REVIEW

Radiological Biomarkers for Diagnosis in PSP: Where Are We and Where Do We Need to Be?

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ABSTRACT: PSP is a pathologically defined neurodegenerative tauopathy with a variety of clinical presentations including typical Richardson's syndrome and other variant PSP syndromes. A large body of neuroimaging research has been conducted over the past two decades, with many studies proposing different structural MRI and molecular PET/SPECT biomarkers for PSP. These include measures of brainstem, cortical and striatal atrophy, diffusion weighted and diffusion tensor imaging abnormalities, [18F] fluorodeoxyglucose PET hypometabolism, reductions in striatal dopamine imaging and, most recently, PET imaging with ligands that bind to tau. Our aim was to critically evaluate the degree to which structural and molecular neuroimaging metrics fulfill criteria for diagnostic biomarkers of PSP. We queried the PubMed, Cochrane, Medline, and PSYCInfo databases for original research articles published in English over the past 20 years using postmortem diagnosis or the NINDS-SPSP criteria as the diagnostic standard from 1996 to 2016. We define a five-level theoretical construct for the utility of neuroimaging biomarkers in PSP, with level 1 representing group-level findings, level 2 representing biomarkers with demonstrable individual-level diagnostic utility, level 3

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representing biomarkers for early disease, level 4 representing surrogate biomarkers of PSP pathology, and level 5 representing definitive PSP biomarkers of PSP pathology. We discuss the degree to which each of the currently available biomarkers fit into this theoretical construct, consider the role of biomarkers in the diagnosis of Richardson's syndrome, variant PSP syndromes and autopsy confirmed PSP, and emphasize current shortfalls in the field.

Key Words: progressive supranuclear palsy; diagnosis; magnetic resonance imaging; positron emission tomography; single-photon emission computed tomography

Progressive supranuclear palsy (PSP) is a pathologic diagnosis with neurodegeneration characterized by abnormal tau pathology in the form of globose neurofibrillary tangles, tufted astrocytes, coiled bodies, and threads,[1] with a predominance of 4-repeat (4R) tau isoforms.[2] Tau pathology is typically observed in the brain stem, basal ganglia, diencephalon, and temporal, motor, and premotor cortices,[1,2] although distribution can vary.[3,4] The most commonly recognized clinical presentation of PSP is Richardson's syndrome (PSP-RS), in which patients have early and notable gait and postural instability, frequent falls, and abnormal vertical eye movements (supranuclear gaze palsy).[5,6] However, a number of other clinical presentations of PSP have been increasingly recognized, including but not limited to PSP with predominant parkinsonism (PSP-P),[6] PSP with progressive gait freezing (PSP-PGF),[7] PSP with predominant frontal presentation (PSP-F),[8] PSP with a predominant speech/language disorder (PSP-SL),[9] and PSP with predominant corticobasal syndrome (PSP-CBS).[10] We have recently developed the Movement Disorder Society-endorsed PSP clinical diagnostic criteria that recognize this heterogeneity and provide criteria for the different clinical variants of PSP.[11] A major challenge faced during the revision of the diagnostic criteria was to determine whether there was enough evidence to support the inclusion of neuroimaging biomarkers in the diagnosis of PSP-RS, the other variant syndromes of PSP (vPSP), or in the diagnosis of pathological PSP, and what role they should play in the diagnostic criteria.

Table 1 provides a theoretical construct to judge the utility of diagnostic neuroimaging biomarkers in PSP. The first step is to demonstrate abnormalities in the group of interest compared with matched healthy controls and other clinically overlapping disease groups (level 1). In the context of PSP, this typically means demonstrating abnormalities in PSP-RS compared with other parkinsonian disorders, such as Parkinson's disease (PD), multiple system atrophy with predominant parkinsonism (MSA-P), and CBS. However, if one wishes to ultimately develop a diagnostic biomarker for PSP pathology, it is also important not to ignore vPSP, for which neuroimaging signatures may differ from PSP-RS. A biomarker differentiating PSP-F, PSP-SL, and PSP-CBS from other frontotemporal lobar degeneration spectrum disorders may also be valuable. For these group-level findings to translate into useful biomarkers, the next step is to demonstrate useful sensitivity and specificity (>80%) for the clinical diagnosis at the individual patient level (level 2). Biomarkers that perform well at this level could be valuable to support the clinical diagnosis. However, because these analyses are based on comparison with clinical diagnosis rather than the gold standard of neuropathology, there is still no evidence at this point that the biomarker adds anything to clinical diagnosis, other than to increase confidence. A biomarker could surpass clinical diagnosis if one can demonstrate utility for early clinical diagnosis, when patients have mild or nonspecific symptoms and signs before they meet clinical criteria for the disease (level 3), or if one can demonstrate that a biomarker has a strong relationship with the presence of PSP pathology regardless of clinical phenotype (level 4). The latter will ideally require the demonstration that a biomarker is highly associated with PSP pathology, not only in patients diagnosed with PSP-RS but also in vPSP, thus representing utility for the entire clinical spectrum of PSP. However, neuroimaging biomarkers that satisfy level 4 may still be considered only a surrogate marker of pathology, meaning that they correlate well with pathology but do not directly measure pathology. Thus, the holy grail in neuroimaging is to identify a biomarker that directly measures underlying pathology and hence could be considered a definitive pathological biomarker (level 5). We are getting closer to this goal with the development of PET ligands that can bind to abnormal tau in the brain, and current knowledge of these biomarkers will be discussed. At levels 4 and 5, the ideal biomarker would be one that is specific to PSP pathology, although biomarkers that could identify a 4R tauopathy could also be diagnostically useful. Another issue to consider when assessing the value of neuroimaging biomarkers is how well the proposed measures would translate into clinical practice; ideally they should be relatively inexpensive, convenient, safe, widely available, and comparable across different centers.

This review will utilize the theoretical construct outlined in Table 1 to evaluate the degree to which

TABLE 1. Levels of evidence for neuroimaging biomarkers in PSP

Level	Utility	PSP-RS	vPSP
1	Research tool	Group-level evidence that a biomarker is abnormal in PSP-RS	Group-level evidence that a biomarker is abnormal in vPSP
2	Supportive of clinical diagnosis	Individual-level data showing diagnostic value (high sensitivity + specificity) for PSP-RS	Individual-level data showing diagnostic value (high sensitivity + specificity) for vPSP
3	Supportive of early clinical diagnosis	Evidence for abnormalities before patients meet clinical criteria for PSP-RS	Evidence for abnormalities before patients meet clinical criteria for vPSP
4	Supportive of pathological diagnosis	Individual-level data showing diagnostic value for PSP pathology, regardless of syndrome	
5	Definitive	Biomarker of actual pathology	

different proposed structural and functional neuroimaging metrics fulfill criteria as diagnostic biomarkers in PSP. As part of our efforts to develop the new diagnostic criteria, a detailed literature search and content evaluation was performed that formed the basis of this review (Supplemental Data).

Structural MRI

Brain Stem Measures

Striking midbrain atrophy is typically observed in PSP-RS, and a number of midbrain metrics have been proposed as potential biomarkers. These metrics include visual assessment of midbrain atrophy, midbrain profile or the presence of specific morphological markers such as the "hummingbird" sign (atrophy of dorsal midbrain resembles hummingbird's head and bill in midsagittal plane[12]), "Mickey Mouse" sign (rounded rather than rectangular midbrain peduncles in axial planes),[13] and "morning glory" sign (concavity of the lateral margin of the midbrain tegmentum in axial planes[14]); see Figure 1. Quantitative measures of midbrain anterior-posterior diameter and midsagittal area or volume have also been assessed. Studies are in general agreement that midbrain measurements are smaller in PSP-RS compared with MSA and PD,[14-31] although overlap can occur at the individual level, particularly between PSP-RS and MSA.[15,16,28,30] Diagnostic sensitivity and specificity values (Table 2) are typically high (>90%) for differentiating PSP-RS from controls and from MSA and PD using midbrain area,[15-17,32] although midbrain diameter[15,18-20,22,23,32] and volume[15,24] and visual assessments[13,14,20,21,25,33,34] have been more variable, not always meeting the 80% cut point required for a level 2 biomarker. Visual assessments of the midbrain can be particularly problematic because they are not quantitative, lack objectivity, and can be highly dependent on image acquisition and patient positioning.[35,36]

A ratio of midbrain to pons area (Fig. 1) in the midsagittal plane has been proposed as a biomarker to differentiate PSP-RS from MSA-P, given that MSA-P is associated with atrophy of the pons and sparing of the midbrain, the opposite pattern to PSP-RS.[15] Some studies have found high sensitivity and specificity for the midbrain-pons area ratio in differentiating PSP-RS from MSA-P and from PD,[15-17,19,32,37-40] although sensitivity has been lower in other studies[22,23,41] (Table 2). The superior cerebellar peduncles (SCPs) are also atrophic in PSP,[42] which contrasts with a relative sparing of the middle cerebellar peduncles (MCPs). This has led to the development of the MR Parkinsonism Index (MRPI), which takes into account both the midbrain-pons area ratio and the ratio of the MCP to SCP width ([P/M] × [MCP/SCP])[38]; see Figure 1. The MRPI is typically increased in PSP-RS compared with controls, MSA-P, and PD, and sensitivity and specificity values for differentiating PSP-RS from MSA-P, PD, and vascular parkinsonism have been excellent[17,22,37-39,41,43,44] (typically >80% and up to 100% sensitive in a few studies that represent different continents[37-40,43,44]); see Table 2. A number of studies have found that the MRPI was superior or equivalent to the midbrain-pons ratio in differentiating PSP-RS from MSA-P and PD[17,37,38,40,41] (Table 2). Fewer data are available to assess how well midbrain measures could differentiate PSP-RS from CBS.[13,45] Therefore, there is plenty of evidence to support brain stem measurements as level 2 diagnostic biomarkers in PSP-RS (Table 3). However, proposing one specific measure for the purposes of diagnostic criteria is challenging because centers differ in how they perform these measurements, and specific cut points vary and will likely be cohort- and acquisition-specific. The MRPI appears to be less affected by aging compared with the midbrain-pons ratio[46] but requires detailed measurement of a number of structures that may be difficult to standardize. Indeed, 1 multicenter study found that the MRPI did not perform as well as the midbrain-to-pons ratio in differentiating PSP-RS from PD and MSA-P.[32] However, another multicenter study showed high sensitivity/specificity for the MRPI in differentiating PSP-RS and PD and showed that an automated MRPI measurement that does not rely on rater reliability performs as well as a manual MRPI measurement.[43] Automated methods for measuring midbrain volume are also now available[47] and may improve standardization.

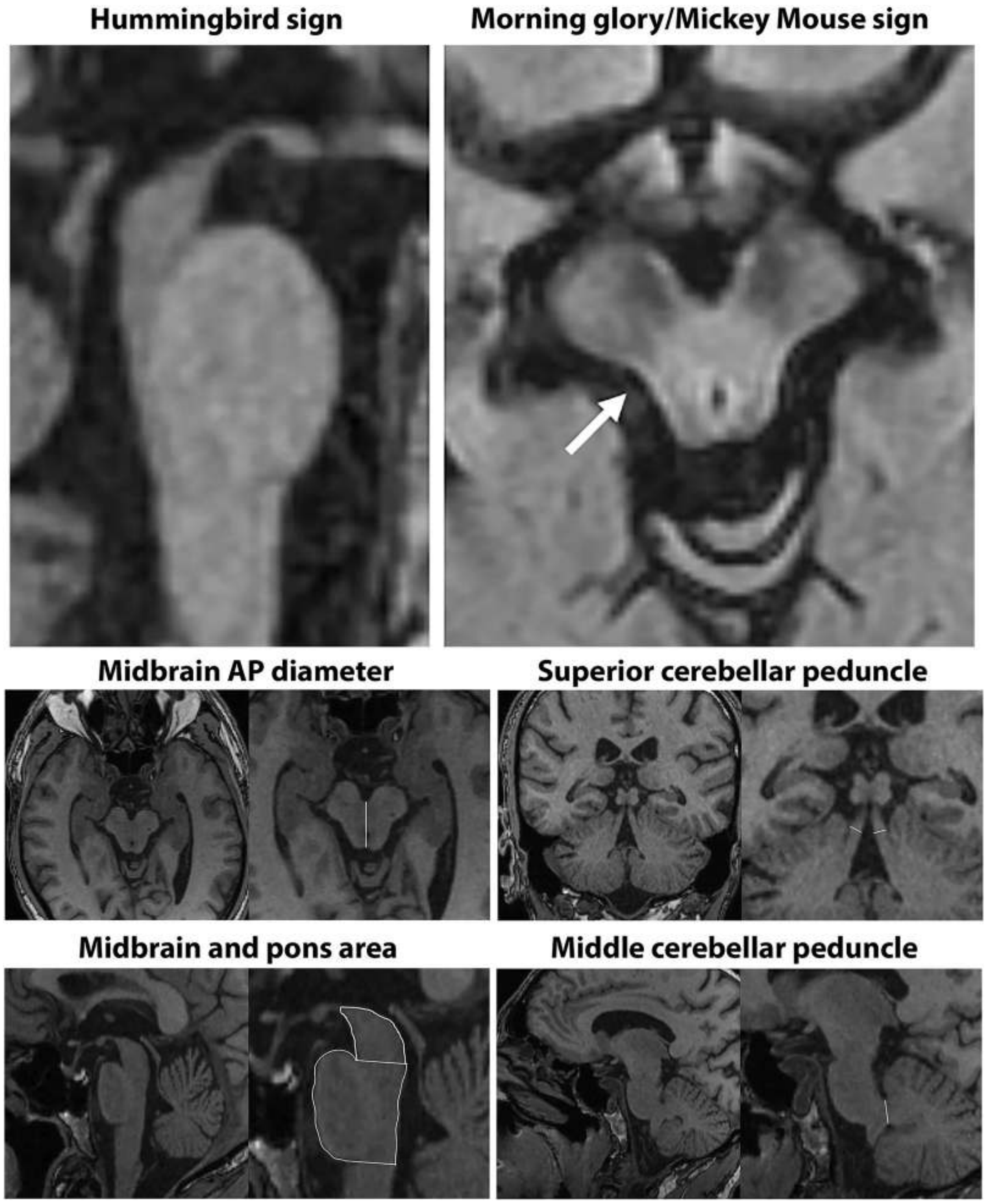

FIG. 1. Structural MRI demonstrating the morphological characteristics of PSP-RS and brain stem measurements. Top left sagittal slice shows the hummingbird sign with atrophy of the dorsal midbrain and relative preservation of the pons. Top right axial slice through the midbrain shows rounded midbrain peduncles (Mickey Mouse sign) and concavity of the lateral margin of the midbrain tegmentum (morning glory sign [arrow]). Bottom images show example measurements of the midbrain anteroposterior (AP) diameter, midbrain, and pons area, superior cerebellar peduncle width, and middle cerebellar peduncle width (modified from reference [32]).

There is evidence that these biomarkers could reach level 3 and show diagnostic value in early PSP-RS (Table 3). Abnormal MRPI and midbrain-pons ratios have been shown to predate and predict the development of PSP-RS in patients with clinically unclassifiable parkinsonism at baseline in a retrospective[23] and prospective study,[48] with abnormalities detected 15 months before patients fulfill criteria for PSP-RS in the retrospective study.[23]

Given that the clinical diagnosis of PSP-RS has high sensitivity and specificity for pathological PSP,[13,49,50] the midbrain-based measures discussed above also tend to perform well in autopsy-confirmed studies.[19,29] However, it is less clear whether these measures add anything to the clinical diagnosis of PSP-RS in predicting pathology and hence could be level 4 biomarkers.[13] Group-level studies have failed to find midbrain atrophy in patients with PSP pathology who presented with clinical syndromes other than PSP-RS,[51] including patients presenting with CBS.[52] Conversely, reduced midbrain areas were identified in PSP-RS that had underlying corticobasal degeneration pathology.[51] It therefore appears that in many instances midbrain atrophy is related to the PSP-RS clinical

TABLE 2. Studies that report sensitivity and specificity of brain stem measurements for the diagnosis of PSP-RS compared with other parkinsonian disorders

First author	Year	Comparison	Measure	Sensitivity	Specificity
Schrag[20]	2000	35 PSP-RS vs 54 MSA	MB visual (MB atrophy)	77	37
Adachi[14]	2004	5 PSP-RS vs 23 PD 14 MSA	MB visual (morning glory sign)	80	97
Righini[25]	2004	25 PSP-RS vs 27 PD	MB visual (superior profile)	68	88.8
Righini[25]	2004	25 PSP-RS vs 27 PD	MB visual (MB atrophy)	68	77.7
Price[33]	2004	12 PSP-RS vs (12 PD, 12CN)	MB visual (MB atrophy)	83	79
Massey[13a]	2012	22 PSP vs 13 MSA	MB visual (MB atrophy)	86.4	66.7
Massey[13a]	2012	22 PSP vs 13 MSA	MB visual (hummingbird)	68.4	100
Oba[16]	2005	21 PSP-RS vs (23 PD, 25 MSA-P, 31 HC)	MB area	100	91.3
Cosottini[15]	2007	15 PSP-RS vs (7 MSA-P, 14 CN)	MB area	100	90.5
Zanigni[17]	2016	23 PSP-RS vs 42 PD	MB area	96	98
Moller[32]	2017	106 PSP-RS vs 204 PD	MB area	84.0	83.8
Moller[32]	2017	106 PSP-RS vs 60 MSA-P	MB area	78.3	81.7
Asato[18]	2000	8 PSP-RS vs 9 MSA-P	MB diameter	100	100
Asato[18]	2000	8 PSP-RS vs 21 MSA-C	MB diameter	100	91
Schrag[20]	2000	36 PSP-RS vs 54 MSA	MB diameter	23	96
Cosottini[15]	2007	17 PSP-RS vs (7 MSA-P, 4 CN)	MB diameter	60	95.2
Massey[19a]	2013	12 PSP-RS vs 7 MSA	MB diameter	83	100
Kim[22]	2015	29 PSP-RS vs 82 PD	MB diameter	50	85.3
Owens[23]	2016	25 PSP-RS vs (25 MSA, 25 PD)	MB diameter	44	100
Paviour[24]	2006	18 PSP-RS vs (9 MSA-P, 9 PD, 18 HC)	MB volume	72.2	91.9
Paviour[24]	2006	18 PSP-RS vs 9 MSA-P	MB volume	83	33
Cosottini[15]	2007	18 PSP-RS vs (7 MSA-P, 14 CN)	MB volume	86.7	76.2
Oba[16]	2005	22 PSP-RS vs (23 PD, 25 MSA-P, 31 HC)	MB-pons ratio	100	100
Cosottini[15]	2007	16 PSP-RS vs (7 MSA-P, 14 CN)	MB-pons ratio	86.7	100
Quattrone[38]	2008	33 PSP-RS vs 108 PD	MB-pons ratio	90.9	93.5
Quattrone[38]	2008	33 PSP-RS vs 19 MSA-P	MB-pons ratio	97	94.7
Hussl[41]	2010	22 PSP-RS vs 75 PD	MB-pons ratio	63.6	94.7
Hussl[41]	2010	22 PSP-RS vs 26 MSA-P	MB-pons ratio	63.6	84.6
Morelli[37]	2011	42 PSP-RS vs 170 PD	MB-pons ratio	92.9	85.3
Longoni[39]	2011	10 PSP-RS vs 25 PD	MB-pons ratio	90	96
Massey[19a]	2013	13 PSP-RS vs 7 MSA	MB-pons ratio	67	100
Kim[22]	2015	30 PSP-RS vs 82 PD	MB-pons ratio	46.2	89.7
Zanigni[17]	2016	24 PSP-RS vs 42 PD	MB-pons ratio	96	90
Owens[23]	2016	25 PSP-RS vs (25 MSA, 25 PD)	MB-pons ratio	68	100
Borroni[45]	2010	18 PSP-RS vs (16 CBS, 28 FTD)	MB-pons ratio + CSF bio	94.2	84
Sankhla[40]	2016	20 PSP-RS vs 13 PD	MB-pons ratio	100	92.86
Moller[32]	2017	106 PSP-RS vs 204 PD	MB-pons ratio	77.4	80.4
Moller[32]	2017	106 PSP-RS vs 60 MSA-P	MB-pons ratio	77.8	89.4
Quattrone[38]	2008	33 PSP-RS vs 108 PD	MRPI	100	100
Quattrone[38]	2008	33 PSP-RS vs 19 MSA-P	MRPI	100	100
Hussl[41]	2010	23 PSP-RS vs 75 PD	MRPI	81.8	76
Hussl[41]	2010	23 PSP-RS vs 26 MSA-P	MRPI	81.8	92.3
Morelli[37]	2011	42 PSP-RS vs 170 PD	MRPI	100	99.4
Longoni[39]	2011	10 PSP-RS vs 25 PD	MRPI	100	92
Kim[22]	2015	31 PSP-RS vs 82 PD	MRPI	92.3	39.7
Zanigni[17]	2016	25 PSP-RS vs 42 PD	MRPI	87	93
Nigro[43]	2016	88 PSP-RS vs 234 PD	MRPI	100	100
Nigro[43]	2016	88 PSP-RS vs 234 PD	MRPI (automated)	97.3	97.4
Sankhla[40]	2016	20 PSP-RS vs 13 PD	MRPI	100	100
Mostile[44]	2016	12 PSP-RS vs 17 vascular parkinsonism	MRPI	100	100
Moller[32]	2017	106 PSP-RS vs 204 PD	MRPI	68.9	67.7
Moller[32]	2017	106 PSP-RS vs 60 MSA-P	MRPI	79.0	64.1

PD, Parkinson's disease; MSA-P, parkinsonian variant of multiple system atrophy; MSA-C, cerebellar variant of multiple system atrophy; CBS, corticobasal syndrome; FTD, frontotemporal dementia; CN, cognitively normal controls; MB, midbrain; MRPI, MR Parkinsonism Index; CSF bio, cerebrospinal fluid biomarkers.
[a]Studies with autopsy-confirmed PSP.

presentation, rather than to the presence of PSP pathology, limiting its value as a level 4 diagnostic biomarker. In fact, midbrain area measures had a 93% sensitivity and 89% specificity in differentiating PSP-RS from other syndromes across a range of pathologies in the same study,[51] once again supporting midbrain measurements as level 2 biomarkers of PSP-RS. Similarly, another autopsy study found that midbrain atrophy was present in only 86.4% of pathologically confirmed PSP, and the hummingbird sign

TABLE 3. Currently available neuroimaging biomarkers that fulfill each level of evidence in PSP

Level	Utility	PSP-RS	vPSP
1	Research tool	• Basal ganglia and thalamic atrophy • DTI abnormalities in the dentatorubrothalamic and frontal lobe tracts • THK-5351 uptake in midbrain and globus pallidus[a] • MRS metabolites • Rates of whole-brain and midbrain atrophy • Resting -fMRI[a] • SPECT frontal hypoperfusion	• Midbrain atrophy (PSP-SL, PSP-F, PSP-P) • Frontal atrophy (PSP-F, PSP-SL, PSP-CBS, PSP-PGF, PSP-P) • Basal ganglia atrophy (PSP-SL, PSP-CBS, PSP-PGF, PSP-P) • DTI abnormalities in frontal lobe tracts (PSP-P)a • Reduced striatal DAT (PSP-PGF, PSP-P)
2	Supportive of clinical diagnosis	• Midbrain area • Midbrain-pons area ratio • MRPI • Frontal atrophy in addition to midbrain atrophy[a] • DWI striatum[a] • DWI/DTI superior cerebellar peduncle[a] • FDG-PET frontal and midbrain hypometabolism[a] • [^{18}F]AV-1451 uptake in midbrain, thalamus, basal ganglia, dentate nucleus of the cerebellum[a] • Reduced striatal DAT/D2 receptor (sensitive only) • Reduced brain stem DAT[a]	
3	Supportive of early clinical diagnosis	• Midbrain-pons area ratio/MRPI[a] • FDG-PET frontal hypometabolism[a]	• MRPI (PSP-P)[a]
4	Supportive of pathological diagnosis	None	
5	Definitive	None	

DTI, diffusion tensor imaging; DWI, diffusion-weighted imaging; MRS, magnetic resonance spectroscopy; fMRI, functional magnetic resonance imaging; SPECT, single-photon emission computed tomography; FDG-PET, [^{18}F] fluorodeoxyglucose positron emission tomography; MRPI, MR Parkinsonism Index; DAT, dopamine transporter.
[a]Level of evidence is supported by ≤3 published studies, suggesting lower level of reliability.

was only present in 68.4%, even after a disease duration of 4.8 years.[13] However, midbrain atrophy has been observed in speech and language disorders that are confirmed or suspected of having PSP pathology,[53-56] as well as in PSP-F[8] and PSP-P.[39,57-59] Midbrain atrophy in vPSP is typically less severe than in PSP-RS,[39,56-58] although there is some suggestion that abnormalities on the MRPI could be an early feature in PSP-P[59] and have some value as a level 3 biomarker.

Cortical Measures

A number of group-level studies have demonstrated cortical atrophy in PSP-RS, typically involving the frontal lobes.[33,60-74] The focus of atrophy appears to be the premotor cortex, but atrophy also spreads into the prefrontal cortex. Studies have demonstrated that whole-brain and frontal atrophy are greater in PSP-RS than in PD[24,64,67,72,75] and MSA-P,[72] although visual assessment of frontal atrophy had poor sensitivity (17% and 57%) and moderate specificity (75% and 83%) in differentiating PSP-RS from MSA[13,20] in 2 studies, reflecting the fact that discernible frontal atrophy is only present in approximately 60% of PSP-RS patients.[13] Frontal atrophy may be more useful if considered in addition to brain stem regions. One study found that adding frontal, third ventricle, and whole-brain volumes to midbrain and SCP volumes improved the differentiation of PSP-RS from PD and MSA (sensitivity, 88.9%; specificity, 97.3%).[24] Another showed that combining frontal, ventricular, and whole-brain volumes could differentiate PSP-RS from PD and controls with 95.2% sensitivity and 90.9% specificity.[64] One caveat to consider, however, is that frontal atrophy is unlikely to differentiate PSP-RS from CBS, given that CBS shows striking frontal atrophy.[60,62,68,76] Quantitative methods for assessing frontal volume or thickness also vary widely across studies and may influence diagnostic utility.

Frontal atrophy also occurs in vPSP, particularly in PSP-F,[8] PSP-SL,[9,54,55] and PSP-CBS[52,77] and can be greater than in PSP-RS,[62] likely reflecting a shift in PSP pathological burden from brain stem to cortex.[78] The degree of frontal atrophy is similar in both PSP-PGF[79] and PSP-P[57] compared with PSP-RS. Although no diagnostic data are available on the value of frontal atrophy in vPSP, the presence of frontal atrophy would be consistent with these diagnoses. Data are needed to determine whether cortical measures could help to differentiate vPSP from other frontotemporal lobar degeneration disorders that are primarily characterized by frontal atrophy.

Other Subcortical Measures

Atrophy of subcortical structures, including the caudate nucleus, putamen, globus pallidus, subthalamus, and thalamus, has also been observed in group-level studies of PSP-RS either using visual assessment or volumetric measurements.[13,28,62,63,74,80-82] There is evidence that volumes of putamen, thalamus, and globus pallidus are smaller in PSP-RS than in PD,[82] with thalamus volumes also being smaller than in MSA-P.[28] However, studies have found that visual assessments of putamen and globus pallidus atrophy are not diagnostically useful in differentiating PSP-RS from MSA or PD.[13,20] The caudate nucleus, putamen, and thalamus have also been reported to be atrophic in CBS[13,62,83] and are unlikely to be diagnostically useful in differentiating PSP-RS and CBS. Basal ganglia structures have been reported to be atrophic in patients with PSP-P,[57] PSP-CBS,[52,77] and PSP-SL,[9] with thalamic atrophy reported in PSP-PGF.[79] However, the diagnostic value of these findings is unclear and limited to level 1 (Table 3). Abnormalities suggesting the presence of iron deposition have been observed in the putamen, globus pallidus, and thalamus in PSP-RS,[84-87] with some evidence for differences from PD and MSA,[84,85,87] although diagnostic performance was suboptimal.[85,86] Results regarding signal increase or decrease of these structures on T2-weighted MRI in PSP-RS have been variable, with signal changes observed in fewer than 50% of patients.[13,20,88-90] Signal alterations in the SCP have also been observed in PSP-RS, but not in MSA-P or PD.[91,92]

Pattern Approaches to Diagnosis

A number of studies have proposed that the assessment of multiple regions of the brain will optimize sensitivity and specificity for PSP-RS. These studies typically develop optimal prediction models[93] or use automated machine-learning techniques to identify diagnostic patterns.[94-100] A number of these studies have found that assessment of multiple regions including the midbrain, basal ganglia,[95,97,98,100] cerebellum,[98,100] or thalamus[99] provided excellent sensitivity and specificity to differentiate PSP-RS from PD and MSA-P. One study found that a prediction model using midbrain, putamen, and cerebellar gray-matter volumes could differentiate PSP-RS from MSA and PD with 90% sensitivity and 100% specificity in an early stage of the disease when not all patients had yet fulfilled clinical diagnostic criteria for these diseases.[100] It has also been suggested that volumetric white-matter measurements may show greater diagnostic utility than gray-matter measures.[94,96] There is also some evidence that a pattern-based approach using brain stem and cortical gray- and white-matter measures could be used in the differential diagnosis of autopsy-confirmed PSP and CBD.[93] Generally, assessing the pattern of atrophy, rather than focusing on specific regions, appears to be a sensible and sensitive and specific approach to differential diagnosis, although there is currently a lack of agreement across studies on which specific regions should be used, and further validation of these results in independent cohorts is necessary. In addition, no data are yet available on how well these approaches perform in vPSP. Further work is needed before these approaches can be incorporated into clinical criteria.

Diffusion Imaging

Measurements of microstructural damage using diffusion-weighted imaging (DWI) show some promise as biomarkers of PSP-RS. Apparent diffusion coefficient (ADC) measurements from DWI have been assessed in gray- and white-matter structures in PSP-RS, showing elevated ADC values in putamen, caudate, globus pallidus, midbrain, SCP, and prefrontal and precentral white matter.[101-107] PSP-RS patients typically show higher ADC values in the putamen, caudate nucleus, globus pallidus, SCP, and midbrain compared with PD,[102,106-108] with 1 study obtaining high sensitivity (90%) and specificity (100%) to differentiate PSP-RS from PD using values from the putamen[107] and another obtaining 100% sensitivity and specificity using the SCP.[103] Compared with MSA-P, PSP-RS has higher ADC values in the caudate nucleus[106] and SCP[103,106] but lower values in the MCP,[105,109] cerebellum,[110] and putamen.[101] Sensitivity and specificity values for differentiating PSP-RS from MSA-P are high using DWI of the SCP (sensitivity, 96.4%; specificity, 93.3%[103]). Therefore, the diagnostic performance of DWI measurements is excellent, supporting these measurements as level 2 biomarkers (Table 3). There is no consensus regarding the best structure to assess, although the SCP appears promising.

Diffusion tensor imaging (DTI) allows for the assessment of directional water diffusion and the interrogation of specific white-matter tracts. White-matter tract degeneration has been demonstrated to be a striking feature of PSP-RS, with abnormalities observed predominantly in the SCP, cerebellum, body of the corpus callosum, cingulum, white-matter laminar of the thalamus, and premotor aspects of the superior longitudinal fasciculus.[63,111-124] The majority of these white-matter tracts show greater degeneration in PSP-RS compared with PD[112,118,122,125-127] and MSA-P.[72,118,126] Little data are currently available on the diagnostic utility of DTI measures, although the corpus callosum[113] and SCP[125] show high sensitivity and specificity in differentiating PSP-RS and PD. There is also evidence that adding DTI measures to the MRPI may help in the differentiation of PSP-RS from controls.[128] The diagnostic value of DTI measures to differentiate PSP-RS and MSA-P is unclear. It is also unclear whether DTI measures could differentiate PSP-RS and CBS, particularly given that patterns of DTI abnormalities overlap to a large degree between these 2 syndromes.[112,129-131] A few studies have assessed DTI measures in PSP-P, which appears to show similar although slightly less severe patterns of tract abnormalities compared with PSP-RS.[128] Some studies have found regions with greater abnormalities in PSP-P compared with PSP-RS, although the results have not been consistent across studies.[117,120,128] In summary, DTI abnormalities are striking in PSP-RS and have the potential to be useful diagnostic biomarkers (Table 3). However, data are needed on the utility of both DWI and DTI measures in vPSP and autopsy-confirmed PSP. The issue of whether DWI and DTI measurements can be translated into clinical practice is also unclear, because there is little standardization of methods across studies and no established diagnostic cut points for these measurements.

PET/SPECT

[^{18}F]FDG-PET

Studies of [^{18}F]-fluorodeoxyglucose PET (FDG-PET) have shown hypometabolism in the midbrain, basal ganglia, thalamus, and frontal lobes in PSP-RS,[132-145] with frontal involvement particularly targeting premotor, precentral, and prefrontal regions[134] and anterior cingulate[146] (Fig. 2A). In an autopsy cohort including 7 PSP patients (all PSP-RS), the most common FDG-PET findings were hypometabolism of the thalamus (100%), caudate (86%), midbrain (86%), and frontal lobes (71%).[145] PSP-RS tends to show greater frontal hypometabolism than PD and MSA,[146] with visual assessments of frontal hypometabolism producing good sensitivity (76%) and specificity (98%) for PSP-RS in 1 study.[147] Visual assessments of midbrain hypometabolism have performed modestly, with 1 study finding 79% sensitivity and 69% specificity in differentiating PSP-RS from MSA and CBS.[144] Consideration of the pattern of hypometabolism may hold more diagnostic promise. Visual assessment of the pattern of hypometabolism associated with PSP-RS (eg, anterior cingulate, midbrain, basal ganglia) gave 93% sensitivity and 90% specificity to differentiate PSP-RS from PD, MSA, and CBS in 1 study.[147] Automated pattern detection techniques have given mixed results.[148-152] Differentiating PSP-RS from CBS can be challenging, given that patterns of hypometabolism overlap between these 2 syndromes to a large degree[138,145,152] although there is some suggestion that PSP-RS may have greater hypometabolism in midbrain and thalamus,[136,153] and CBS patients have greater hypometabolism in parietal lobes.[135,138,153] The presence of hemispheric asymmetry in CBS may further help to differentiate it from PSP-RS.[145,152] Therefore, current evidence provides some support for frontal and midbrain hypometabolism or the combination of both as potential level 2 biomarkers of PSP-RS (Table 3). There is some evidence that hypometabolism in the striatum and cortex can be present before the development of clinical PSP-RS (level 3 biomarker), although this has only been observed in familial PSP.[154]

Some FDG-PET findings have been reported in vPSP. One study found that PSP-P was associated with slightly greater hypometabolism of the putamen than PSP-RS, with less severe involvement of the thalamus, and that a putamen-to-thalamus ratio differentiated PSP-RS from PSP-P and PD with 100% sensitivity and 75% specificity.[155] The PSP-P patients in that study did not show much frontal hypometabolism.[155] Frontal hypometabolism has also not been observed in PSP-PGF, with midbrain hypometabolism only observed in 25% of patients.[156] Patients with PSP-SL have shown frontal, basal ganglia, and midbrain hypometabolism,[157,158] although these studies did not have autopsy confirmation. Taken together, these studies show that neither frontal nor midbrain hypometabolism is present consistently across the vPSP syndromes. Therefore, the presence of these features could be supportive of PSP, but the absence does not preclude underlying PSP.

However, there is a lack of standardization in the quantitative methods used across FDG-PET studies, particularly in regard to the choice of reference regions used to standardize regional uptake values, which vary across studies, including cerebellum, pons, cortical regions, or global mean values, each of which may have different limitations in PSP.

Dopamine Imaging

Striatal presynaptic dopamine binding, measured using dopamine active transporter (DAT) imaging using [123I]-FP-CIT SPECT or [18F]FP-CIT-PET, is consistently decreased in PSP-RS compared with controls[159] (Fig. 2B). However, decreased DAT binding has also been observed in PD, MSA-P, and CBS,[160-164] without differences in the degree of general striatal binding observed across groups.[160,162,165] However, studies have found that the caudate nucleus is affected to a greater degree in PSP-RS than in PD[161,163,166,167] and that regional patterns of binding, such as ratio of caudate to ventral striatum (sensitivity, 94%; specificity, 92%),[163] ratio of caudate to putamen,[166] or ratio of anterior-posterior putamen,[167] could help to differentiate PSP-RS from other parkinsonian disorders; however, diagnostic performance has not always been consistent with these measures.[164,167] It has also been shown that PSP-RS shows more symmetric striatal binding than PD,[168] although the diagnostic value of this finding is unclear. Overall the finding of reduced striatal DAT binding is highly supportive and sensitive

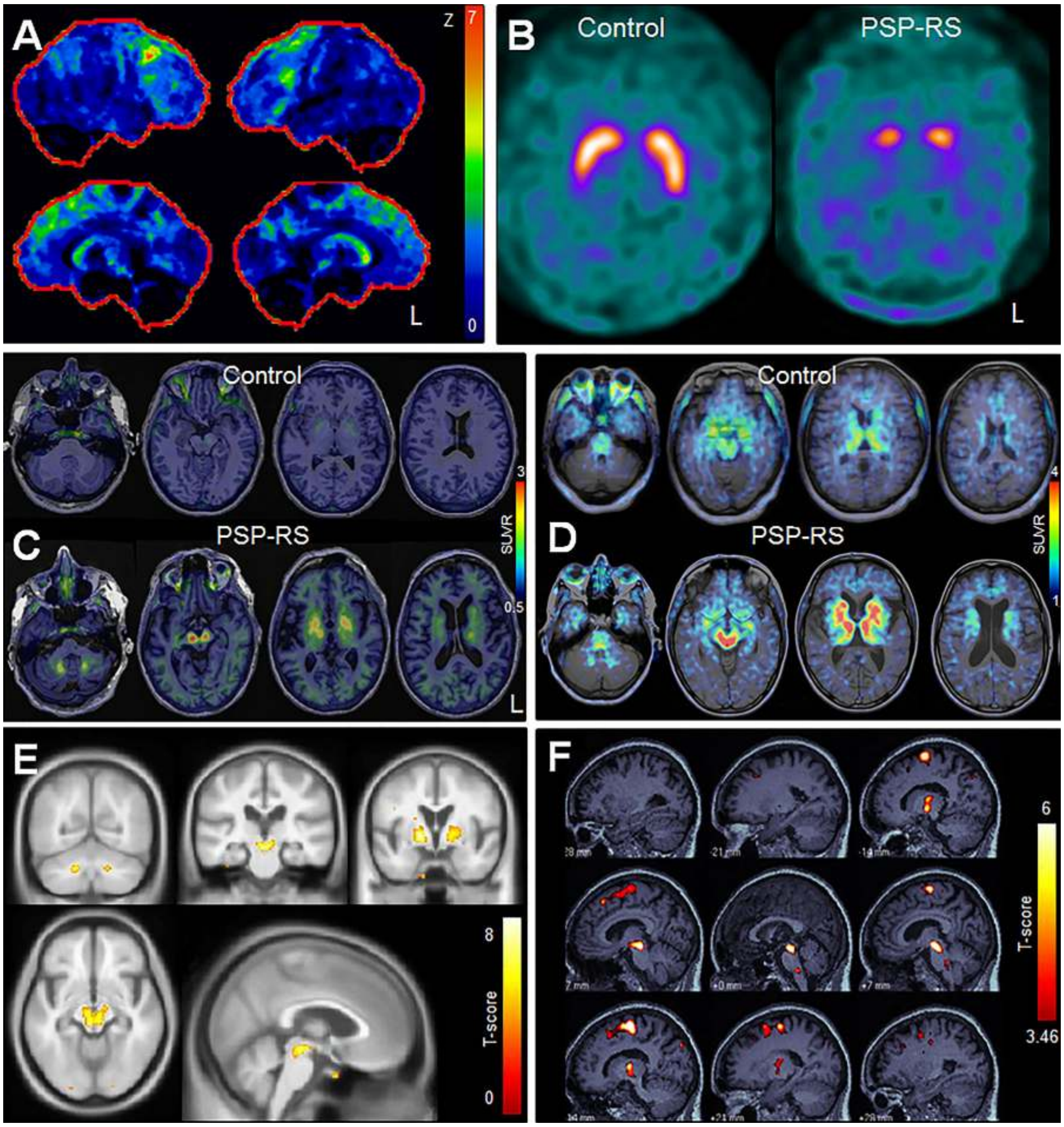

FIG. 2. FDG-PET, DAT, and tau PET findings in PSP-RS. (A) Statistical stereotactic surface projection map of an FDG-PET scan for a PSP-RS patient for whom *Z* scores represent differences from a normal cohort and are color-coded, as indicated in the color scale (0 = normal; 7 = most abnormal). Hypometabolism is observed in the frontal lobes, midbrain, and caudate nucleus. (B) Absent putamen DAT binding and reduced caudate binding in a patient with PSP-RS compared with a control subject. (C, E) $[^{18}F]$AV-1451 results. (C) $[^{18}F]$AV-1451 tau-PET scans in a patient with PSP-RS and an age-matched control. The control shows some uptake in midbrain and basal ganglia, although uptake in these regions is greater in the PSP-RS patient. In addition, the PSP-RS patient shows uptake in the dentate nucleus of the cerebellum and thalamus. (E) Group-level $[^{18}F]$AV-1451 findings in 10 patients with PSP-RS compared with healthy controls. Increased uptake in PSP-RS compared with controls is identified in dentate nucleus of the cerebellum, midbrain, thalamus, and basal ganglia (modified from reference [183]). (D, F) THK-5351 results. (D) THK-5351 tau-PET scans in a patient with PSP-RS and a healthy control. The control and PSP-RS patient show uptake in the midbrain, thalamus, and basal ganglia, although the degree of uptake is greater in PSP-RS. (F) Group-level THK-5351 findings in 10 patients with PSP-RS compared with healthy controls. Increased uptake in PSP-RS compared with controls is identified in midbrain, thalamus, basal ganglia, and posterior lateral and medial frontal lobes. Modified from reference.[232]

for a diagnosis of PSP-RS, but heterogeneity across studies and lack of diagnostic data limit its value in differentiating across parkinsonian disorders (Table 3). Midbrain DAT binding is also decreased in PSP-RS, with lower binding than in PD but a degree of binding similar to in MSA.[160,169] Brain stem DAT levels could differentiate PSP-RS and MSA from PD with 89.7% sensitivity and 94.1% specificity in 1 study.[169] Little is currently known about the diagnostic utility of DAT findings in vPSP, although there is evidence from a few studies that both PSP-PGF and PSP-P are associated with striatal DAT reductions similar to those in PSP-RS,[156,170-172] with similar putamen-to-caudate ratios.[171,172]

Imaging using D2 receptor ligands, most commonly [123I]-IZBM SPECT, to assess postsynaptic dopaminergic function also appears to be sensitive in PSP-RS, with the majority of patients showing striatal reductions.[172-176] However, the value of D2 receptor ligand imaging in the differential diagnosis from other parkinsonian disorders is unclear.[162,175,176] In addition, there is some evidence that striatal uptake may not be reduced in PSP-P.[172]

Tau-PET Imaging

The development of PET ligands that can bind to aggregated tau inclusions in the brain has been an exciting recent advance in the field with the potential of becoming a biomarker of tau pathology. A number of tau-PET ligands have been developed,[177] but the [^{18}F]AV-1451 (previously known as T807) ligand[178,179] has been the most widely used to date. Studies have demonstrated relatively consistent patterns of increased [^{18}F]AV-1451 uptake in PSP-RS compared with controls in the globus pallidus, putamen, caudate nucleus, thalamus, subthalamic nucleus, midbrain, and dentate nucleus of the cerebellum[180-184] (Fig. 2C and E). The cortex has typically shown less striking uptake in PSP-RS,[183] with measures from subcortical structures showing the most promise as potential diagnostic biomarkers.[180,182,183] Quantification of globus pallidus retention provided sensitivity and specificity of 93% in differentiating PSP-RS from controls and 93% sensitivity and 100% specificity in differentiating PSP-RS and PD in 1 study,[180] although the thalamus provided the best separation between PSP-RS and controls in another.[182] There is also evidence that the pattern of uptake in PSP-RS differs from that in Alzheimer's disease (AD), with many of the PSP-RS-related regions showing greater uptake in PSP-RS than in AD despite AD showing greater cortical [^{18}F]AV-1451 uptake.[183,184] Therefore, there is some evidence to support [^{18}F]AV-1451 as a level 2 biomarker of PSP-RS. A caveat is that overlap in the [^{18}F]AV-1451 signal is observed between PSP-RS and controls,[182] with 1 study failing to observe differences between PSP-RS and controls.[185] Standardization of methods will also be required, including optimizing scan time and quantitative outcomes. Current studies have analyzed standard uptake value ratio (SUVR) values referenced to cerebellar gray-matter[180,182,183] or binding potentials.[184]

Although early studies are certainly encouraging, several limitations of [^{18}F]AV-1451 need to be considered. One caveat is that regions that show [^{18}F]AV-1451 uptake in PSP, including the basal ganglia, thalamus, midbrain, and dorsal cerebellum, also show some degree of "off-target" binding in normal subjects, which increases with age.[186,187] The nature of this binding is unclear. Although age correction in quantitative studies may go some ways to correct for this off-target binding, it will likely limit the value of [^{18}F]AV-1451 in the differential diagnosis of individual patients. Furthermore, it is unknown whether the off-target signal may also be altered by the disease in PSP, confounding any potential true signal of tau. Another caveat comes from an apparent disconnect between in-vivo and *ex vivo* studies. Although regions that show elevated binding typically show tau deposition at autopsy, autoradiographic studies have found little or no binding of [^{18}F]AV-1451 to tau in autopsied brains of PSP patients,[182,187-192] casting doubt on whether the signal identified by [^{18}F]AV-1451 reflects tau pathology and whether it could be considered a level 5 biomarker of tau. This kind of disconnect is not uncommon for PET tracers, and the utility of such in vitro studies has been questioned.[193] However, a recent article found that tau pathology discovered postmortem in a patient with PSP correlated with antemortem FDG-PET but not with [^{18}F]AV-1451 signal.[190] Another caveat is that elevated [^{18}F]AV-1451 uptake has also been observed in nontau diseases,[187,194] which again questions the specificity of the ligand to 4R tau. Another chemically distinct tau PET ligand, THK-5351,[195] was found to have high affinity for PSP tau lesions in an autoradiographic study[196] and has shown uptake in the globus pallidus and midbrain[196] in patients with PSP-RS (Fig. 2D and F). However, the degree of off-target THK-5351 binding in PSP-related regions is at least as high, if not higher, than that observed with [^{18}F]AV-1451.[197] Overall, much more work needs to be done to evaluate these PET tracers. It is likely that different tau-PET ligands may bind to tau conformers with differing sensitivity and specificity and show different off-target binding, and hence head-to-head and indirect comparisons of the currently available tau imaging agents are needed.

Other Biomarkers

There are a number of other neuroimaging biomarkers that have been assessed in PSP-RS with fewer data available to assess diagnostic value. MR modalities that demonstrate abnormalities in PSP-RS include magnetic resonance spectroscopy and magnetization transfer imaging,[73,198-205] although the ability of these modalities to differentiate PSP-RS from other parkinsonian disorders is unclear.[181,184,185,205] Resting-state (task-free) functional MRI has also been used to demonstrate abnormalities in functional connectivity in PSP-RS across the network of PSP-RS-associated regions,[63,206,207] but the loss of cortical connectivity is not specific to PSP-RS versus PD.[208] Longitudinal MR studies have shown increased rates of whole-brain, cortical, and midbrain atrophy and SCP diffusivity in PSP-RS compared with controls,[209-218] with some evidence for greater rates than in PD, but similar rates of whole-brain and midbrain atrophy as in MSA-P.[212,215] However, cortical and whole-brain rates of atrophy are greater in CBS than in PSP-RS.[209,213] Cerebral blood flow single-photon emission computed tomography studies have demonstrated frontal[219-225] and, less commonly, thalamic[220] and striatal[222] hypoperfusion in PSP-RS.[221,226] Findings concerning differentiating PSP-RS from other parkinsonian disorders are lacking here, although PSP-RS may show greater frontal hypoperfusion than PD.[224,227] Abnormalities in other neurotransmitter systems, such as the cholinergic[228-230] and serotoninergic[231] systems, have also been demonstrated in PSP-RS.

Conclusions

Neuroimaging research over the last several decades has improved our understanding of the neurobiology of PSP but has not yielded many confirmed diagnostic biomarkers (Table 3). The most mature research area is the assessment of midbrain measurements, which has yielded a number of measures that have good sensitivity and specificity for PSP-RS versus other parkinsonian disorders, such as midbrain-pons area and the MRPI, which appear to be the most reliable biomarkers for the diagnosis of PSP-RS. The presence of frontal atrophy and hypometabolism are also prominent features of PSP-RS and may improve diagnosis when considered together with midbrain atrophy. It is clear that PSP-RS is associated with striking damage to the white matter, with DWI measures of the SCP providing good sensitivity and specificity for PSP-RS diagnosis, although data supporting this measure come from only a couple of studies. DTI measures could prove to be very valuable, although more work is needed to provide and validate standardized measures of the kind that could be used in diagnostic criteria. Measures of dopamine function are highly sensitive to PSP-RS and many of the vPSP syndromes, but specificity is low, and thus they are less useful in ruling out other parkinsonian syndromes. Data so far only support neuroimaging biomarkers as level 2 biomarkers for PSP-RS. Only a handful of studies have assessed patients early in the disease course to suggest level 3 biomarkers. More work is needed to assess the value of these measures in vPSP and in autopsy-confirmed cases to determine whether they could be useful level 4 biomarkers. Capturing the disease in its earliest phase will also be critical for developing well-validated level 3 biomarkers. Last, tau-PET imaging techniques are exciting, but more work is needed to truly understand the biological underpinnings of the tau-PET signal in PSP. However, these are early days in tau-PET imaging, and we expect our understanding of these biomarkers to increase exponentially over the coming years. ■

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Appendix

MDS-endorsed PSP study group: Adam L Boxer, Alex Rajput, Alexander Pantelyat, Angelo Antonini, Anthony E. Lang, Armin Giese, Brit Mollenhauer, Carlo Colosimo, Caroline Kurz, Christer Nilsson, Claire Troakes, David J. Irwin, Dennis W. Dickson, Ellen Gelpi, Florian Krismer, Gerard D. Schellenberg, Gesine Respondek, Gil Rabinovici, Gregor K. Wenning, Günter U. Höglinger, Huw R. Morris, Irene Litvan, James B Rowe, Jan Kassubek, Jean-Christophe Corvol, Jennifer L. Whitwell, Johannes Levin, John van Swieten, Kailash P. Bhatia, Keith A. Josephs, Klaus Seppi, Lawrence I Golbe, Maria Stamelou, Murray Grossman, Peter Nestor, Richard Dodel, Stefan Lorenzl, Thilo van Eimeren, Thomas Arzberger, Ulrich Müller, Wassilios G Meissner, Werner Poewe, Wolfgang H Oertel, Yaroslau Compta, Yvette Bordelon.

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Supporting Data

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