by a short list of related tauopathies. By far the most common cause is PSP pathology, which makes PSP-S one of the strongest predictors of a single histopathological entity across the entire neurodegenerative disease spectrum. Rare causes of PSP-S include CBD, Pick disease, and a scattering of other protean disorders. In a patient with typical PSP-S owing to PSP pathology, the burden of tau pathology and neurodegeneration is most severe in the midbrain, subthalamic nucleus, globus pallidus, and dentate nucleus of the cerebellum. Globose tau-positive tangles and other neuronal cytoplasmic inclusions in these regions are variably accompanied by neuropil threads and glial inclusions, which may include tufted astrocytes, coiled bodies (curvilinear oligodendroglial cytoplasmic inclusions), and thorny astrocytes (Fig. 18.7C) (Dickson, Ahmed, Algom, Tsuboi, & Josephs, 2010). In the cortex, the tauopathy is milder and distributed across premotor and supplementary motor, primary motor, affective-motivational, and relevant cognition-associated regions.

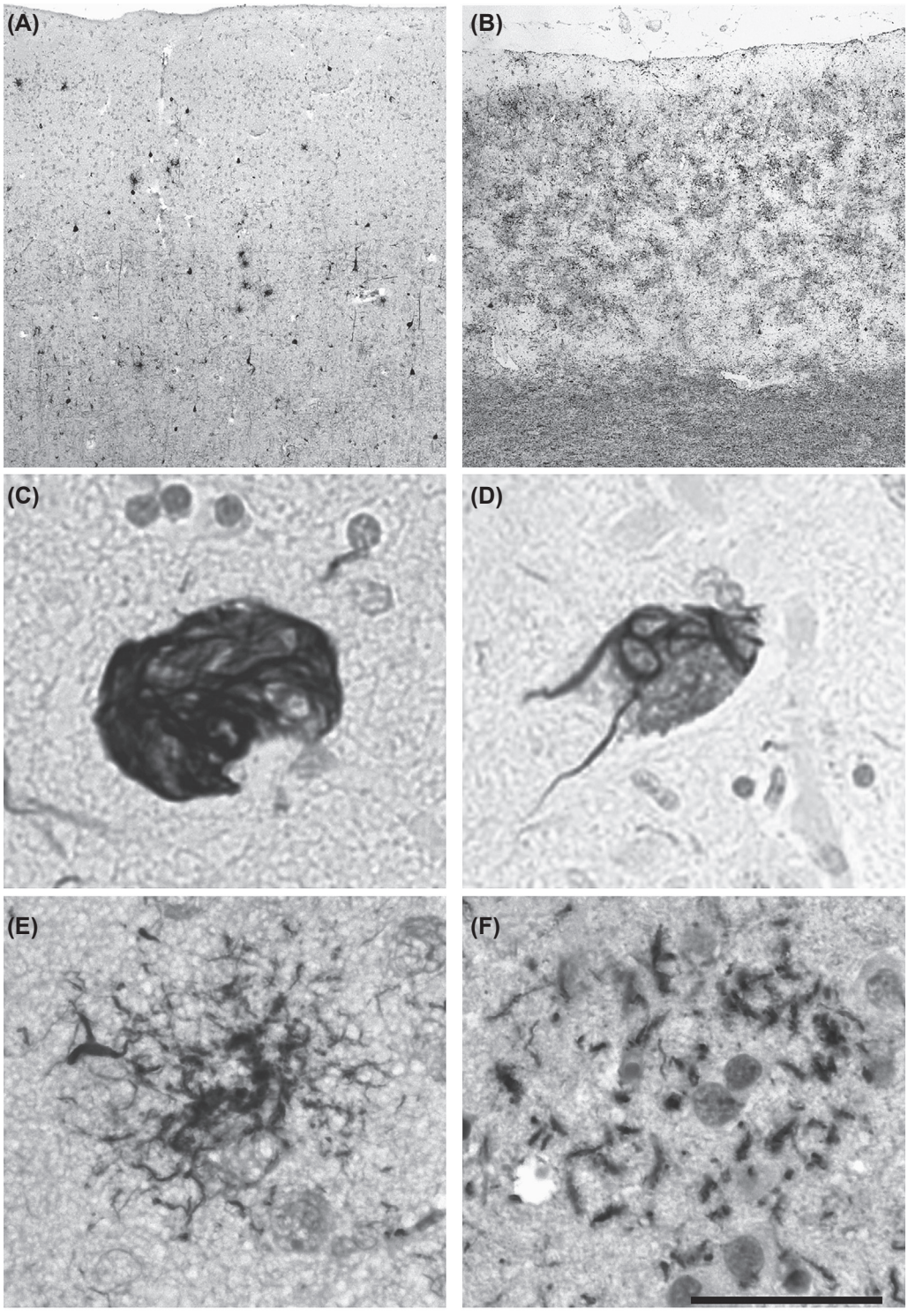

FIGURE 18.7 Histopathology in PSP and CBD. In PSP (A, C, and E), the cortical burden is mild but most prominent in deep layers and consists of neuronal cytoplasmic, tangle-like inclusions, tufted astrocytes (A), and coiled oligodendroglial inclusions, among others. The tau burden is most pronounced in subcortical, diencephalic, and brain stem nuclei, where globose tangles (C) are observed. CBD (B, D, and F), in contrast, features characteristic teeming white matter threads and coiled oligodendroglial tau inclusions (B). Neuronal inclusions may form as coiled tangles (D) or other neuronal cytoplasmic inclusions. Astrocytic plaques (F) are a signature feature and are composed of short, stubby, tau-filled astroglial processes. Sections were stained with antibodies to tau phosphorylated at Ser202 (CP-13, courtesy of Peter Davies, A, B, E, and F) or the Gallyas silver stain (C and D). Scale bar in F applies to all panels and represents 1 mm in A and B and 50 μM in C—F.

Pathological Causes of Corticobasal Syndrome

Although CBD is the most common histopathological cause of CBS, it represents barely a majority in modern series (Boeve et al., 1999; Lee et al., 2011; Litvan et al., 1997; Murray et al., 2007). Other important causes include Alzheimer disease, Pick disease, PSP, and FTLD with TDP-43 inclusions (type A), and, less commonly, inherited tauopathies, LBD, or even Creutzfeldt−Jakob disease. Most CBS cases resulting from FTLD-TDP pathology occur in the setting of a mutation in progranulin (*GRN*), although sporadic cases have been reported (Neumann et al., 2006; Tartaglia et al., 2010). This diversity of proteinopathies causing CBS suggests that the perirolandic network is vulnerable to multiple misfolded protein "seeds," although the pattern of spread from within the target CBS network into off-target networks may differ subtly across these pathological entities.

The essential features of a CBD pathological diagnosis are tau-immunoreactive lesions in neurons and glia in the cortex and striatum (Fig. 18.7). Both neuronal and glial lesions are prominent. Neuronal inclusions are diffuse and granular, filling the cytosol, and are most prominent in layer 5. Astrocytic plaques are the most characteristic glial lesion. The most essential diagnostic feature is the presence of copious tau-positive threads in white matter subjacent to affected cortices accompanied by teeming coiled oligodendroglial inclusions. The highest burden of CBD pathology is found in the perirolandic cortex, in contrast to PSP, where the concentration is highest in basal ganglia, diencephalon, and brain stem.

CBD and PSP tau aggregates are made up of the hyperphosphorylated four-repeat isoforms of tau. Tau, a microtubule-associated protein, normally functions to assemble and stabilize microtubules and is highly concentrated in axons (Grundke-Iqbal et al., 1986). Tau aggregates isolated from postmortem tissue samples in both diseases have been shown to undergo self-propagating prion-like spread between cells in culture and in living mice (Clavaguera et al., 2013; Sanders et al., 2014). These findings and increasing additional support from the field are consistent with the candidate mechanism of disease protein spread via intercellular transmission from a selectively vulnerable epicenter out through an intrinsic connectivity network (de Calignon et al., 2012; Frost & Diamond, 2010; Zhou et al., 2012).

Progressive Supranuclear Palsy and Corticobasal Degeneration Histopathology Can Cause Multiple Clinical Syndromes

General Principles of Syndromic Diversity

Syndromes other than PSP-S and CBS caused by an underlying pathology of PSP or CBD manifest when the disease originates outside the most commonly affected network. The likelihood of the pathology affecting another network can be determined by looking to the nearest neighbors of the core disease network. This is illustrated in Fig. 18.1, in which the dotted circles−edged box outlines the regions affected in bvFTD, the most common syndrome other than PSP-S and CBS caused by 4R tauopathy. Patients with bvFTD experience apathy, disinhibition, and loss of awareness of both self and others. They become detached and socially tactless, and lose empathy. The disease primarily affects the anterior insula, anterior cingulate, orbitofrontal cortex, striatum, thalamus, and amygdala, regions that are all part of the salience network vital for social and emotional processing (Seeley et al., 2007). The salience network has strong transnetwork connectivity with the cingulo-opercular network, a core affected network in PSP-S and CBS. It is likely that the vulnerability of cells in the salience network to four-repeat tau aggregation is related in some way to the vulnerability in the neighboring cingulo-opercular network. Graded vulnerability to 4R tau is likely to be driven by the concentration of vulnerable cell populations in these paralimbic areas with similar genetic expression profiles. Neurodegenerative diseases typically have a subclass of cells that show early vulnerability, such as von Economo neurons and fork cells in bvFTD (Kim et al., 2012), entorhinal cortex layer II pyramidal neurons in Alzheimer disease (Gómez-Isla et al., 1996), or upper and lower motor neurons in amyotrophic lateral sclerosis (Cleveland & Rothstein, 2001), but the precise neuronal identities most vulnerable in to PSP and CBD remain uncertain.

Other Syndromes Caused by Progressive Supranuclear Palsy or Corticobasal Degeneration

A study by Williams and colleagues in 2005 reported that of 103 cases of definite PSP under examination, 32% clustered into a subgroup that was typified by asymmetric motor onset, tremor, response to treatment with levodopa, and less dementia (Williams et al., 2005). This subgroup was classified as "PSP-parkinsonism" (PSP-P), in distinction from patients with classical Richardson syndrome. The PSP-rs has been shown not differentiate between these patients subgroups (Golbe & Ohman-Strickland, 2007). However, patients with PSP-P exhibit less widespread atrophy in gray and white matter, less involvement of infratentorial brain structures, and less tau deposition (Longoni et al., 2011; Williams, Holton, Strand,

Pittman, et al., 2007). Thus, neuroimaging biomarkers may have an important role in differentiating PSP-P and typical PSP-S (Richardson syndrome).

Pure akinesia with gait freezing (PAGF) is a syndrome closely related to PSP-S in which patients exhibit early gait disturbance that eventually leads to gait freezing, micrographia, and hypophonia (Williams, Holton, Strand, Revesz, & Lees, 2007). Patients with PAGF have focal atrophy and neuronal loss almost exclusively in subcortical and brain stem regions including the globus pallidus, substantia nigra, and subthalamic nucleus (Ahmed, Josephs, Gonzalez, DelleDonne, & Dickson, 2008).

The most comprehensive study of phenotypic diversity in PSP was an examination of 100 autopsy-confirmed patients by Respondek and colleagues (Respondek et al., 2014). One hundred subjects were classified by "predominance type," a summary of the predominant clinical features in that group during the first 2 years of the disease. Only 24% exhibited classical Richardson syndrome, as distinguished by falls and supranuclear gaze palsy. The remainder was distributed between PSP-P (19% with tremor and asymmetric onset), postural instability (18%), frontotemporal dysfunction (12% with frontal and cognitive dysfunction), corticobasal syndrome (7%), occulomotor dysfunction (7%), and a clinically heterogeneous set that was unclassifiable (13%).

The most frequent FTLD syndromes that can result from either PSP or CBD are nonfluent variant primary progressive aphasia (nfvPPA) and bvFTD. nfvPPA and apraxia of speech (AOS) are related disorders in which speech production is impaired. Patients with nfvPPA exhibit a nonfluent aphasia with effortful and agrammatic speech (Gorno-Tempini et al., 2011). Atrophy is marked in perisylvian regions including Broca's area in the frontal operculum, along with the precentral gyrus, supplemental motor area, and dorsal anterior insula (Seeley et al., 2009), implicating the cingulo-opercular network, ventral attention network, and anterior components of the sensory-somatomotor network, especially in the dominant hemisphere. AOS is characterized by slow speech rate, abnormal prosody, and distorted sound selections, all related to a deficiency in speech motor planning (Josephs, Duffy, et al., 2006). The underlying atrophy is most prominent in the superior lateral premotor cortex and supplementary motor area (Josephs et al., 2012). These areas belong to cingulo-opercular network and premotor portions of the network adjacent ICNs. Interestingly, longitudinal study of patients with AOS have shown that a substantial portion later develop a PSP-like syndrome involving parkinsonism, vertical gaze palsy, and balance problems (Josephs et al., 2014). Both nfvPPA and AOS are often caused by an underlying tauopathy, CBD more commonly than PSP (Josephs et al., 2005; Karageorgiou & Miller, 2014; Lee et al., 2011; Rohrer et al., 2010). bvFTD, the FTLD syndrome with the most diverse set of underlying proteinopathies, can be also be caused by CBD or PSP (Bigio, Brown, & White, 1999; Hassan, Parisi, & Josephs, 2012; Rankin et al., 2011).

GENETIC FACTORS IN PROGRESSIVE SUPRANUCLEAR PALSY AND CORTICOBASAL DEGENERATION

As at the molecular, cellular, and systems levels, striking similarities in genetic risk factors for PSP and CBD suggest overlapping pathogenic mechanisms.

Rare Monogenic Causes

Although most cases of PSP and CBD are sporadic, cases of familial aggregation have been reported. In one study, 12 of 172 patients with PSP fulfilled the criteria for autosomal dominant inheritance, in which at least three first- or second-degree relatives had the disease. One of these cases revealed a P301L *MAPT* mutation (Donker Kaat et al., 2009). An instance of familial CBS was discovered in a Canadian family of Chinese origin with a splice donor site mutation in *PGRN* (Masellis et al., 2006).

Risk Factors

The strongest genetic association for PSP is the H1 haplotype of the *MAPT* gene on chromosome 17 and is seen in over 90% of patients (Fogel, Clark, & Geschwind, 2014). This gene encodes the tau protein, and H1 results in alternative splicing of exon 10, which may cause a shift toward more 4R tau and less 3R tau. Possession of the H1 haplotype is also the most well-established genetic risk factor for CBD (Di Maria et al., 2000). In a study of 38 patients with CBD, inheritance of the H1/H1 haplotype was associated with the severity of motor dysfunction, which suggests a dose-dependent genotype−phenotype association (Litvan, Chism, Litvan, Cambon, & Hutton, 2010). Assessment of point mutations in *MAPT* in 109 pathologically confirmed CBD cases found an association between p.N410H that increased the ratio of 4 and 3R tau (Kouri et al., 2013). In vitro experiments on recombinant tau with the p.N410H mutation showed increased tau

filament formation and a slower rate of microtubule formation. An additional risk factor related to tau, the rare tau variant p.A152T, has been found to increase the risk for PSP, Alzheimer disease, and FTD (Coppola et al., 2012). The exact mechanisms of pathogenesis of this variant remain a topic of intense investigation.

Genome-Wide Association Studies

A landmark genome-wide association study (GWAS) by Höglinger and colleagues in 2011 assessed two samples, one with 1114 autopsy-confirmed PSP cases and 3287 population-based controls and a second with 1051 patients clinically diagnosed with PSP-S and 3560 controls, with no overlap in individuals (Höglinger et al., 2011). This work confirmed two independent variants of MAPT that increased risk for PSP, along with three additional genes: *STX6*, *EIF2AK3*, and *MOBP*, whose respective cellular pathways are intracellular tracking, endoplasmic reticulum−mediated clearance of misfolded proteins, and myelination. No functional links have yet been established between these genes and disease pathophysiology. An epigenetic association has been established between the level of methylation at the 17q21.31 region and the H1 haplotype, indicating that epigenetic mediators have a contribution to disease risk (Li et al., 2014).

A GWAS study was completed in 152 cases and 3311 controls of CBD in a discovery phase and 67 cases and 439 controls in a replication phase (Kouri et al., 2015). Associations were found at the 17q21 locus of *MAPT*, *Inc-KIF13B-1*, a long noncoding RNA, and *SOS1*, a potential tau phosphatase. Tests also revealed associations at known PSP SNP sites for *MOBP* and *MAPT H1c*. This study confirmed that CBD and PSP have shared genetic risk factors for both *MAPT* and *MOBP*. This study strengthened the known association between variants in *MAPT* and tau pathology evident in both diseases. Importantly, it also revealed a novel pathogenic linkage common to both diseases between *MOBP* and white matter oligodendrocyte pathology. Studies in the near future have an opportunity to understand how failure of MOBP's normal role in myelin sheath stabilization may contribute to a common disease mechanism, and what relationships may exist for transsynaptic spread of misfolded tau.

CONCLUSION

Substantial evidence suggests that PSP-S and CBS are caused by progressive loss of function within the cingulo-opercular, sensory-somatomotor, and subcortical intrinsic connectivity networks. The selective vulnerability of neurons, astrocytes, and oligodendrocytes in these networks is highest to 4R tauopathy. Conversely, 4R tauopathy tends to originate in these networks, with a decreasing gradient of likelihood farther out from the network epicenter. Earlier diagnosis and prediction of disease progression will depend on monitoring the network core for signs of abnormality, in which functional imaging may provide an advantage over structural imaging or clinical evaluation. Uncertainty about the underlying pathology should be clarified with further development and a combination of genetic screening, molecular imaging, and cerebrospinal fluid−based biomarkers. Finally, advancement in understanding biological disease mechanisms will depend on exhaustive next-generation efforts to map the systems-level cellular composition and genetic expression profiles of vulnerable brain networks.

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