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## **THE RELATIONSHIP BETWEEN CLINICAL AND PATHOLOGICAL VARIABLES IN RICHARDSON'S SYNDROME**

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## **Abstract**

In order to determine the relationship between regional neuropathology and severity of clinical features in Richardson's syndrome (PSP-RS), the following hypotheses were tested; 1) executive dysfunction relates to prefrontal pathology; 2) language difficulties to pathology in Broca's area and/or the perirhinal cortex and 3) visuospatial impairment to pathology in the supramarginal region. A prospectively studied case series of brain donors at a specialist clinic in Addenbrooke's Hospital Cambridge, UK, were examined. All those fulfilling postmortem criteria for PSP-RS and their last cognitive assessment within 24 months of death (N=11/25) were included. The degree of regional neuronal loss and neuronal tau deposition across a number of cortical brain regions was performed and compared to 10 age and sex matched controls from the Sydney Brain Bank. Stepwise multiple linear regressions were used to determine the neuropathological correlates to cognitive scores and revealed the following. Executive dysfunction, as indexed by letter fluency, related to the degree of tau deposition in the superior frontal gyrus and supramarginal cortices ( $p < 0.020$ ), language deficits related to neuron loss in the perirhinal gyrus ( $p < 0.001$ ) and tau deposition in Broca's area ( $p = 0.020$ ), while visuospatial dysfunction and global cognitive impairment related to tau deposition in the supramarginal gyrus ( $p < 0.007$ ). The severity of cognitive deficits relate to regional cortical tau deposition in PSP-RS, although language impairment related to neuronal loss in the perirhinal region. Global cognitive dysfunction related most to the severity of tau deposition in the supramarginal gyrus warranting further research on the role of this brain region in PSP-RS.

**Keywords: Richardson's syndrome - progressive supranuclear palsy – neuropathology – cognition – tau - correlations**

## **Introduction**

Recent work has suggested that PSP is a heterogeneous disorder with a number of sub syndromes each with a distinctive clinical profile and pattern of tau neuropathology [17, 30, 45].

Richardson's syndrome (PSP-RS), the most common form, is associated with more substantial subcortical and cortical tau pathology compared to the other forms of PSP [46]. PSP-RS is clinically characterised by postural instability, supranuclear gaze palsy, progressive axial rigidity, bulbar palsy and most notably by prominent cognitive impairment [47]. Such impairment is often severe and affects a number of cognitive functions [11, 20]. Detailed pathological analyses have revealed marked atrophy and neuronal loss involving the supramarginal gyrus as well as prefrontal cortical regions [1, 32, 41]. The finding of atrophic frontal regions is to be expected given the prominence of executive deficits and apathy in PSP-RS [39], but the finding of supramarginal atrophy was novel and the clinical significance uncertain.

The important role of cortical pathology in the genesis of PSP symptoms was identified some time ago [7, 8, 24, 28, 43]. Only a few studies have since investigated relationships between cortical pathology and clinical features [14, 31, 46]. Based upon a wealth of data from traditional lesion-based neurological and functional MRI studies, the following hypotheses were tested. Executive dysfunction, the most consistent deficit in PSP-RS [35], would be related to superior (dorsolateral) frontal cortex pathology [2]. Deficits in attention and orientation are more likely to relate to pathology in the anterior cingulate cortex [26]. Adynamism of speech and motor speech disorders in PSP-RS are well described [4, 19, 31]. We hypothesised that pathology in the inferior frontal region, notably Broca's area, is likely to be the main anatomical locus related to tasks requiring spoken output, while semantic comprehension tests should relate to the degree of perirhinal damage [16]. Visuospatial impairment is more variable in PSP-RS [3] but might reflect pathology in the supramarginal region. It is difficult to make specific hypotheses about the relationship between global cognitive dysfunction and regional neuropathology. Given the prominence of executive dysfunction in PSP it could be deduced that frontal pathology is most likely to contribute to the overall level of dementia. On the other hand, the recent finding of marked supramarginal atrophy in PSP-RS [41] could suggest that pathology in this multi-modal association region important for attention [12, 40] may contribute to global cognitive dysfunction. This study aimed to test these hypotheses using prospectively collected clinical data from pathologically confirmed PSP-RS cases that had been assessed cognitively in close

proximity to their death.

## **Patients and Methods**

### ***Case Selection***

Brain donors fulfilling pathological criteria for PSP [25, 37] were selected from a series of prospectively-studied patients enrolled into the Cambridge Brain Bank who had attended the Disorders of Movement and Cognition (DMC) Clinic at Addenbrooke's Hospital Cambridge between 1996 and 2003. Patients fulfilled clinical criteria for probable PSP [36] of the PSP-RS subtype (early prominent falls, eye signs and cognitive dysfunction)[47]. All had undergone serial cognitive assessments ( $3 \pm 1$  assessments on average, range 2-6) and their families had provided informed consent for brain donation after death. From a total of 25 potential PSP cases, only those with their last clinical evaluation less than 24 months prior to death were included, totalling 11 (5 male, 6 female, last assessment on average  $17 \pm 7$  months prior to death, and  $58 \pm 29$  months after disease onset). These cases had a mean disease onset at  $67 \pm 4$  years (range, 59-72 years) and mean disease duration of  $6 \pm 2$  years (range, 4-12 years). Ten age- and sex-matched controls ( $73 \pm 7$  years at death, range 61-82 years; 4 male, 6 female) were selected for pathological comparison from the Sydney Brain Bank. Controls had no significant neuropathological abnormality and were also prospectively evaluated using standardised questionnaires, with no neurological or psychiatric deficits noted in their last clinical assessment on average  $10 \pm 7$  months prior to death. There was no significant difference in age between PSP and controls (Man Whitney U,  $p=0.83$ ) nor in gender distribution (Pearson Chi-Square,  $p=0.80$ ). At autopsy, whole brains were collected according to previously published protocols [41] with no difference in fixed whole brain weight between PSP and control groups (mean:  $1206 \pm 169$ ).

### ***Evaluation of clinical domains for hypothesis testing***

A number of published tests were used to assess the clinical domains described below. For some domains, the average of several tests was calculated to create a single index. Patient scores were expressed as a percentage deficit from published control scores for each test.

Global cognitive dysfunction –The severity of overall cognitive dysfunction was measured using the Addenbrooke's Cognitive Examination (ACE) [38], a brief but comprehensive cognitive screening tool assessing six cognitive domains (attention and orientation, verbal fluency, memory, language and visuospatial functions). The ACE has been shown to be sensitive to

cognitive dysfunction in PSP [4]. The ACE was measured at several time points in 8/11 patients and the average decline in performance was found to be 8% per annum.

Attention/Orientation - To assess this ability we used the attention and orientation score from the ACE.

Letter fluency – As a measure of executive ability, fluency scores for words beginning with the letters F, A, S and P (from the ACE) were used [18, 27].

Language – To assess language dysfunction we combined the following scores: the language subsection of the ACE, the Graded Naming Test (GNT), [9] the Pyramids and Palm Trees test (PPT) [5, 29], the Test of Reception and Grammar (TROG) [10, 15] and category fluency.

Visuospatial deficits – Scores on the Visual Object and Space Perception Battery (VOSP) [44] were used to assess patients for visuospatial deficits. This battery combines object-perception (incomplete letters, silhouettes and object decision) and space-perception (dots, number location and cubes) [3].

Global motor impairment (to assess specificity) –The severity of motor impairment prior to death was assessed by extracting the limb, gait and falls scores from the PSP Rating Scale [21].

### ***Quantitative histopathology***

Regions assessed were the substantia nigra, caudate nucleus, amygdala and multiple cortical regions, including five samples from the frontal lobe (orbito-frontal cortex or Brodmann's areas (BA) 10 and 11, inferior frontal gyrus/Brocca's area/BA 44 and 45, superior frontal gyrus/BA 9, precentral motor gyrus/BA 4, anterior cingulate gyrus/BA 24 and 32), two samples from the temporal lobe (perirhinal cortex, superior temporal cortex/BA 22 (anterior) or 41/42 (posterior) and one sample from the parietal lobe (supramarginal gyrus/BA 40). These tissue samples were paraffin-embedded and 10µm thick sections cut and stained with 1) cresyl violet (0.5%) to label cells within the section, and 2) immunohistochemistry for abnormally phosphorylated tau protein (AT8 antibody; Pierce Endogen, Woburn, MA, USA; diluted 1:10,000) using peroxidase visualization and cresyl violet counterstaining, as previously published [23].

Neuron death and neuronal tau accumulation, rather than glial pathology, were hypothesised to be the pathological variables most directly related to neurological dysfunction. For this reason neuron and neuronal tau densities were measured as opposed to overall tau burden. Neuron loss and tau inclusion density in the substantia nigra was graded for severity (by GH) on a scale of 0-4 for neuron loss and 0-3 for tau-immunoreactive neuron density (a score of 0 representing no

change from control and 1 being least severe for each scale). For all other regions, the density of all cresyl violet-stained and tau-immunoreactive neurons was assessed at 200x magnification on a brightfield 'Zeiss' microscope using a previously published quantitative procedure [33, 34]. Briefly, for all cresyl violet-stained neurons five strips in each cortical region were randomly marked on the coverslip, and five equidistant locations marked along the longest span of the subcortical nucleus, then neurons within a 400X400µm optical field counted at each marked location with separate counts for the upper (II and III) and lower (V) cortical layers. In each section stained for tau protein, neurons with and without cytoplasmic inclusions (roughly spherical, or flame-shaped fibrillar aggregates) were counted in five microscopic fields randomly placed in the cortical and subcortical areas containing the greatest density of tau-immunoreactivity identified at low magnification. Quantitation performed by two independent researchers blind to case details gave an average inter-rater and intra-rater variability of  $\leq 10\%$  for all measurements.

In each region, the density of cresyl violet-stained neurons in each case (mean of five measurements) was calculated and standardised to the mean control neuron density for that region (standardised PSP-RS neuron density = (neuron density / mean control neuron density)\*100). The percentage neuronal loss (100% - neuron density (%)) was used for correlations to clinical indices. Secondly, for each region, the mean density of remaining neurons that were tau-immunoreactive was calculated as a percentage of the density of all remaining neurons in that case. The variation in counts across control cases is shown in Table 1.

**\*\*\*Table 1 about here\*\*\***

### ***Statistical analysis***

SPSS 10 software (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses and a p value  $<0.05$  accepted as the level of significance. Patients more than 1.5 standard deviations from mean control values were considered to have deficits. Mann-Whitney U tests were used to determine regions of significant neuronal loss and/or tau-immunoreactive neuronal inclusions for further regression analyses. A significance level of  $p < 0.01$  was used to determine those regions with substantive differences and also accommodate for multiple comparisons at this step. Step-wise multiple linear regressions were used to test the hypotheses outlined in the introduction in the PSP-RS cases by examining the relationships between the severity of their clinical scores in a particular domain and the severity of regional neuron loss and neuronal tau deposition,

controlling for age at onset and disease duration. For these analyses all regional pathological variables were included to determine the selectivity of any regional degeneration, as predicted in the hypotheses described in the introduction.

## **Results**

### ***Variation in the clinical deficits***

Global motor function was universally impaired with the majority of patients having moderate to severe motor deficits (Table 2). Two patients had relatively preserved gait (scores of 3/20 and 4/20) but otherwise there was little variation in the severity of motor impairment. Supranuclear gaze palsy was universally present, and severe in most cases, with only two patients scoring less than 50% in the oculomotor exam used for the PSP Rating Scale [21]. In 5/11 patients, the first symptoms were falls, dysarthria, dysphagia and/or bradykinesia. In the remaining patients the early clinical profile was dominated by behavioural changes (apathy, personality change, and disinhibition) with postural instability and falls within 2 years of symptom onset.

**\*\*\*Table 2 about here \*\*\***

### ***Cognitive Findings***

Cognitive and behavioural domain scores were more variable than motor impairment. While 9/11 (82%) were judged to meet criteria for dementia (ACE <82) the degree of dementia was moderate in the majority of patients (Table 2). As expected, the greatest deficits were in executive function with impaired letter fluency a ubiquitous finding (Table 2). Attention was impaired in the majority (80%) but the impairment was relatively mild compared to letter fluency. Despite almost universal dysarthria, language function was relatively mildly impaired with a mean 25% deficit and just half of patients experiencing a deficit by end-stage disease. Most patients showed a mild deficit in object perception. In contrast, greater variation was present in space perception scores, where a smaller number of patients showed a much more severe deficit (Table 2).

### ***Neuronal loss***

The degree of neuron loss varied considerably across the regions sampled (Table 3 and Figure 2), but was similar between cases suggesting a relatively homogeneous cohort. All subjects had neuron loss in the substantia nigra (average 65% loss), superior temporal (average 41% loss) and supramarginal gyrus (average 45% loss, Figure 1A,B and **Figure 2**). The inferior frontal gyrus had neuronal loss in all but one patient. There was no reduction in neurons in the orbito-frontal,

anterior cingulate and motor cortices and amygdala. Other regions examined had milder neuronal loss, including the caudate nucleus, superior frontal and perirhinal cortices.

**\*\*\*Figure 1, Figure 2 and Table 3 about here \*\*\***

### *Neuronal tau deposition*

Neuronal tau deposition in most regions was typical of PSP with predominantly rounded “globose” inclusions found within the cytoplasm of neurons (Figure 1D) and some additional “flame-shaped” neurofibrillary tangles occasionally found in other neurons. More diffuse and granular neuronal tau deposits were identified in the perirhinal cortex and amygdala. Tau-immunoreactive neurons were found at levels greater than normal in the substantia nigra, inferior frontal gyrus and primary motor cortex (Figure 2). In these regions neuronal tau was highly variable, with the focus of pathology in the substantia nigra. Tau deposition was significantly greater than controls in every region assessed except the perirhinal gyrus (Table 3 and Figure 2).

### *Clinicopathological Relationships*

To test the hypotheses outlined in the introduction, the relationships between the severity of cognitive behavioural subdomains and the severity of regional pathological variables was investigated using stepwise multiple regression analyses, controlling for age at onset and disease duration (see Table 4).

**\*\*\*Table 4 about here\*\*\***

Attention/orientation deficits related to the degree of tau deposition in the superior frontal gyrus rather than the cingulate cortex as hypothesised. Executive dysfunction was hypothesised to relate to superior frontal pathology. In keeping with this we found that reduced letter fluency related to tau deposition in the superior frontal region as well as the supramarginal cortices. In keeping with a priori hypotheses, overall language function related to neuronal tau deposition in the inferior frontal gyrus (Broca’s area) and to neuron loss in the perirhinal gyrus. Visuospatial dysfunction related to the degree of neuronal tau deposition in the supramarginal gyrus, consistent with our hypotheses. Global cognitive dysfunction was found to relate to an increase in neuronal tau deposition in the supramarginal gyrus only.

## Discussion

This study is the first to relate the extent of neuropathological changes post-mortem in PSP-RS to the typical array of cognitive dysfunction in PSP-RS. While the sample is relatively small in statistical terms due to difficulties in prospectively collecting longitudinal clinical data, the relative rarity of the disease and the obstacles of human tissue donation, it has provided the best platform currently available for an investigation of this nature. Although it is difficult to ascribe clinically measured neuropsychological deficits to discrete brain regions (given that networks of regions are likely to be degenerating) we confirm the considerable regional variability in frontal, temporal and parietal tau pathology, and that this variation relates to the severity of specific cognitive deficits. We also confirm a number of hypotheses derived from current literature, including the relationships between executive function and the superior dorsolateral prefrontal region, between language deficits and the perirhinal cortex, and between visuospatial impairment and the supramarginal gyrus. In addition, unexpected functional relationships were identified, as overall cognitive dysfunction related most to the severity of tau deposition in the supramarginal gyrus rather than to the frontal regions more commonly thought to represent the greatest deficits in PSP. The identification of the importance of supramarginal gyrus dysfunction in PSP-RS is novel and warrants further research.

Turning to the neuropathological aspects, abnormal neuronal tau deposition was found in practically all subcortical and cortical regions sampled. By contrast, neuronal cell loss was more circumscribed and involved predominantly the superior and inferior frontal cortices, the superior temporal gyrus, the perirhinal cortex and particularly the supramarginal gyrus. There was a disassociation between tau deposition and cell loss: the primary motor cortex contained significant tau deposition but no loss of neurones, while the perirhinal cortex demonstrated severe neuronal depletion without significant deposition of tau. This clearly suggests that additional, and possibly independent, processes contribute to the neuronal cell death in PSP.

The distribution of neuronal loss across cortical regions was somewhat surprising. In contrast to *in vivo* MRI studies [13, 14] we found no significant neuronal density change in the orbital frontal cortex, but instead the inferior and superior frontal regions showed substantial neuronal depletion. For instance, in the inferior frontal cortex there was on average 41% cell depletion and 90% of the individuals were affected. Of the temporoparietal regions sampled, the supramarginal gyrus showed the most profound neuronal loss (a mean at 45% loss and present in 100% of

cases). There was an almost equivalent degree of involvement of the superior temporal region. This pattern of neuronal loss does not seem to have been appreciated previously in the literature.

As predicted, there was a significant relationship between impaired executive function and tau deposition in the superior dorsolateral prefrontal cortex. Pathology in this region was also implicated in attention and concentration, as measured by the appropriate sub score of the ACE, rather than the anterior cingulate cortex, which was only mildly affected. We speculated that pathology in the supramarginal gyrus was likely to be important for visuospatial function which indeed was substantiated. The language dysfunction was more heterogeneous but again as predicted was correlated with pathology in the inferior frontal and perirhinal cortices. The composite language measure combined tests sensitive to syntactic impairment, the TROG, which would be expected to relate to inferior frontal (BA 44/45) [6] and measures of semantic processing, the GNT and PPT which would be expected to relate to perirhinal pathology [16]. An attempt to use individual tests revealed no significant effects due to small numbers of cases.

The overall level of cognitive impairment on the ACE also correlated with the extent of neuronal tau deposition in the supramarginal gyrus, as already mentioned this was also the most severely affected cortical brain region. Previous *in-vivo* and pathological work in PSP has focused on subcortical and frontal regions with the widespread belief that the cognitive syndrome of PSP reflects frontostriatal dysfunction. Our study suggests an involvement of supramarginal gyrus may be important for functional decline in PSP-RS. The finding of substantial pathology in the supramarginal gyrus is not, however, without precedent. An earlier study from our laboratories, based upon an independent PSP-RS pathological cohort, also showed that the most affected brain region was the supramarginal gyrus [41]. The function of this area, Brodmann area 40, is relatively obscure. It is known to be a multi-modal processing region with widespread connectivity [12, 40]. Functional brain imaging studies suggests a key role in spatial attention and spatial working memory [42]. It is quite plausible, therefore, that some of the cognitive deficits characteristic of PSP-RS are secondary to pathology in this region.

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The authors declare that they have no conflict of interest and have no further financial disclosures to make.

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Table 1. Variation in raw density counts per region for controls and Richardson syndrome cases

Region	Controls		Richardson's syndrome	
	Neuron density (/field)	Tau-ir neuron density (/field)	Neuron density (/field)	Tau-ir neuron density (/field)
Caudate nucleus	170 ± 14	1 ± 1	144 ± 25	3 ± 2
Inferior frontal cortex	65 ± 12	0 ± 1	38 ± 8	4 ± 2
Superior frontal cortex	101 ± 13	0 ± 1	79 ± 10	3 ± 2
Orbitofrontal cortex	134 ± 35	0 ± 1	111 ± 19	2 ± 1
Anterior cingulate cortex	111 ± 18	0 ± 1	100 ± 18	5 ± 3
Motor cortex	109 ± 16	0 ± 1	107 ± 17	6 ± 2
Superior temporal cortex	171 ± 31	0 ± 1	104 ± 17	3 ± 2
Perirhinal cortex	114 ± 21	9 ± 12	82 ± 7	13 ± 16
Amygdala cortex	95 ± 12	6 ± 14	87 ± 17	8 ± 8
Supramarginal cortex	171 ± 16	0 ± 1	93 ± 18	3 ± 1

Values are expressed as the average and standard deviation of the number of neurons or tau-ir neurons per microscopic field.

**Table 2.** Scores in each clinical domain for each group and the proportion of patients with deficits.

<b>Clinical Domain</b>	<b>Controls</b> (% maximum score <sup>a</sup> )	<b>Patients</b> (raw scores)	<b>Mean patient deficit</b> (% deficit from mean control score)	<b>% of patients with deficits<sup>g</sup></b>
Global motor function (/41)	0 ± 0 <sup>b</sup>	23 ± 9 (6-31)	60 ± 21 (16-75)	100
Global cognitive function (/100)	94 ± 12 <sup>c</sup>	62 ± 18 (32-89)	28 ± 19 (0-60)	80
Attention/Orientation (/18)	95 ± 25 <sup>c</sup>	12 ± 4 (6-18)	29 ± 21 (0-62)	80
Letter fluency (/44)	93 ± 5 <sup>c</sup>	14 ± 7 (6-26)	62 ± 20 (29-93)	100
Language (/203)	92 ± 20 <sup>d</sup>	140 ± 38 (75-200)	25 ± 21 (0-60)	55
Visuospatial (object perception, /70)	84 ± 8 <sup>e</sup>	45 ± 11 (30-59)	18 ± 15 (0-39)	71
Visuospatial (spatial perception, /30)	94 ± 15 <sup>e</sup>	19 ± 10 (0-30)	42 ± 36 (4-94)	57

<sup>a</sup>Scores are derived from published data of large control cohorts; <sup>b</sup>[22]; <sup>c</sup>[18]; <sup>d</sup>(ACE language: 99 ± 3 % [18], GNT: 80 ± 13 % [9], PPT: 96 ± 2 % [5], TROG: 100 ± 0 % [15], Category Fluency: 85 ± 2%).

<sup>g</sup>Proportion of PSP-RS patients more than 1.5 standard deviations from mean control scores.

**Table 3.** Variation in the pathological variables for controls and the PSP-RS groups

Anatomical Region		Pathological variable	Mean severity of	Patients affected <sup>b</sup> %	PSP-RS v's controls <i>p</i> -value <sup>c</sup>	
			pathology in PSP-RS % control density % remaining neurons			
<b>Basal ganglia</b>	Substantia nigra	neurons <sup>a</sup>	65 ± 16 (40-80)	100	<0.001	
		tau-ir neurons <sup>a</sup>	71 ± 15 (25-75)	100	<0.001	
	Caudate nucleus	neurons	15 ± 15 (0-50)	55	0.003	
		tau-ir neurons	2 ± 1 (1-6)	91	<0.001	
<b>Frontal lobe</b>	Inf. frontal cortex	neurons	41 ± 12 (13-56)	90	<0.001	
		tau-ir neurons	11 ± 6 (4-19)	100	<0.001	
	Sup. frontal cortex	neurons	21 ± 10 (4-33)	73	0.002	
		tau-ir neurons	4 ± 2 (0-7)	91	<0.001	
	Orbito-frontal cortex	neurons	18 ± 14 (0-32)	0	NS	
		tau-ir neurons	2 ± 1 (0-3)	55	<0.001	
	Ant. cingulate cortex	neurons	10 ± 16 (0-35)	18	NS	
		tau-ir neurons	5 ± 3 (1-11)	91	<0.001	
	Motor cortex	neurons	1 ± 16 (0-30)	9	NS	
		tau-ir neurons	5 ± 2 (2-9)	100	<0.001	
	<b>Temporal lobe</b>	Sup. temporal cortex	neurons	41 ± 10 (28-53)	100	<0.001
			tau-ir neurons	2 ± 2 (0-7)	80	0.007
Perirhinal cortex		neurons	28 ± 6 (19-35)	67	0.002	
		tau-ir neurons	10 ± 10 (2-29)	13	NS	
Amygdala		neurons	9 ± 18 (0-33)	30	NS	
		tau-ir neurons	8 ± 7 (0-24)	78	0.003	
<b>Parietal lobe</b>	Supramarginal cortex	neurons	45 ± 10 (17-57)	100	<0.001	
		tau-ir neurons	3 ± 1 (1-5)	82	0.002	

<sup>a</sup> Percentage cell loss and neuronal tau density calculated from severity scores, see methods, <sup>b</sup> Proportion of PSP-RS patients more than 1.5 standard deviations from mean control scores, <sup>c</sup> Mann-Whitney U test

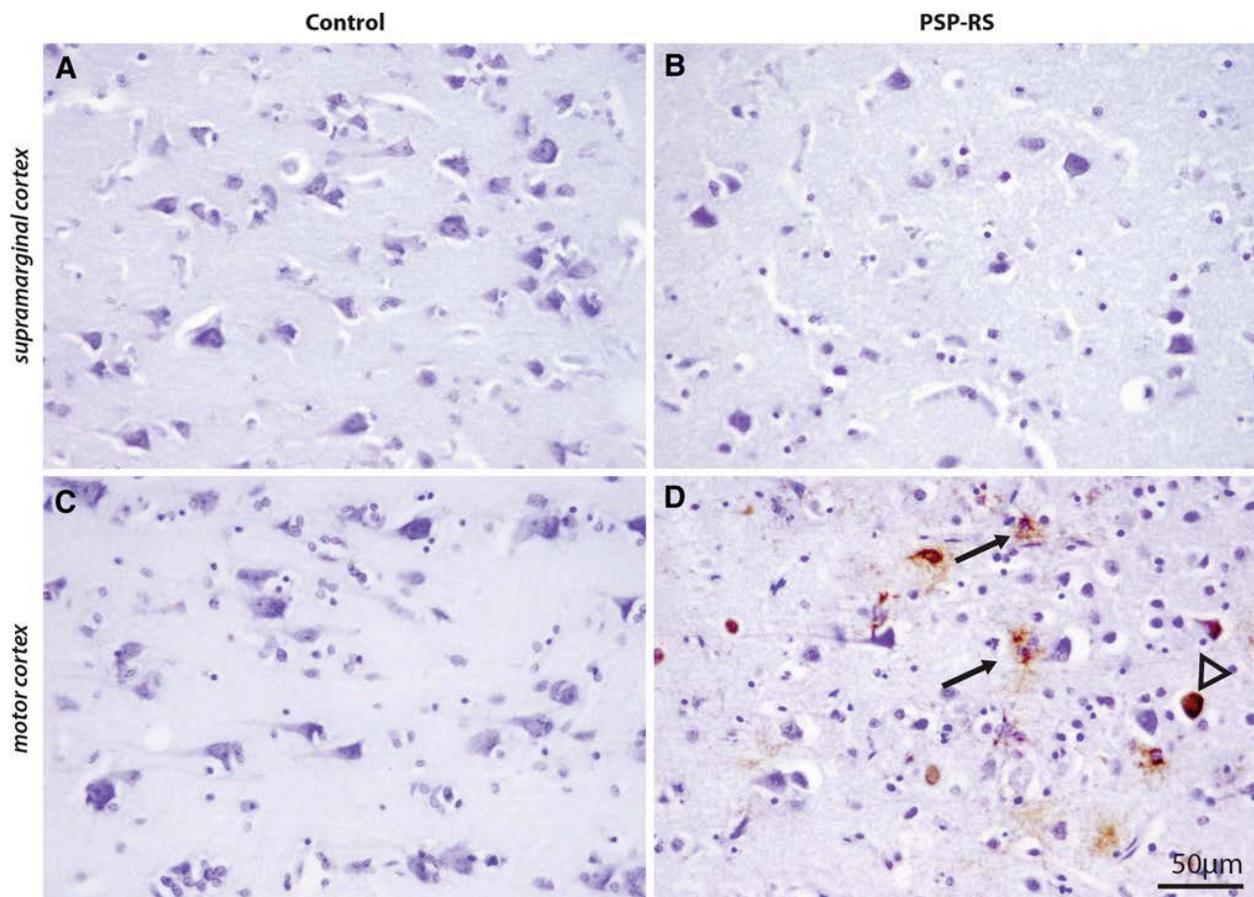
**Table 4.** Relationships between cognitive deficits and regional neuropathology in PSP-RS

Clinical deficit	Correlates		<i>p</i> -value <sup>a</sup>	Beta <sup>a</sup>
	Pathology	Region		
Global motor function	no correlates			
Global cognition	↑ neuronal tau	Supramarginal gyrus	0.026	0.813
Attention/Orientation	↑ neuronal tau	Superior frontal gyrus	0.009	0.878
Letter fluency	↑ neuronal tau	Supramarginal gyrus	0.023	0.546
	↑ neuronal tau	Superior frontal gyrus	0.026	0.525
Language	↓ neurons	Perirhinal gyrus	<0.001	0.875
	↑ neuronal tau	Inferior frontal gyrus	0.020	0.230
Visuospatial	↑ neuronal tau	Supramarginal gyrus	0.007	0.967

<sup>a</sup>Results of step-wise linear regression

**Figure 1. Neuron density changes and tau deposition in the supramarginal and primary motor cortices**

Photomicrographs are of cortical layer 3 at 200X magnification in 10µm sectioned, paraffin-embedded tissue. **A and B:** Cresyl violet staining of supramarginal cortex in control and PSP-RS respectively. Severe neuron loss is apparent in PSP-RS. **C and D:** Tau immunohistochemistry, counterstained with cresyl violet in the primary motor cortex in control and PSP-RS respectively. A relatively high density of neuronal tau deposition, including globose tangles (arrowheads), as well as tufted astrocytes (arrows) is present in PSP-RS in the presence of relatively mild neuron loss. The scale bar in D is equivalent for all photomicrographs.



**Figure 2. Distribution of neuron loss and tau pathology**

Pictorial representation of the distribution of neuronal loss (left diagrams) and tau pathology (right diagrams) in subcortical and cortical regions sampled in Richardson's syndrome. The pictures illustrate that there is somewhat of a continuous frontotemporoparietal strip of

neuron loss in the cortex. Also that tau deposition in the cortex relative to that in the substantia nigra is relatively mild, although widespread. Abbreviations are as follows;

- |            |   |              |                                    |
|------------|---|--------------|------------------------------------|
| <b>SN</b>  | substantia nigra                                | <b>Motor</b> | precentral motor cortex, BA4       |
| <b>Cd</b>  | caudate nucleus                                 | <b>AC</b>    | anterior cingulate gyrus, BA 24/32 |
| <b>Amg</b> | amygdala nucleus                                | <b>Prh</b>   | perirhinal cortex                  |
| <b>SF</b>  | superior frontal cortex, BA 9                   | <b>ST</b>    | superior temporal cortex BA 22     |
| <b>IF</b>  | inferior frontal gyrus/Brocca's area, BA 44/ 45 | <b>SMG</b>   | supramarginal gyrus,, BA 40        |

