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Neuropathological analysis of cognitive impairment in progressive supranuclear palsy

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ABSTRACT

Background: Cognitive impairment is an important symptom in progressive supranuclear palsy (PSP), but the pathological changes underlying the cognitive impairment are unclear. This study aimed to elucidate relationships between the severity of cognitive impairment and PSP-related pathology.
Methods: We investigated the clinicopathological characteristics of 10 autopsy cases of PSP, including neuronal loss/gliosis and the burden of PSP-related tau pathology by using a semiquantitative score in 17 brain regions. Other concurrent pathologies such as Braak neurofibrillary tangle stage, Thal amyloid phase, Lewy-related pathology, argyrophilic grains, and TDP-43–related pathology were also assessed. We retrospectively divided the patients into a normal cognition group (PSP-NC) and cognitive impairment group (PSP-CI) based on antemortem clinical information about cognitive impairment and compared the pathological changes between these groups.
Results: Seven patients were categorized into the PSP-CI group (men = 4) and three into the PSP-NC group (men = 3). The severity of neuronal loss/gliosis and concurrent pathologies were not different between the two groups. However, the total load of tau pretangles/neurofibrillary tangles was higher in the PSP-CI group than in the PSP-NC group. In addition, the burden of tufted astrocytes in the subthalamic nucleus and medial thalamus was higher in the PSP-CI group than in the PSP-NC group.
Conclusion: Cognitive impairment in PSP may be associated with the amount of tufted astrocyte pathology in the subthalamic nucleus and medial thalamus.

1. Introduction

Progressive supranuclear palsy (PSP) is an atypical parkinsonism syndrome characterized by vertical gaze palsy, pseudobulbar palsy, postural instability, and cognitive impairment [1]. In the Movement Disorders Society criteria for clinical diagnosis of PSP proposed in 2017 [2], "cognitive dysfunction" became one of four core functional domains in addition to "ocular motor dysfunction," "postural instability," and "akinesia". Assessing cognitive function in PSP is important for diagnosis. In PSP, impairment of verbal fluency and deficits in attention, executive function, and processing speed are often observed [3]. The frequency of general cognitive impairment in PSP has also been reported to be high; 57% of 311 PSP patients had a high score on the Mattis Dementia Rating Scale [4], and dementia was diagnosed in 10% and memory/cognitive dysfunctions in 32% of 90 patients pathologically diagnosed with PSP [5]. Thus, cognitive dysfunctions in PSP are common and important, but their pathological mechanisms have not been clarified.

The neuropathological diagnosis of PSP is based on the accumulation of tau in the neurons and glial cells of multiple brain regions. The characteristic features are tufted astrocytes (TA), oligodendroglial coiled bodies (CB), and neuropil threads (NT), in addition to pretangles/neurofibrillary tangles (PT/NFT) [6–8]. Because of pathological heterogeneity among the PSP subtypes [9,10], it is very difficult to detect the pathological changes responsible for the cognitive impairments in PSP [7,11–13], and few neuropathological investigations have been

Abbreviations: CB, oligodendroglial coiled body; CBS, corticobasal syndrome; CI, cognitive impairment; FAB, Frontal Assessment Battery; MMSE, Mini-Mental State Examination; NC, normal cognition; NFT, neurofibrillary tangle; NT, neuropil thread; PSP, progressive supranuclear palsy; STN, subthalamic thalamus; TA, tufted astrocyte.

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performed on this matter [11–13]. Here, we aim to clarify the correlation between the severity of cognitive impairment and the pathological burden of PSP-related pathology.

2. Materials and methods

2.1. Subjects

From 54 consecutive autopsy cases at Tottori University Hospital from 2013 through 2021, we pathologically diagnosed 10 cases as PSP. Brain autopsies were obtained after consent of the next of kin.

Clinical information for age at onset, age at death, and cognitive impairment were gathered from medical records. Clinical phenotypes of PSP were classified retrospectively using the clinical diagnosis criteria of PSP from the Movement Disorders Society [2]. Cognitive function was evaluated with the Mini-Mental State Examination (MMSE) [14], and the score was used to divide patients into a normal cognition group (PSP-NC) and cognitive impairment group (PSP-CI) with a cut off of 23/24 points [15]. If the patient was evaluated with the MMSE several times, the final score was used to categorize the patients. Cognitive function was also assessed using the Frontal Assessment Battery (FAB) [16] in cases that were evaluated. Patients were also divided into a high FAB score group and a low FAB score group with a cut off of 11/12 points [17].

2.2. Neuropathological assessment

Neuropathological examination was conducted in accordance with the following methods. Eight-micrometer-thick serial sections of representative brain regions, fixed with formalin and embedded in paraffin, were stained with hematoxylin and eosin and by the Klüver–Barrera method. Immunohistochemistry was performed with the following antibodies: anti-phosphorylated α-synuclein (psyn#64, monoclonal; Wako, Osaka, Japan), anti-phosphorylated tau (AT8, monoclonal; Innogenetics, Temse, Belgium), anti-beta amyloid 11–28 (12B2, monoclonal; IBL, Fujioka, Japan), and anti-phosphorylated TDP-43 (pSer409/410, monoclonal; Cosmobio, Tokyo, Japan).

Neuronal loss and gliosis were graded by two neuropathologists (M. S. and T.A.), who were blinded to the clinical information, by using a semiquantitative score on a three-point scale (0, none; 1, minimal/mild; 2, moderate/severe). Four kinds of tau pathology (PT/NFT, TA, CB, and NT) were graded with a semiquantitative score on a four-point scale (0, none; 1, mild; 2, moderate; 3, severe) [10,11,18]. The following 17 brain regions were examined: the cortex and white matter in frontal, temporal, parietal, and occipital lobes; motor cortex; caudate/putamen; globus pallidus; subthalamic nucleus (STN); medial thalamus (TH); substantia nigra; midbrain tectum; locus coeruleus; pontine base; medulla oblongata; dentate nucleus; amygdala; and posterior hippocampus. In each region, AT8-positive pathologies were assessed separately in randomly placed microscopic fields using a 20× objective (Fig. 1).

Neurofibrillary tangles of Alzheimer's disease–related pathology were classified into seven stages (from 0 to 6) in accordance with the criteria of Braak et al. [19]. Senile plaques with amyloid β deposits were classified into six stages (from 0 to 5) in accordance with the Thal amyloid phases [20]. The diagnosis of dementia with Lewy bodies was based on the revised consensus guidelines [21]. The diagnosis of argyrophilic grains was based on Saito's staging [22]. Based on previous research, we counted argyrophilic grains in at 400 × magnification and were classified into the following grades: Grade 1, 0 to 20; Grade 2, 20 to 50; Grade 3, 50 to 100; Grade 4, 100 to 200; and Grade 5, >200 [47]. The diagnosis of TDP-43–related pathology was based on the staging of TDP-43 pathology in Alzheimer's disease [23].

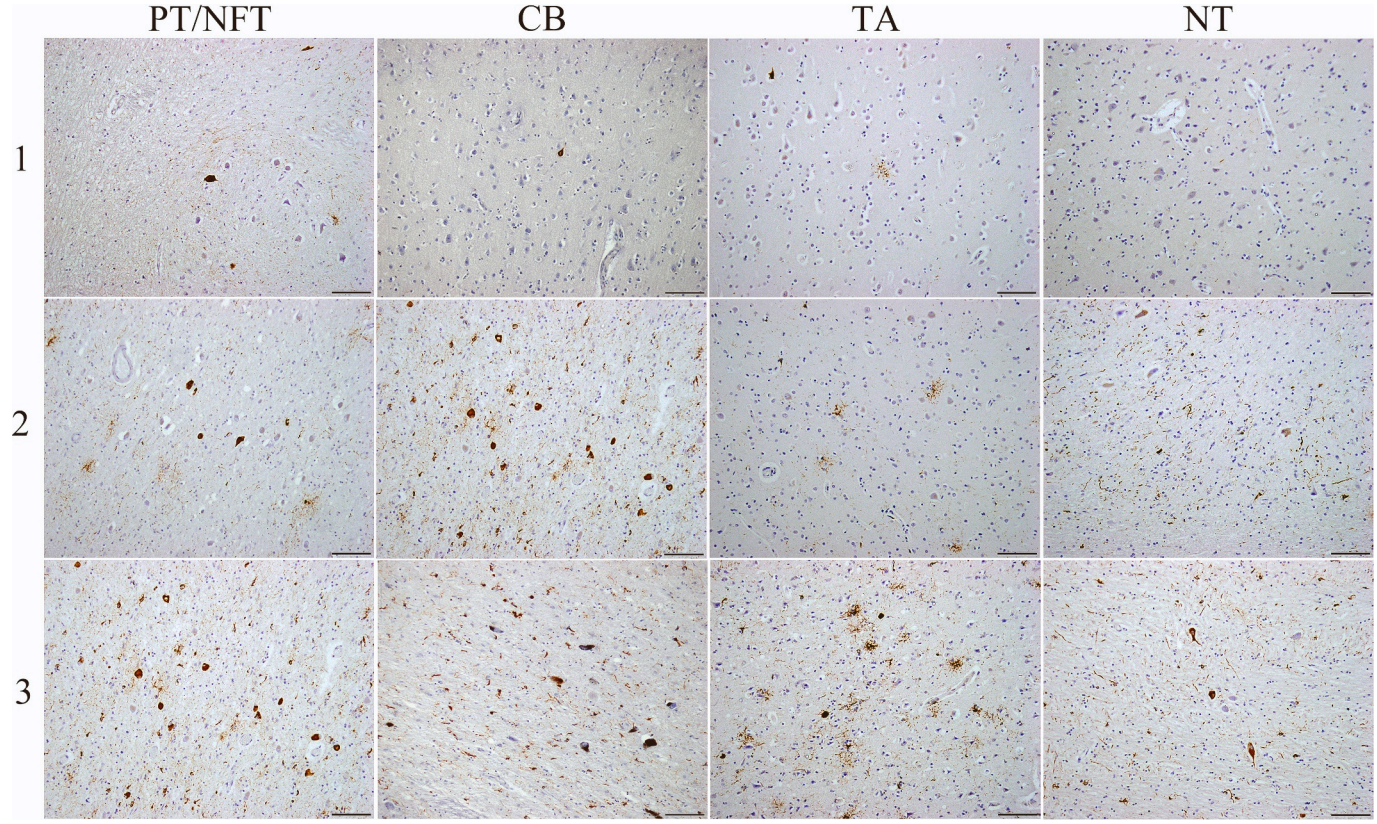

Fig. 1. Examples of immunostaining with anti-phosphorylated tau.
We evaluated pretangles/neurofibrillary tangles (PT/NFT), oligodendroglial coiled bodies (CB), tufted astrocytes (TA), and tau-positive neuropil threads (NT) by using a semiquantitative four-point rating score: 0 = absent, 1 = sparse, 2 = moderate, 3 = severe (immunostaining with anti-phosphorylated tau). Bars = 100 μm.

2.3. Statistical analysis

All statistical analyses were performed in SPSS Statistics Version 25 for Windows (IBM Corp., Armonk, NY). Differences between two groups were analyzed with Student's *t*-test for normally distributed variables, the Mann–Whitney *U* test for non-parametric data, or the chi-square test for comparison of frequencies. The threshold for statistical significance was set at $P < 0.05$.

3. Results

3.1. Clinical and pathological comparison of PSP-CI and PSP-NC

The clinical demographics are summarized in Table 1. The ages at onset ranged from 63 to 77 years (mean ± SD = 71.9 ± 4.1 years), at death ranged from 70 to 92 years (mean ± SD = 79.3 ± 5.8 years), and the male-to-female ratio was 7:3. Of the 10 patients, five met the clinical criteria for probable PSP with Richardson's syndrome (PSP-RS); one for probable PSP with predominant parkinsonism combined with definite amyotrophic lateral sclerosis [24]; two for suggestive PSP with predominant postural instability (one combined with probable corticobasal syndrome [CBS]) [25]; one for suggestive PSP with predominant frontal presentation or behavioral presentations, or diagnosed possible behavioral variant frontotemporal dementia [26]; and one for probable CBS and not PSP [25]. All cases of PSP-RS were in the PSP-CI group.

No clinical information or histologic evaluation other than tau pathology differed between the PSP-CI group (7 patients) and PSP-NC group (3 patients) (Table 2). The male-to-female ratio, age at onset, age at death, and disease duration did not differ between the two groups (Table 2). We compared the total tau load between males and females in all cases, it did not differ between two groups (Mann-Whitney *U* test, NCI:$P = 0.667$, GCI:$P = 0.383$, ACI:$P = 1.0$, NT:$P = 0.667$). Braak NFT stage, Thal amyloid phase, Lewy-related pathology, argyrophilic grains pathology, and TDP-43 related pathology were not different between the two groups.

To know which domains are affecting cognitive impairment, we compared sub-items of MMSE between the PSP-CI group and PSP-NC group. There was a significant difference in the item of "Orientation to time" and "Recall", but not in the other items (Supplementary Table1).

3.2. Relation of neuronal loss/gliosis and tau pathology to cognitive impairment of PSP

The severity of neuronal loss/gliosis varied among the cases, as did the regional tau burden. The total tau load was calculated as the sum of the semiquantitative scores of all brain regions for each lineage (PT/NFT, CB, TA, and NT). Total tau load of PT/NFT was higher in the PSP-CI group (median 20) than in the PSP-NC group (median 18, Mann–Whitney *U* test, $P = 0.033$) (Fig. 2). In contrast, the total tau load of CB, TA, and NT were not significantly different between the two groups (Mann–Whitney *U* test, CB: $P = 0.833$, TA: $P = 0.383$, NT: $P = 0.667$).

The severity of neuronal loss and gliosis evaluated by semiquantitative scores did not differ between the two groups in each region. Of the brain regions, only STN and TH differed in the burden of TA between the two groups, with a higher burden in the PSP-CI group than in the PSP-NC group (Table 3; Mann–Whitney *U* test, STN: $P = 0.048$, TH: $P = 0.048$).

Table 2
Comparison of clinical and pathological features between the PSP-CI and PSP-NC groups.

	Total ($N = 10$)	PSP-CI ($N = 7$)	PSP-NC ($N = 3$)	*p* value
Male, no. (%)	7 (70%)	4 (57%)	3 (100%)	0.292
Age at onset (years)	71.9 ± 4.1	73.9 ± 3.3	68.7 ± 5.5	0.13
Age at death (years)	79.3 ± 5.8	81.1 ± 5.8	75.0 ± 5.6	0.159
Disease duration (years)	7 (5, 7)	7 (5.5, 10)	7 (6, 7)	0.833
Pathology				
Braak NFT stage	3 (2,3)	3 (2.5, 3)	2 (2, 2.5)	0.383
Thal amyloid phase	1 (0,1)	1 (0.5, 1)	0 (0, 1)	0.667
AGD Saito stage	3 (3,3)	3 (3, 3)	2 (2, 2.5)	0.117
Lewy-related pathology	0 (0,0)	0 (0, 0)	0 (0, 0)	0.833
TDP-43–related pathology	0 (0, 0)	0 (0, 0)	0 (0, 0)	0.833

Values are n (%), mean ± SD, and median (IQR). Statistical analysis was performed as follows: chi-square test for male-to-female ratio; *t*-test for age at onset, age at death, and disease duration; and Mann–Whitney *U* test for other concurrent pathology stage.
AGD: argyrophilic-grain dementia; NFT: neurofibrillary tangle; PSP-CI: PSP with cognitive impairment group; PSP-NC: PSP with normal cognition group.

3.3. Relation of tau pathology to Frontal Assessment Battery of PSP

Of the 10 patients, seven evaluated FAB score (Table 1). The high FAB score group included 2 patients, and the low FAB score group included 5 patients. The semiquantitative scores of each brain regions and sum of the scores of all brain regions for each lineage did not differ between the two groups (Mann-Whitney *U* test, PT/NFT: $P = 0.095$, CB: $P = 1.00$, TA: $P = 0.571$, NT: $P = 0.875$, data not shown).

4. Discussion

We investigated the relationship between cognitive impairment and PSP-related pathology. A previous study suggested that significant cognitive impairment can be an early and prominent sign of PSP [27],

Table 1
Summary of the clinical demographics.

	PSP-CI							PSP-NC		
Case number	1	2	3	4	5	6	7	8	9	10
Sex	Male	Female	Male	Male	Male	Female	Female	Male	Male	Male
Age at onset (years)	71	74	75	70	77	69	77	74	69	63
Age at death (years)	84	76	80	77	83	76	92	81	74	70
Disease duration (years)	13	2	5	7	6	7	15	7	5	7
MDS PSP criteria	prob. RS	prob. RS	prob. RS	s.o. PI	prob. RS	prob. RS		s.o. F	prob. P	s.o. PI
Other clinical diagnosis				prob. CBS			prob. CBS	poss. bvFTD	def. ALS	
Final MMSE score	15	13	3	16	15	21	21	24	25	29
Final FAB score	7	5	4	8	NE	9	NE	13	16	NE
Duration from MMSE to death (years)	0	0	1	4	1	3	12	2	0	3

ALS: definite amyotrophic lateral sclerosis; FAB: Frontal Assessment Battery; MDS: Movement Disorder Society; MMSE: Mini-Mental State Examination; NE: not examined; poss. bvFTD: possible behavioral variant of frontotemporal dementia; prob. CBS: probable corticobasal syndrome; prob. P: probable PSP with predominant parkinsonism; prob. RS: probable PSP with Richardson's syndrome; PSP-CI: PSP with cognitive impairment group; PSP-NC: PSP with normal cognition group, s.o. F: suggestive of PSP with predominant frontal presentation; s.o. PI: suggestive of PSP with postural instability.

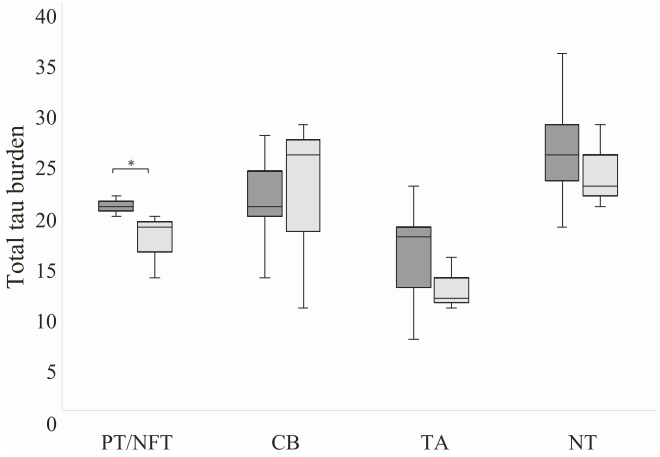

Fig. 2. Median overall tau load (sum of grades for tau load in all regions) in the PSP-CI group (dark grey) and PSP-NC group (light grey). The total tau load of PT/NFT was higher in the PSP-CI group than in the PSP-NC group. *PSP-CI versus PSP-NC, Mann–Whitney *U* test, $P < 0.033$. CB: oligodendroglial coiled bodies; NT: tau-positive neuropil threads; PT/NFT: pretangles/neurofibrillary tangles; TA: tufted astrocytes. Data are shown as median (black line), 25th and 75th percentiles (bottom and top of box, respectively), and the minimum and maximum (error bars).

and Brown et al. showed that cognitive impairment is related to disease severity as assessed with the Clinician Global Impression of disease severity, Hoehn and Yahr stage, or Short Motor Disability Scale [4]. However, the regions responsible for this cognitive impairment in PSP have not been identified. Here we showed that the PSP-CI group had a significantly higher total tau load of PT/NFT and astrocytic tau burden in STN and TH than the PSP-NC group.

Koga et al. reported that the burden of PSP-related tau pathology correlates with the severity of cognitive impairment and assumed that higher amounts of tau pathology in PSP patients reflects more severe disease, which would be linked to more severe cognitive impairment [11]. Our result that the total tau load of PT/NFT was higher in the PSP-CI patients than the PSP-NC patients was consistent with this report [11]. Also similar to the findings for all patients in the previous report [11], the Hoehn and Yahr stage of our patients at the time of the final MMSE assessment was not different between the two groups (median 4 vs 3, Mann–Whitney *U* test, $P = 0.383$). This could indicate that the total tau load of PT/NFT reflects cognitive impairment in PSP, independent of the severities of motor symptoms. Therefore, when we evaluate the cognitive function of PSP patients, we should interpret it carefully, taking bradykinesia into account.

STN is one of the main regions affected by the marked neuronal loss and gliosis with neuronal and glial tau pathology in PSP [1]. Recently, Fujioka et al. [28] reported that atrophy of the STN captured by conventional MRI is a hallmark of PSP by which one may easily differentiate it from other neurodegenerative parkinsonian disorders. In a pathological study of PSP patients [29], both neuronal loss and gliosis were detected in the ventromedial area of the STN, but tau pathology did not show remarkable differences from the other area of the STN. In rodents, STN has roles in cognitive and emotional function, and the medial STN receives projections from the prelimbic-medial orbital areas of the prefrontal cortex as part of the limbic loop [30–32]. Therefore, it is possible that the pathological changes of the medial STN, especially tau pathological changes, could relate to cognitive impairment in PSP. Here, we detected a high burden of TA in the STN in PSP-CI, which could support the above hypothesis.

Thalamic nuclei such as the medial dorsal nucleus, anterior nucleus, and lateral dorsal nucleus are also thought to be involved in memory, emotion, and arousal [33]. No association between tau pathology of these nuclei and cognitive symptoms in PSP has been reported, but Steele et al. [1] reported the presence of tangle formation in the thalamic reticular nucleus and the intralaminar nuclei of the thalamus in PSP. In addition, the centromedian nucleus shows more neuronal degeneration and atrophy in PSP than in Parkinson's disease, whereas there is no difference in the anterior ventral nucleus and the medial dorsal nucleus between PSP and Parkinson's disease [34]. Another paper [35] reported severe TH lesions, particularly in three PSP patients with severe dementia. These lesions showed neuronal loss and gliosis in the medial nucleus, and severe NFT and glial tau pathology in the medial nucleus, reticular nucleus, and zona incerta. They concluded that these regions are related to periodic episodes of stupor in advanced PSP. The medial dorsal nucleus affects executive processes pertaining to declarative memory strategies for storage and recall [36]. In order to assess the role of the thalamus in cognitive impairment, we mainly evaluated the medial dorsal nucleus, and the high burden of TA in the medial thalamus in our results suggest that this region is significantly related to cognitive impairment in PSP.

In STN and TH, only the astrocytic tau load was different between the PCP-CI group and PSP-NC group. In tauopathies, including PSP, functional impairment may be at least in part a consequence of synaptic loss [37,38]. Bigio et al. reported that cortical synapse loss assessed by measuring synaptophysin levels might correlate with dementia in PSP [39]. Perisynaptic astrocytic processes are essential components of the synapse structurally, trophically, and functionally, and phosphorylated tau accumulation in astrocytes is directly involved as an upstream mechanism of synaptotoxicity [40–42]. Thus, our results suggest that higher TA burden may be associated with cognitive impairment in PSP.

We showed that other neuropathological features were not different between the two groups, including Alzheimer-related, Lewy-related, and TDP-43–related pathology and argyrophilic grains. Recently, TDP-43 co-pathology was reported to be present in some cases of PSP and to influence the clinical characteristics [43,44]. PSP patients often have argyrophilic-grain co-pathologies [45], and case 8 is the patient from our previous case report [46]. The patient was clinically diagnosed with PSP with frontal lobe cognitive or behavioral presentations (PSP-F) according to the MDS criteria or possible behavioral variant frontotemporal dementia. However, this patient's MMSE and FAB scores were also relatively high at 24/30 and 13/18 points, so this patient was classified in the PSP-NC group. This patient had only a few tau pathology in the frontal cortex, we concluded that the psychiatric symptoms of PSP-F should be considered as being due to the presence of limbic argyrophilic grains. Although there is no significant difference between PSP-CI and PSP-NC, argyrophilic grain Saito stage of all cases was high. As it has been reported, the progression of argyrophilic grain pathology may be associated with development of the astrocytic tau pathologies characteristic of PSP [45], and we thought it necessary to discuss the association between argyrophilic grains and TA. Based on previous research, we counted argyrophilic grains in TH and STN [47]. Pearson's correlation coefficient was tested to examine the correlation between argyrophilic grains and TA stages in TH and STN, but none of these correlations were significant (TH: $R = 0.457$, $P = 0.216$, STN: $R = 0.520$, $P = 0.152$). Although it has already been proven that the spread of argyrophilic grains is closely related to PSP pathology, in our study, argyrophilic grain stages were already advanced and there were no significant differences between the burden of argyrophilic grains and TA in TH and STN. Thus, because the cognitive impairment of PSP may occasionally be due to co-pathology, neuropathological examinations are important to identify its cause.

Cognitive function was evaluated with MMSE and FAB. In particular, FAB used to detect frontal lobe dysfunction [16] and has been shown to be probably useful in detecting cognitive dysfunction in PSP [48], but in our study, no significant differences were found unlike MMSE. We also considered which sub-items of MMSE influenced a low score. There was a significant difference between the PSP-CI and PSP-NC only in the items of “Orientation to time” and “Recall”. The reason why there were no differences in frontal function considered MMSE and FAB can detect

Table 3
Comparison of AT8-tau semiquantitative scores in PSP-CI and PSP-NC.

		PSP-CI ($n = 7$)	PSP-NC ($n = 3$)	*P* value			PSP-CI ($n = 7$)	PSP-NC ($n = 3$)	*P* value
	NL/gliosis	1 (1, 1.75)	2 (1.5, 2)	0.548		NL/gliosis	2 (2,2)	1 (1, 1.5)	0.117
	PT/NFT	2 (2,2.75)	2 (1.5, 2.5)	0.905		PT/NFT	1 (1,2)	2 (1.5, 2)	0.667
STN	CB	2 (2, 2.75)	2 (2, 2)	0.714	**DE**	CB	1 (1, 2)	2 (1, 2)	1
	TA	2 (1.25, 2)	0 (0, 0)	0.048*		TA	0 (0, 0.5)	0 (0, 0.5)	1
	NT	2.5 (2, 3)	2 (2,)	0.262		NT	2 (2, 2)	2 (1.5, 2.5)	1
	NL/gliosis	1 (1,1)	1 (1, 1.5)	0.714		NL/gliosis	1 (1, 1.5)	1 (1, 1.5)	1
	PT/NFT	2 (1.25, 2)	1 (1, 1.5)	0.548		PT/NFT	2 (2, 2.5)	2 (1.5, 2)	0.383
TH	CB	2 (2, 2)	1 (0.5, 1.5)	0.262	**AM**	CB	2 (1, 2)	1 (1, 1.5)	0.833
	TA	2.5 (2, 3)	1 (0.5, 1)	0.048*		TA	1 (1, 2)	2 (1.5, 2)	0.833
	NT	1.5 (1, 2)	1 (1, 1)	0.262		NT	2 (2, 3)	2 (1.5, 2.5)	0.517
	NL/gliosis	2 (2, 2)	2 (2, 2)	0.833		NL/gliosis	1 (0.5, 1)	1 (1, 1)	0.833
	PT/NFT	1 (1, 2)	2 (1.5, 2)	0.667		PT/NFT	2 (2, 3)	2 (2, 2.5)	1
GP	CB	2 (1.5, 2)	3 (2.5, 3)	0.067	**HI**	CB	1 (0, 1.5)	1(0.5, 1)	0.833
	TA	2 (0.5, 2)	2 (1, 2.5)	0.833		TA	1 (0,2)	1 (0.1, 1.5)	1
	NT	1 (1, 2)	2 (2, 2.5)	0.117		NT	2 (2, 2.5)	2 (2, 2.5)	0.833
	NL/gliosis	2 (1.5, 2)	2 (1.5, 2)	1		NL/gliosis	1 (1, 1)	1 (1, 1)	0.833
	PT/NFT	1 (1, 1.5)	1 (0.5, 1)	0.267		PT/NFT	0 (0, 0.5)	0 (0, 0)	0.517
SN	CB	2 (1, 2)	2 (1.5, 2.5)	0.517	**FR**	CB	1 (1, 1)	1 (0.5, 1.5)	1
	TA	0 (0, 0)	0 (0, 1)	0.667		TA	1 (1, 2)	0 (0, 1)	0.267
	NT	2 (1.5, 2)	3 (2.5, 3)	0.067		NT	1 (1, 1)	0 (0, 0.5)	0.183
	NL/gliosis	1 (0.1, 1)	1 (1, 1)	0.517		NL/gliosis	1 (0.5, 1)	0 (0.5, 1)	0.383
	PT/NFT	1 (0.5, 1)	1 (1, 1)	0.833		PT/NFT	0 (0, 0.5)	0 (0, 0.5)	1
ST	CB	1 (1, 1)	1 (0.5, 1.5)	1	**PA**	CB	1 (1, 1.5)	1 (0.5, 1.5)	0.833
	TA	2 (2, 2)	1 (1, 1.5)	0.267		TA	1 (1, 2)	0 (0, 1)	0.383
	NT	1 (1, 2)	1 (1, 1)	0.517		NT	1 (1, 1)	0 (0, 0.5)	0.183
	NL/gliosis	1 (1, 2)	2 (1.5, 2)	0.667		NL/gliosis	0 (0, 1)	0 (0, 0.5)	0.833
	PT/NFT	1 (1, 1.75)	1 (0.5, 1.5)	0.714		PT/NFT	0.5 (0, 1)	0 (0, 0)	0.262
TG	CB	2 (2, 2)	2 (1, 2.5)	1	**TE**	CB	1 (1, 1)	1 (0.5, 1)	0.714
	TA	1 (1, 1.75)	1 (1, 1.5)	1		TA	1 (1, 1)	0 (0, 0.5)	0.262
	NT	2 (2, 2.75)	2 (1.5, 2)	0.262		NT	1 (1, 1)	1 (0.5, 1)	0.548
	NL/gliosis	1 (1, 1.5)	1 (1, 1)	0.517		NL/gliosis	0 (0, 0.5)	0 (0, 0)	0.517
	PT/NFT	3 (3, 3)	2 (1.5, 2)	0.067		PT/NFT	0 (0, 0)	0 (0, 0)	1
LC	CB	2 (2, 2)	2 (1.5, 2)	0.667	**OC**	CB	0 (0, 0.5)	0 (0, 0.5)	1
	TA	0 (0, 0)	0 (0, 1)	0.667		TA	0 (0, 0)	0 (0, 0.5)	0.517
	NT	2 (1.5, 2)	2 (2, 2)	0.833		NT	0 (0, 0)	0 (0, 0.5)	0.517
	NL/gliosis	1 (1, 1)	1 (1, 1.5)	0.383		NL/gliosis	1 (0.5, 1)	1 (1, 1)	0.833
	PT/NFT	2 (1.5, 2)	1 (1, 1)	0.117		PT/NFT	1 (0.5, 2)	0 (0, 1)	0.517
PB	CB	2 (1.5, 2)	1 (1, 1)	0.183	**MC**	CB	1 (2,1)	1 (0.5, 1.5)	0.383
	TA	0 (0, 1)	0 (0, 0.5)	0.833		TA	1 (0.5, 2.5)	0 (0, 1)	0.383
	NT	2 (1.5, 2)	1 (0.5, 1)	0.067		NT	2 (1.5, 2)	1 (1, 1.5)	0.383
	NL/gliosis	1 (1, 1.5)	1 (1, 1)	0.517					
	PT/NFT	2 (1, 2)	1 (1, 1)	0.183					
MO	CB	1 (1, 1)	2 (1.5, 2)	0.183					
	TA	1 (0, 1)	0 (0, 0.5)	0.667					
	NT	2 (2, 2.5)	2 (1.5, 2)	0.383					

Values are given as median (IQR). *PSP-CI versus PSP-NC, Mann–Whitney *U* test, $P < 0.05$. AM: amygdala; CB: oligodendroglial coiled body; DE: dentate nucleus; FR: frontal lobe; GP: globus pallidus; HI: hippocampus; LC: locus coeruleus; MC: motor cortex; MO: medulla oblongata; NL: neuronal loss; NT: tau-positive neuropil thread; OC: occipital lobe; PA: parietal lobe; PB: pontine base; PT/NFT: pretangle/neurofibrillary tangle; SN: substantia nigra; ST: striatum; STN: subthalamic nucleus; TA: tufted astrocyte; TE: temporal lobe; TG: midbrain tegmentum; TH: thalamus.

characteristic of PSP only in the early stage. If the cognitive impairment has progressed to memory impairment and disorientation on MMSE, the tau pathology of TH and STN may be severe. In order to elucidate the pathological changes for each cognitive function, we need to perform various other batteries to assess cognitive function.

The main limitation of our study was its small sample size. Anatomical vulnerability patterns differ between clinical subtypes in PSP, and we need to study each subtype in the future. Further exploration of the regions responsible for cognitive impairment in PSP may help with early diagnosis of and intervention for PSP.

In conclusion, we demonstrated the clinicopathological importance of STN and TH in PSP with cognitive impairment. Further exploration of the regions responsible for cognitive impairment in PSP may help with early diagnosis of and intervention for PSP.

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Appendix A. Supplementary data

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