

# Neuropsychological follow up in patients with Parkinson's disease, striatonigral degeneration-type multisystem atrophy, and progressive supranuclear palsy

Paola Soliveri, Daniela Monza, Dominga Paridi, Francesco Carella, Silvia Genitrini, Daniela Testa, Floriano Girotti

## Abstract

**Objectives**—Impairment of executive function is frequent in Parkinson's disease (PD), striatonigral degeneration-type multisystem atrophy (SND), and progressive supranuclear palsy (PSP); sometimes frank dementia is also present. However, the progression of cognitive decline has not been adequately studied. The objectives were to delineate the progression of cognitive impairment in these parkinsonisms and to elucidate inter-disease differences.

**Methods**—Twenty three patients with SND and 21 with PSP, referred consecutively, and 18 patients with PD matched for severity of parkinsonism were compared on a comprehensive battery of cognitive tests and motor invalidity scales. A mean of 21 months later (range 18–24 months) the patients were called for retesting.

**Results**—Only 12 patients with PD (66.6%), 14 with SND (60.8%), and 11 with PSP (52.4%) were retested; those who dropped out refused, had died, or were too disabled. The patients with PSP performed worse than patients with PD or SND in the short tale, verbal fluency, visual search, and Benton tests at first evaluation. Overall cognitive performance was similar in the PD and SND groups except that the SND group did significantly worse on the verbal fluency test. Between group comparison of changes in scores from first to second evaluation showed that patients with PSP deteriorated significantly in the Nelson test compared with patients with PD or SND, and that patients with PSP or SND declined significantly on the visual search test compared with patients with PD. There was no difference between the groups for motor decline. Two patients with PSP were demented (DSM IV criteria) at first evaluation and six at second evaluation; no patients with PD or SND were demented at either evaluation.

**Conclusions**—The greater decline of patients with PSP in attention, set shifting, and categorisation abilities is probably related to the conspicuous frontal deafferentation associated with direct premotor and prefrontal involvement, and to dys-

## function of the midbrain ascending activating system, known to occur in PSP.

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**Keywords:** Parkinson's disease; striatonigral degeneration-type multisystem atrophy; progressive supranuclear palsy; neuropsychological follow up

Parkinson's disease (PD), multisystem atrophy (MSA), and progressive supranuclear palsy (PSP) are the commonest degenerative parkinsonisms; all are characterised by an akinetic-rigid syndrome. Although motor impairment is the hallmark of these diseases, cognitive dysfunctions, sometimes with frank dementia, are often seen, especially in PSP.<sup>1</sup> Furthermore, different patterns of cognitive impairment have been identified<sup>2</sup> and may be of use in clinical diagnosis especially in early disease stages when the clinical signs of these conditions often overlap. The earliest and most evident cognitive findings in all three conditions are impaired executive functions,<sup>3–5</sup> which correlate with disruption of the corticostriatal pathways.<sup>6</sup> Although the common clinical experience is that cognitive deterioration is progressive, few longitudinal studies have been performed and most have been concerned with PD only.

In PD, memory, visuomotor, and executive function deficits have been described in the early stages,<sup>7</sup> and as the disease progresses a few patients develop dementia,<sup>8</sup> due presumably to dysfunction of the subcortico-cortical dopaminergic, noradrenergic, and cholinergic circuits<sup>9</sup> or to lesions typical of Alzheimer's or diffuse Lewy body disease.<sup>10</sup> Portin and Rinne found that 70% of their patients with PD deteriorated significantly on cognitive evaluation over an 8 to 10 year period<sup>11</sup>. By contrast Growdon and Corkin reported fairly stable cognitive performance in their patients with PD in a 6 month to 1 year follow up study.<sup>12</sup> In a more recent 12 month follow up study, Starkstein *et al*<sup>13</sup> reported greater cognitive decline in patients with PD with major depression than in those with minor depression or who were not depressed.

Bayles *et al*<sup>14</sup> compared worsening of MMSE score in patients with PD and age matched normal controls and found that 22% of patients but no controls deteriorated significantly over 2 years. The patients with cognitive deterioration did not differ significantly in age,

Department of  
Neurology, Istituto  
Nazionale Neurologico  
"C Besta", Via Celoria  
11, 20133 Milano, Italy  
P Soliveri  
D Monza  
D Paridi  
F Carella  
S Genitrini  
D Testa  
F Girotti

Correspondence to:  
Dr Floriano Girotti, Istituto  
Nazionale Neurologico "C  
Besta", Via Celoria 11,  
20133 Milano, Italy  
panigada@istituto-besta.it

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Table 1 Characteristics (means (SD)) of PD, SND, and PSP patients at initial evaluation

	PD (n=18; 10 M, 8 F)	SND (n=23; 10 M, 13 F)	PSP (n=21; 14 M, 7 F)	p Value*
Age (y)	57.8 (6.1)†	58.7 (7.6)‡	63.2 (6.5)†‡	0.04
Education (y)	8.4 (2.8)	7.3 (3.3)	8.2 (4.6)	0.34
Disease duration (y)	10.7 (4.7)†§	4.0 (2.1)§	3.1 (2.6)†	<0.0001
ADL scale	15.8 (5.9)	16.2 (5.9)	17.0 (6.1)	0.08
Hoehn and Yahr stage	3.4 (0.4)	3.6 (0.6)	3.6 (0.6)	0.20

\*Between group comparison by Kruskal-Wallis ANOVA.

Post hoc comparisons by Mann-Whitney U test: p<0.05; †PSP v PD, ‡PSP v SND, §PD v SND.

education, disease duration, or severity of bradykinesia from those who were cognitively stable; however, the first group were taking dopamine agonists and the second group were not. Palazzini *et al*<sup>15</sup> studied the progression of motor and cognitive impairment in patients with PD over a mean of about 7 years, during which time 18% developed dementia. The demented patients were older and had greater motor impairment and more psychotic symptoms than the non-demented patients, perhaps in part because of greater susceptibility to the toxic effects of dopaminergic therapy.

Cognitive decline and behavioural abnormalities are more frequent in PSP than PD, and are often present in the early stages of disease.<sup>16</sup> Pillon *et al*<sup>17</sup> compared the severity and specificity of cognitive impairment in Alzheimer type dementia, Huntington's disease, PSP, and PD after stratifying the patients according to global intellectual deterioration. They found that the frequency of dementia was much greater in patients with PSP than those with PD (58% v 18%); in addition patients with PSP had significantly lower scores in frontal and behavioural tests than patients with PD, at all levels of cognitive impairment. Similar findings were reported by Robbins *et al*<sup>18</sup> and Monza *et al*<sup>18</sup> in studies that compared PSP, MSA, and PD. Pillon and Dubois followed up a group of 24 patients with PSP and found that the frequency of dementia increased greatly (from 37.5% to 70%) over the 15 month observation period.<sup>19</sup>

Several cross sectional studies on MSA<sup>4-5</sup> have reported a pattern of cognitive compromise similar to that in PD, with specific impairment in executive functions. However, to our knowledge, no longitudinal studies have been published on cognition in MSA.

It is evident, therefore, that literature findings on longitudinal cognitive decline in PD are rather disparate, probably in relation to the various study designs and differing patient selection criteria; whereas cognitive functions in MSA and PSP have mainly been examined by cross sectional studies. We therefore set about investigating the progression of cognitive impairment in patients with PSP, MSA, and PD by monitoring cognitive and motor performance over time.

### Patients and methods

Twenty three patients with striatonigral degeneration-type (SND) MSA (10 men and 13 women) and 21 patients with PSP (14 men and seven women) consecutively referred to our institute from June 1993 to July 1996 as

outpatients or admitted patients were enrolled. Eighteen patients with PD (10 men and eight women) were selected as having the same disease severity as the patients with PSP or SND, as assessed by the Hoehn and Yahr scale and the activity of daily living (ADL) section of the unified Parkinson's disease rating scale (UPDRS, table 1).<sup>20</sup> Probable PD was diagnosed according to the UK Brain Bank criteria,<sup>21</sup> probable SND-type MSA according to Quinn's criteria<sup>22</sup> and probable PSP according to the criteria of Litvan *et al*.<sup>23</sup>

The clinical diagnoses of SND and PSP were supported by MRI studies, which showed putaminal signal hypointensity in T2 weighted images (suggesting deposition of iron or other paramagnetic substances) in all patients with SND, and slight to severe midbrain atrophy in all patients with PSP.<sup>24</sup> Dementia and major depression were diagnosed according to DSM IV criteria.<sup>25</sup> Based on the Edinburgh Inventory<sup>26</sup> all but two patients (one with PD and one with PSP) were right handed. All patients with PD or SND were receiving levodopa; seven patients with PD were also taking dopamine agonists. All patients with PD and six with SND had a good levodopa response and were experiencing motor fluctuations and dyskinesias. Ten of the 21 patients with PSP were receiving levodopa with small benefit. The cognitive examination was performed when patients on levodopa were at peak motor response.

Neuropsychological examination comprised the mini mental state examination (MMSE) a screening test for mental decay<sup>27</sup>; the Raven progressive matrices, which measures logical reasoning and visuospatial organisation<sup>28</sup>; the short tale test for long term verbal memory<sup>29</sup>; the phonemic verbal fluency test which evaluates word searching strategy<sup>30</sup>; the visual search test, to assess attention and visual scanning<sup>30</sup>; the visuospatial orientation line test of Benton<sup>31</sup> which assesses the visual ability to distinguish the orientation of lines in space; and the Nelson modification of the Wisconsin card sorting test<sup>32</sup> which examines set shifting and categorisation abilities. In the last test we scored the number of sorting categories reached by the patients. Raven test scores were adjusted for age and education according to Basso *et al*<sup>33</sup>; MMSE scores were similarly adjusted using the method of Measso *et al*.<sup>34</sup> Other cognitive test scores were adjusted for age and education according to Spinnler and Tognoni,<sup>35</sup> except for the Nelson test, for which this adjustment is not available.

Only 12 patients with PD (66%), 14 with SND (60%), and 11 with PSP (52%) were retested a mean of 21 months (range 18–24 months) after the initial evaluation: five patients with PD, one with PSP, and two patients with SND refused; one patient with PD, five with SND, and six with PSP were too disabled to attend for retesting; and two with SND and three with PSP died before retesting.

### STATISTICAL ANALYSIS

Only the patients who presented for both tests were included in the statistical analyses.

Table 2 Characteristics (means (SD)) of PD, SND, and PSP patients who completed the follow up at initial evaluation.

	PD (n=12; 7 M, 5 F)	SND (n=14; 5 M, 9 F)	PSP (n=11; 5 M, 6 F)	p Value*
Age (y)	57.7 (6.3)	59.6 (6.4)	62.8 (6.5)	0.20
Education (y)	8.6 (2.8)	7.2 (3.7)	8.0 (4.5)	0.31
Disease duration (y)	12.1 (5.0)††	3.4 (1.4)‡	2.4 (1.0)†	<0.0001
ADL scale	12.3 (6.6)††	16.6 (6.2)‡	19.7 (6.5)†	0.02
Hoehn and Yahr stage	3.1 (0.3)††	3.6 (0.3)‡	3.6 (0.4)†	0.002

\*Between group comparison by Kruskal-Wallis ANOVA.

Post hoc comparisons by Mann-Whitney U test: p<0.05; †PSP v PD, \*PSP v SND, ‡PD v SND.

Table 3 Between group comparison (means (SD)) at initial evaluation of cognitive results of PD, SND, and PSP patients who completed the follow up. Cognitive test scores except the Nelson test's were adjusted for age and education<sup>33-35</sup>

	PD (n=12; 7 M, 5 F)	SND (n=14; 5 M, 9 F)	PSP (n=11; 5 M, 6 F)	p Value*
MMSE	27.7 (2.1)	27.4 (1.5)	25.5 (2.7)	0.10
Raven test	29.0 (6.1)	26.2 (6.1)	22.2 (6.7)	0.08
Short tale test	12.1 (4.2)†	11.8 (3.4)‡	8.0 (2.9)††	0.01
Verbal fluency	37.1 (13.8)†§	27.0 (5.9)‡§	15.1 (7.6)††	0.0001
Visual search test	44.6 (4.1)†	43.9 (9.5)‡	32.3 (14.7)††	0.03
Benton's test	22.8 (3.5)†	23.4 (6.0)‡	14.4 (6.4)††	0.001
Nelson's test (No of categories)	4.3 (2.1)	4.6 (1.6)	3.0 (1.7)	0.12

\*Between group comparison by Kruskal-Wallis ANOVA.

Post hoc comparisons by Mann-Whitney U test: p<0.05; †PSP v PD, ‡PSP v SND, §PD v SND.

Between group comparisons employed the non-parametric Kruskal-Wallis analysis of variance (ANOVA). Post hoc comparisons with the non-parametric Mann-Whitney U test were applied where appropriate. Linear correlations between indices of cognitive and motor decline using Pearson's correlation coefficient were sought when useful to clarify the results.

## Results

### INITIAL EVALUATION

Although the PD group was selected to have the same disease severity as the SND and PSP groups, evaluation considering only the patients who presented for both tests showed that at the outset the three groups differed significantly in motor performance as assessed by the Hoehn and Yahr and ADL scales, with patients with PD less compromised than patients with SND or PSP. The PD group also had longer disease duration than the SND and PSP groups, but there were no differences in age or education (table 2). Post hoc comparison of the dropout and retested patients in each disease group for illness duration, Hoehn and Yahr, ADL, and MMSE showed a significant difference only for patients with PD, where mean illness duration was shorter (8.0 (SD 3.0) v 12.1

Table 4 Between group comparison (means (SD)) of percentage changes in cognitive and motor scores in PD, SND, and PSP patients. Cognitive test scores except the Nelson test were adjusted for age and education

	PD (n=12; 7 M, 5 F)	SND (n=14; 5 M, 9 F)	PSP (n=11; 5 M, 6 F)	p Value*
MMSE	-0.4 (6.2)	-1.8 (9.1)	-17.6 (25.9)	0.15
Raven test	+3.3 (13.3)	+1.5 (24.4)	-27.3 (45.4)	0.25
Short tale test	-1.6 (29.3)	-0.1 (25.4)	-14.0 (41.2)	0.89
Verbal fluency	-2.0 (18.2)	-19.2 (23.9)	-18.3 (33.0)	0.14
Visual search test	+0.8 (11.6)†§	-18.1 (22.3)§	-40.0 (43.7)†	0.03
Benton's test	-8.1 (16.1)	-20.1 (21.6)	-44.5 (40.6)	0.11
Nelson's test (No of categories)	+14.8 (46.1)†	-5.8 (62.4)‡	-62.7 (54.5)††	0.01
ADL scale	+37.9 (40.1)	+57.1 (37.5)	+80.3 (76.1)	0.16
Hoehn and Yahr stage	+13.9 (22.3)	+16.2 (15.7)	+8.0 (19.4)	0.14

A plus sign indicates increasing score over time, a minus sign indicates score reduction.

\*Between group comparison by Kruskal-Wallis ANOVA.

Post hoc comparisons by Mann-Whitney U test: p<0.05; †PSP v PD, ‡PSP v SND, §PD v SND.

(SD 5.0) years, p=0.03) and mean ADL score was greater 22.5 (SD 5.3) v 12.3 (SD 6.6), p=0.01) in those who dropped out. Motor disability, as assessed by the ADL scale, was lower in patients with PSP who dropped out, but not significantly so.

Between group comparison at first evaluation on patients who attended both test sessions showed that the PSP group performed significantly worse than the PD and SND groups in the short tale, verbal fluency, visual search and Benton's test, while the SND group was significantly worse than the PD group only in the verbal fluency test (table 3). Two patients with PSP but no patients with PD or SND had an MMSE score<24 (indicating dementia); the two patients with PSP were also demented according to DSM IV criteria. None of the patients had major depression according to DSM IV criteria.

### SECOND EVALUATION

At the second evaluation the three groups still differed significantly in disease severity as assessed by the Hoehn and Yahr (p=0.003) and ADL (p=0.001) scales. Post hoc comparison showed that the mean Hoehn and Yahr score for patients with PD (3.5 (SD 0.7)) was significantly lower than those of the SND and PSP groups (4.1 (SD 0.6) and 4.5 (SD 0.5) respectively). The mean ADL score of the PD group (16.7 (SD 9.0)) was significantly lower than those of the SND and PSP groups (25.1 (SD 8.4) and 31.9 (SD 5.6) respectively); in addition, patients with SND scored significantly lower than the patients with PSP.

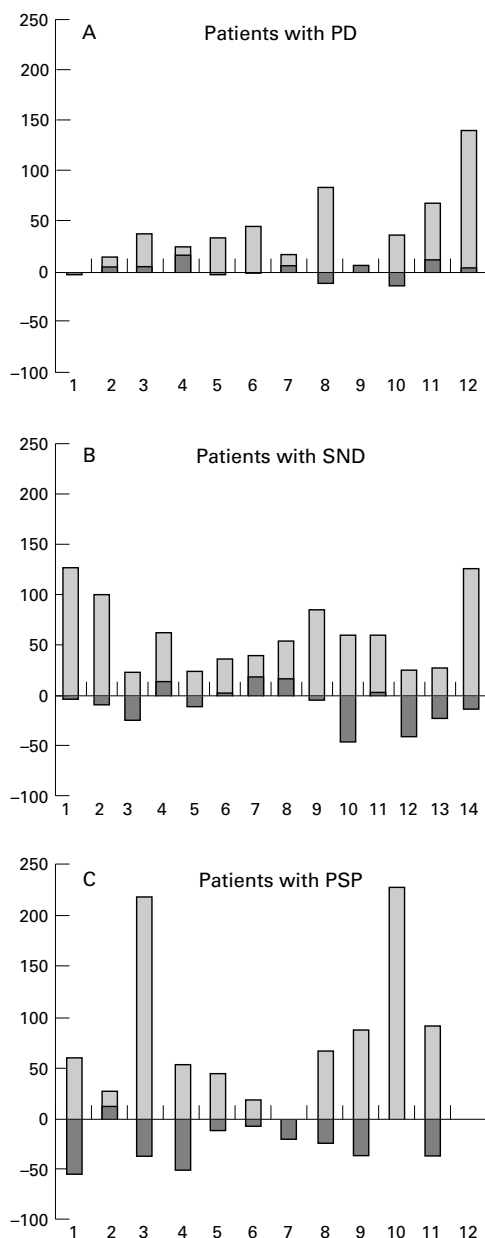
Between group comparison of percentage changes in cognitive and motor scores between the first and second evaluations showed significantly greater deterioration of performance in the Nelson test by the PSP group compared with the other two groups and in the visual search test by the PSP and SND groups compared with the PD group. The same statistical test failed to show significant differences between the groups in the progression of motor compromise (table 4).

Six patients with PSP (54%) but no patients with PD or SND had MMSE scores below 24 at second evaluation; the six patients with PSP also met the DSM IV criteria for dementia. Two of the six demented patients with PSP had dementia at the initial evaluation.

A global cognitive decay index (DI) was calculated for each patient as the algebraic sum of the percentage change in each cognitive test, divided by the number of tests. Percentage changes (deterioration) in DI and ADL scores  $\geq 30\%$  were arbitrarily considered as "clinically significant" markers of mental decay and motor disability, respectively.

None of the 12 patients with PD had a DI  $\geq 0\%$ , but in seven the ADL score worsened by  $\geq 30\%$ . In the SND group, two of 14 patients had a DI  $\geq 30\%$  and nine had an ADL change  $\geq 0\%$ . Of the 11 patients with PSP, six had a DI of  $\geq 30\%$  (all of whom were demented according to DSM IV) and eight had an ADL change  $\geq 0\%$  (figure).





Change in cognitive (dark bars) and motor performance (light bars) of individual patients with time.

No significant correlations were found between the indices of cognitive (DI) and of motor decline (ADL percentage change). Furthermore, we found no within group correlation of percentage changes in Nelson and visual search scores with motor disability at first evaluation, or with changes in ADL scores.

### Discussion

At first evaluation the PSP group did worse than the PD and SND groups in the short tale, verbal fluency, visual search, and Benton tests. This is in agreement with the existing literature, which finds greater cognitive impairment in patients with PSP than patients with PD or SND<sup>4,5</sup> when the groups are well matched for age and education (as was the case in the present study).

Greater cognitive impairment in PSP is presumably due to the marked deafferentation,

particularly of the premotor and prefrontal areas, which occurs as a result of the striatal-thalamocortical pathway alteration well known in this disease.<sup>36</sup> However, dysfunction of the ascending reticular formation of the pontomesencephalic tegmentum,<sup>37</sup> which projects diffusely to prefrontal cortical areas, as well as direct cortical alterations, recently demonstrated in prefrontal and premotor areas,<sup>38,39</sup> could also play a part in mental decay in PSP.

Analysis of the percentage changes in cognitive and motor performance over time showed that the groups differed significantly only on the visual search test, where deterioration was more marked in SND and PSP than in PD, and on the Nelson test, where deterioration was greater in PSP than in PD and SND. From clinical experience and the results of previous cross sectional studies,<sup>4,5</sup> we expected to see increasingly marked differences between the groups on cognitive performance with time, with PSP deteriorating faster. Instead, deterioration in most cognitive tests did not differ greatly between the three groups. High dropout rate, large within group variation in test performance, a floor effect in test performance, and relatively short follow up may all have contributed to this.

Post hoc comparison showed that dropout patients with PD had shorter disease duration and greater mean motor disability at first evaluation than the remaining patients with PD, whereas dropout patients with SND or PSP did not differ significantly in any clinical features from those who reattended. However, most of the patients with PD were reluctant rather than unable to come, whereas the main reason why patients with PSP or SND did not attend for retesting was, they said, because of motor disability; in addition two patients with SND and three with PSP died before retesting. It is reasonable to suppose that the patients who did not attend, especially the patients with PSP or SND who complained of disability, deteriorated in all respects more than those who did attend.

The large within group variation in test performance in the patients with PSP or SND, evident by inspection of the SDs in table 4, may also have contributed to the lack of significant differences between the groups. One reason for this intergroup variability could have been differences in disease stage within the groups. However, there were no significant correlations between cognitive decline (DI) and motor decline (as assessed by percentage changes). Furthermore decline in Nelson and visual search tests did not correlate either with age or motor disability at first evaluation, or deterioration in ADL score, within each group. For this reason we do not think that differences in initial motor compromise had any effect on the mean cognitive changes over time.

This lack of correlation between motor and cognitive indices is illustrated graphically in the figure where patients with PSP or SND who deteriorated most cognitively were not those with the greatest deterioration in motor performance. Neurofibrillary tangles are normally present in the basal ganglia and

brainstem of necropsied patients with PSP; however, recent pathological studies have shown that such lesions may also occur, to a variable extent, in the premotor cortex, prefrontal cortex, and hippocampus.<sup>38–39</sup> It may be, therefore, that the variable presence of these lesions<sup>40</sup> is responsible for the variability of cognitive deterioration found in our patients with PSP, with greater DI perhaps related to greater compromise of the cortical premotor and prefrontal areas.

There may also have been a floor effect: performance was poor at initial evaluation in the verbal fluency test and Benton's test in patients with PSP, and the verbal fluency test in patients with SND.

Short follow up was probably the main reason for the lack of deterioration seen in the PD group. Although PD seems to progress at a slower pace than PSP and SND, significant cognitive deterioration becomes evident with sufficient follow up. In a previous longitudinal study we found that 18% of patients with PD became demented 7 years after initial evaluation.<sup>15</sup> However, in a longitudinal study by Bayles *et al.*,<sup>14</sup> the duration (24 months) of which was comparable with ours, 20% of patients with PD deteriorated by four or more points in MMSE score (defined as significant). None of our patients with PD had similar changes in MMSE score and none was demented at second evaluation. Perhaps the smaller sample size of our study (12 *v* 77 in Bayles *et al.*) and high dropout rate of our patients with PD (34%) also contributed to these differences.

For motor disability, we found that although this deteriorated significantly over time in all groups, between group differences in percentage changes in motor performance were not significant. This is again at variance with clinical experience and the literature. Faster disease progression and greater mortality compared with PD have been reported in both PSP<sup>41–42</sup> and SND.<sup>43–44</sup> The result is probably due to patient selection by dropout: as noted dropout patients with PD had more severe illness at first evaluation than those who were retested; and although dropout patients with PSP or SND did not differ at the outset from those who reattended, at the time of second evaluation five had died and the others gave severe motor disability as a reason for not reattending.

Nevertheless, we did find significant deterioration differences between the groups in the Nelson and visual search tests, indicating that these tests are the most sensitive in showing differences between degenerative parkinsonisms with time. The Nelson test taps executive functions, and worse performance in PSP is probably related to the greater striatofrontal pathway dysfunction documented in this condition.<sup>36</sup> This is also in agreement with the finding of Pillon *et al.*<sup>1</sup> of greater impairment in "reactive flexibility" in their patients with PSP which they contrasted with impairment in "spontaneous flexibility"<sup>45</sup> in their patients with SND.

Both patients with PSP and those with SND deteriorated significantly more than patients

with PD on the visual search test. Although this test mainly examines focused attention, it also taps other cognitive functions such as ability to shift between contrasting responses, speed of cognitive processing, and visual scanning ability. Previous publications have noted attentional impairment, deficit in cognitive set shifting ability,<sup>5</sup> and bradyphrenia in PSP.<sup>46–47</sup>

The continuation of focused attention requires integrated activity of brainstem, thalamus, and neocortex. The critical brainstem structures involved in this activating system are the reticular formation and adjacent nuclei (raphe nucleus, locus coeruleus, and segmental nuclei) whereas the intralaminar, midline, and reticular thalamic nuclei<sup>48</sup> are the most important relay stations; these project diffusely to multimodal associative cortical areas, among which the prefrontal areas are the most important for attention.<sup>49</sup> It is not surprising, therefore, that attention was particularly impaired in PSP, as distinct alterations in the midbrain tegmentum and less prominent damage to premotor and prefrontal areas have been demonstrated pathologically.<sup>38–39</sup> Marked alterations in the superior colliculi and the periaqueductal region could well be responsible for the poor performance of patients with PSP in this test, as also found by Kimura *et al.*<sup>50</sup>

It is more difficult to account for the visual search deterioration in patients with SND. This could have been due to degeneration of the striatal-cortical circuits, although this is less prominent than in PSP. Because cortical oligodendroglial bodies in MSA are restricted to the motor and premotor cortex<sup>51</sup> and their relation to cell damage is not fully understood; their pathogenetic role in the cognitive deficits of patients with MSA is unclear.

The similarity between patients with PD and those with SND in cognitive performance emphasises the role of subcortical deafferentation in cognitive impairment in these diseases. However, patients with SND deteriorated slightly more than those with PD and this may be due to neuronal loss in the caudate nucleus in SND.<sup>52</sup>

In conclusion, our longitudinal study has shown that patients with PSP undergo greater cognitive impairment than patients with SND or PD, and this would correlate with greater anatomical compromise in PSP involving both subcortical (pallidum, mesencephalic tegmentum, striatum) and cortical structures (prefrontal and premotor cortex). Progression to dementia was prominent in PSP but not uniform in all patients, and the differences may be related to differential development of neurofibrillary tangles in the cortex. The cognitive performance of patients with SND was similar to that of patients with PD both at first and second evaluations; however, the SND group was characterised by slightly greater worsening with time. Longitudinal studies with serial examinations over a short period of time on greater numbers of patients are required to further elucidate the pattern of cognitive regression in these diseases.

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