Cognitive Dysfunction and Impaired Organization of Complex Motility in Degenerative Parkinsonian Syndromes

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Background: A frontostriatal pattern of cognitive decline, consisting of a frontal lobe–like syndrome without genuine cortical defects such as amnesia, apraxia, aphasia, or agnosia, is well established in basal ganglial diseases. Recent pathological investigations, however, have again noted cortical damage in progressive supranuclear palsy (PSP), suggesting that cortical defects could be present.

Objectives: To delineate the pattern of cognitive impairment and to detect higher-order motor impairments (including ideomotor apraxia) in parkinsonian syndromes.

Patients and Methods: We assessed ideomotor apraxia, and simple and sequential tapping in patients with Parkinson disease, multiple system atrophy, and PSP with similar disease severity, age range, and education. We also administered a comprehensive battery of neuropsychological tests to examine general intelligence, memory, executive functions, attention, and visuospatial orientation. The results were compared between groups and with a matched normal control group.

Results: Sequential tapping and the imitation of sequences of gestures were impaired in all patient groups, with patients with PSP performing worse than the other groups. Based on ideomotor apraxia scores and a qualitative analysis of errors, 3 patients with PSP and 2 with multiple system atrophy were considered apraxic. General intelligence and executive functions were compromised in all patient groups. The impairment of patients with PSP was more pervasive than that of the other groups, and included compromise of visuospatial functions, attention, and memory. Discriminant analysis of all cognitive and motor tests showed that the tapping and ideomotor apraxia tests best identified the patients vs control subjects.

Conclusions: The presence of cortical as well as subcortical damage in patients with PSP and those with multiple system atrophy is indicated by the presence of pervasive cognitive and motor disturbances in the former, substantial motor disorganization in the latter, and the finding of ideomotor apraxia in some patients with these diseases. Furthermore, the discovery that tests of motor and gesture best identified all patients vs control subjects is consistent with the existence of a common motor disorganization in these parkinsonian syndromes, in agreement with the known damage to the corticostral pathways in these conditions.


The fully developed clinical pictures of Parkinson disease (PD), multiple system atrophy (MSA), and progressive supranuclear palsy (PSP) are usually distinctive, but uncertainties may arise at disease onset, and misdiagnoses are often reported in clinicopathological series.1,2 According to a recent review,3 neuropsychological testing may assist the clinical diagnosis of these diseases because PD and MSA are characterized by the absence of dementia, despite planning and recall deficits in the early stage of the diseases, whereas more severe disturbances of memory, executive functions, and behavior, often amounting to frank dementia, are present relatively early in PSP.

Following criticisms in the mid-1980s4 of the concept of subcortical dementia as applied to basal ganglial diseases, the notion of subcortical frontal decay has been used5 to describe a frontal lobe–like syndrome without genuine amnesia, aphasia, apraxia, or agnosia. A frontal lobe–like syndrome implies a conspicuous impairment of executive functions important for effective, self-sufficient adult behavior, including goal formulation, planning, carrying out goal-directed plans, and performing effectively.5 In patients with PD, MSA, and PSP, impairment of these functions is considered the earliest and most pronounced facet of cognitive deterioration,6,7 with dysfunction of the various striatofrontal circuits being regarded as the anatomical basis of these and the motor function impairments.8

The prefrontal areas of the cortex and their connections with the caudate nucleus are involved in the control of cognition and behavior, while the connections between the striatum and the premotor areas, especially the supplementary motor area (SMA), are implicated in the control of complex motility, particularly when guided by internal cues.5

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SUBJECTS AND METHODS

Nineteen patients with MSA (7 men and 12 women) and 19 patients with PSP (10 men and 9 women) consecu-
tively referred to the Istituto Nazionale Neurologo, Mi-
lano, Italy, from the beginning of December 1994 through
February 1996 as outpatients or hospitalized patients were
considered for the study. We selected 14 patients with PD
(7 men and 7 women) matched to those with PSP and with
MSA for age, education, and disease severity (Hoehn and
Yahr scale at the time of cognitive evaluation) from among
those being treated at the same hospital. In addition, 18 nor-
mal control subjects (4 men and 14 women) were en-
rolled from patients’ relatives and patients with lumbar disk
herniation. None of the patients or control subjects had ma-
jor depression according to criteria of the Diagnostic and
Statistical Manual of Mental Disorders, Fourth Edition (DSM-
IV). Four patients with PSP were demented according to
criteria of the DSM-IV and were excluded. All subjects in-
cluded in the study had a Mini-Mental State Examination
(MMSE) score greater than 24 after adjustment for age and
education.

Parkinson disease was diagnosed by the presence of
akinesia plus 1 or more of the following: muscular rigi-
dity, rest tremor, or postural instability. All patients with PD
had a progressive disease course, a good response to le-
vodopa therapy, and motor fluctuations as a result of this
therapy, characterized by dyskinesias and on-off. None had
any of the exclusion criteria for PD established by the Par-
kinson Disease Society Brain Bank.

The patients with MSA had probable striatonigral de-
genation–type illness, according to Quinn’s clinical crite-
ria. The clinical diagnosis was supported by magnetic reso-
nance examination, which revealed putamenal signal hypo-
tensity on T2-weighted images, suggesting the deposition of
iron or other paramagnetic substances. None had mag-
netic resonance signs of cerebellar or brainstem atrophy.

Progressive supranuclear palsy was diagnosed using the
clinical criteria of the National Institute of Neurological Dis-
orders and Stroke Society for PSP International Workshop.
All patients had probable PSP as diagnosed by a gradually pro-
gressive course, vertical supranuclear palsy (with down-gaze
abnormalities), and prominent postural instability with un-
explained falls. In addition, none had the exclusion criteria of
Litvan et al, including unilateral dystonia, alien-limb syndrome,
early cortical dementia, prominent cerebellar signs, dysauto-
nomia, hallucinations, or focal lesions on clinical and radi-
ological examinations. The clinical diagnosis of PSP was sup-
ported in 9 patients by magnetic resonance findings that showed
atrophy of the midbrain and the region around the third ventricle.
In the other 5 patients, magnetic resonance imaging showed
only moderate and symmetric cerebral atrophy.

All patients with PD were receiving levodopa at a mean
(±SD) daily dosage of 1084.8 mg (±369.3 mg); 4 patients
were also taking dopamine agonists (1, cabergoline; and
3, bromocriptine mesylate), and 2 patients were taking
small doses of anticholinergic agents. Of the 19 patients
with MSA, 16 were taking levodopa at a mean (±SD) daily
dosage of 754.6 mg (±474.4 mg); 1 of these was also tak-
ing cabergoline; another patient was receiving anticholin-
eric medication only; and 2 were not receiving any medi-
cation. Twelve patients with PSP were taking levodopa
(mean ±SD) daily dosage, 609.4 (±258.6) mg; 1 was also
receiving bromocriptine; and another was also receiving
selegiline hydrochloride; 3 patients with PSP were not re-
ceiving any medication. Motor and cognitive tests were
performed when patients taking levodopa were receiving
Continued on next page

Because of striatal dysfunction, prefrontal and pre-
motor areas (including the SMA) become deafferented
in parkinsonian syndromes. Impairments in the execu-
tion of rapid, alternating, and sequential movements, the
reproduction of rhythms, and bimanual coordination are
found in SMA dysfunction in humans and other pri-
mates. These findings are not explained by the pres-
eence of bradykinesia alone and raise the possibility that
there may be a higher-order motor impairment associ-
ated with premotor area dysfunction in parkinsonian syn-
dromes. Furthermore, the relationship between these im-
pairments and apraxia has not been explored.

Apraxia is defined as a disorder of skilled move-
ments not caused by weakness, akinesia, deafferentation,
or intellectual deterioration. According to Heilman and
Rothi, patients with ideomotor apraxia are impaired in the
selection, sequence, and spatial orientation of move-
ments involved in gestures (including emblems and pantomimes). Apraxia due to frontal lesions is much less com-
mon than that due to parietal lesions, and few cases due to
SMA lesions have been described. Watson et al studied 2
patients with lesions of the left mesial hemisphere, includ-
ing the SMA, and found evidence of ideomotor apraxia, par-
ticularly for transitive gestures that required complex dis-
tal movements of the hands. The authors suggested that
the left SMA translates the temporospatial representations
of learned transitive movements—that are stored in the left
inferior parietal lobe—into motor programs.

The role of the basal ganglia in apraxia also re-
quires clarification. In a review on basal ganglia and
apaxia, apraxia due solely to basal ganglial lesions was rare; however, it was concluded that the term limb-
kine Apraxia should be used to describe some motor
disturbances found in basal ganglial diseases.

In view of these considerations, it appeared to us that
the assertion that apraxia was absent in the frontal lobe–like
syndromes of parkinsonian disorders should be reconsid-
ered. In this study, therefore, we sought to determine whether
ideomotor apraxia is present in parkinsonian syndromes and
to reassess the pattern of cognitive impairment to define which
cognitive dysfunctions best distinguish patients with these
syndromes from normal control subjects. We tested patients
with PD, MSA, and PSP compared with a group of normal
control subjects using a comprehensive neuropsychologi-
cal battery, an ideomotor apraxia test evaluating arm and
finger gestures, and a computerized tapping test.

RESULTS

The 4 patients with PSP who were excluded from the analy-
sis because of dementia did not differ in age, education, mean
disease duration, or disease stage from the other patients with
PSP. The 3 groups included in the final analysis consisted of 19 patients with MSA, 15 with PSP, and 14 with PD.

The patient groups and the control groups did not differ in age or education. The duration of illness was significantly greater in patients with PD than in those with MSA or PSP (P<.0001). As expected, illness severity assessed by the Hoehn and Yahr scale did not differ in the 3 groups. Table 1 shows the main characteristics of the 4 groups. The results of the cognitive tests are summarized in Table 2.

Analysis of variance revealed significant differences between the 4 groups in all cognitive tests. Post hoc comparisons showed that the scores of patients with PD were significantly worse than those of control subjects on the Raven, the attention, and the Nelson tests, whereas the scores of patients with MSA and those with PSP were significantly worse than those of control subjects on all cognitive tests. In addition, patients with MSA performed significantly worse than those with PD in the verbal fluency test, whereas patients with PSP performed worse than patients with PD and those with MSA in the verbal fluency, the Visual Search Test, and the Visuospatial Orientation Line Test of Benton; they were worse than patients with MSA but not those with PD on the Nelson test and worse than those with PD but not those with MSA on the Raven test.

Therefore, although no patient was demented according to DSM-IV criteria or had an MMSE score lower than 24, all patient groups performed worse than control subjects in the Raven intelligence test, with patients with PSP being especially compromised.

Considering the results of the tests examining executive functions, patients with MSA did significantly worse than patients with PD in verbal fluency, patients with PD did worse than those with MSA on the Nelson test (although the difference was not significant), and patients with PSP were the worst on both tests.

In the simple tapping task, there was a significant difference between groups (P=.001). Post hoc comparisons showed that patients with MSA and those with PSP were significantly slower than control subjects. Sequential tapping scores were also significantly different between groups (P<.001), with control subjects performing significantly better than the other 3 groups and patients with PD doing significantly better than patients with MSA and those with PSP.

To dissociate the effect of movement slowing (typical of all parkinsonian syndromes) from an impairment of sequencing, the results of sequential tapping were adjusted for simple tapping. The presence of bradykinesia could have affected the performance especially of patients with MSA and those with PSP, who generally responded poorly to levodopa or who were not receiving the drug. After this adjustment, the difference between the 4 groups in sequential tapping was still significant.
significantly worse than those with MSA or PD (worse than controls, and patients with PSP doing significantly worse, respectively), with all disease groups doing significantly worse compared with controls; in addition, patients with MSA and those with PSP performed significantly worse than patients with PD, 4 (20%) of 19 patients with MSA, and 4 (27%) of 15 patients with PSP scored between 53 and 62 (borderline). None of the patients with PD scored below 53 (appraxia score) but 2 (10%) of 19 patients with MSA and 3 (20%) of 15 patients with PSP scored less than 53. How-

**Table 1. Characteristics of Patients With PD, MSA, and PSP and Control Subjects**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients With PD (n=14 [7 M/7 F])</th>
<th>Patients With MSA (n=19 [7 M/12 F])</th>
<th>Patients With PSP (n=15 [9 M/6 F])</th>
<th>Controls (n=18 [4 M/14 F])</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mini-Mental State Examination</td>
<td>27.9±1.5</td>
<td>27.3±1.5‡</td>
<td>27.2±1.4§</td>
<td>28.7±1.4§</td>
<td>.02</td>
</tr>
<tr>
<td>Age, y</td>
<td>58.9±7.9</td>
<td>59.2±7.9</td>
<td>65.9±6.4</td>
<td>60.3±8.9</td>
<td>.06</td>
</tr>
<tr>
<td>Education, y</td>
<td>8.2±3.6</td>
<td>7.3±3.6</td>
<td>8.3±5.0</td>
<td>9.2±4.0</td>
<td>.50</td>
</tr>
<tr>
<td>Duration of illness, y</td>
<td>13.4±6.8</td>
<td>4.2±1.2</td>
<td>4.0±3.6</td>
<td>. . . .</td>
<td>.0001</td>
</tr>
<tr>
<td>Hoehn and Yahr scale</td>
<td>3.2±0.6</td>
<td>3.6±0.8</td>
<td>3.5±0.4</td>
<td>. . . .</td>
<td>.20</td>
</tr>
</tbody>
</table>

* PD indicates Parkinson disease; MSA, multiple system atrophy; and PSP, progressive supranuclear palsy. All values are presented as mean±SD.
† P values were obtained by analysis of variance with post hoc comparisons using the least significance difference test.
‡ Post hoc comparisons (P<.05): controls vs patients with MSA.
§ Post hoc comparisons (P<.05): controls vs patients with PD.
¶ Post hoc comparisons (P<.05): patients with PD vs patients with MSA.

**Table 2. Cognitive Test Results in Patients With PD, MSA, and PSP and Control Subjects**

<table>
<thead>
<tr>
<th>Cognitive Tests</th>
<th>Patients With PD (n=14 [7 M/7 F])</th>
<th>Patients With MSA (n=19 [7 M/12 F])</th>
<th>Patients With PSP (n=15 [9 M/6 F])</th>
<th>Controls (n=18 [4 M/14 F])</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raven</td>
<td>28.1±6.0#</td>
<td>25.5±6.3§</td>
<td>21.9±6.6#</td>
<td>32.2±3.2‡§</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Short Tare</td>
<td>12.1±4.8</td>
<td>10.4±2.6</td>
<td>9.5±4.0</td>
<td>13.6±4.9§</td>
<td>.038</td>
</tr>
<tr>
<td>Phonemic Verbal Fluency</td>
<td>36.6±12.6#</td>
<td>26.9±6.6**</td>
<td>17.4±7.0**</td>
<td>33.3±8.4§</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Visual Search</td>
<td>42.0±7.6§</td>
<td>42.8±10.9**</td>
<td>34.3±13.7**</td>
<td>51.9±5.4§§</td>
<td>.0001</td>
</tr>
<tr>
<td>Visuospatial orientation line of Benton et al</td>
<td>21.9±4.4#</td>
<td>21.4±5.0**</td>
<td>17.6±7.6**</td>
<td>25.7±3.6§§</td>
<td>.0009</td>
</tr>
<tr>
<td>Nelson</td>
<td>3.4±1.7</td>
<td>4.1±1.4**</td>
<td>2.8±1.0</td>
<td>5.8±1.7**</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

* PD indicates Parkinson disease; MSA, multiple system atrophy; and PSP, progressive supranuclear palsy. All values are presented as mean±SD.
† P values were obtained by analysis of variance with post hoc comparisons using the least significance difference test.
‡ Post hoc comparisons (P<.05): controls vs patients with PD.
§ Post hoc comparisons (P<.05): controls vs patients with MSA.
¶ Post hoc comparisons (P<.05): patients with PD vs patients with MSA.
* Post hoc comparisons (P<.05): patients with MSA vs patients with PSP.

**Table 3. Tapping Test in Patients With PD, MSA, and PSP and Control Subjects**

<table>
<thead>
<tr>
<th>Tapping Tests</th>
<th>Patients With PD (n=14 [7 M/7 F])</th>
<th>Patients With MSA (n=19 [7 M/12 F])</th>
<th>Patients With PSP (n=15 [9 M/6 F])</th>
<th>Controls (n=18 [4 M/14 F])</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple</td>
<td>49.3±11.3</td>
<td>37.2±14.7§</td>
<td>40.8±23.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sequence</td>
<td>30.8±11.1†#</td>
<td>21.3±8.3§</td>
<td>21.7±8.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* PD indicates Parkinson disease; MSA, multiple system atrophy; and PSP, progressive supranuclear palsy. All values are presented as mean±SD.
† With P values, Kruskal-Wallis 1-way analysis of variance was used; means of sequence tapping were adjusted for simple tapping.
‡ Post hoc comparisons (P<.05): controls vs patients with PD.
§ Post hoc comparisons (P<.05): controls vs patients with MSA.
¶ Post hoc comparisons (P<.05): patients with PD vs patients with MSA.
# Post hoc comparisons (P<.05): patients with MSA vs patients with PSP.

(P= .01), and all disease groups were significantly impaired compared with controls; in addition, patients with MSA and those with PSP performed significantly worse than patients with PD (Table 3). This result implies that the impairment in sequential tapping in patients with PD, MSA, and PSP is not simply the result of bradykinesia but due to an impairment of sequencing capability.

Performance imitating single and sequence of gestures differed significantly between groups (P=.002 and P<.0001, respectively), with all disease groups doing significantly worse than controls, and patients with PSP doing significantly worse than those with MSA or PD (Table 4). According to De Renzi et al scoring,28 ideomotor apraxia is certainly present when a total score is less than 53 and certainly absent when a total score is greater than 62, with a score between 53 and 62 considered borderline. When the scores were examined individually, all normal subjects scored more than 62; 7 (50%) of 14 patients with PD, 4 (20%) of 19 patients with MSA, and 4 (27%) of 15 patients with PSP scored between 53 and 62 (borderline). None of the patients with PD scored below 53 (appraxia score) but 2 (10%) of 19 patients with MSA and 3 (20%) of 15 patients with PSP scored less than 53. However, all subjects recognized the symbolic gestures even when they could not imitate them correctly. Qualitative analysis of uncorrected gestures showed that all errors made by patients with PD were due to clumsiness. Patients with MSA and PSP often made more than 1 type of error: 85%
of the errors made by patients with MSA were due to clumsiness, and 15% were due to sequence errors. Patients with PSP showed greater variability of error types: 50% were location errors, 30% were clumsiness errors, 10% were sequence errors, and 10% were due to orientation errors. Patients with MSA had a greater variability of error types compared with control subjects, and they confirm the presence of frontal dysfunction, those with PD were impaired in reactive flexibility, those with MSA were impaired in spontaneous flexibility, and patients with MSA were not selected for cognitive deterioration, but were referred consecutively to our center as outpatients or inpatients. The patients with PD were then selected as having motor impairment similar to that of patients with MSA and PSP.

Our findings on the Nelson and verbal fluency tests reproduce those of a recent article by Pillon et al.67 comparing patients with MSA, PD, and PSP and control subjects, and they confirm the presence of frontal dysfunction in basal ganglia diseases. Pillon et al.67 concluded that patients with MSA were impaired in spontaneous flexibility, those with PD were impaired in reactive flexibility, and patients with PSP were compromised in both. A qualitatively different pattern of impairment of executive functions among patients with PD, MSA, and PSP was also found by Robbins et al.12 and Owen and Robbins31 but again with more extensive compromise in PSP. Furthermore, Robbins et al.12 and Pillon et al.67 found that the executive functions that are controlled by the striatofrontal circuits are the earliest and most compromised functions in patients with parkinsonian syndromes.67

The cognitive test results in our patients with PD and MSA were similar to those found previously,6,34 whereas the patients with PSP had greater cognitive impairment, which is probably related to the greater striatal damage com-

Table 5. Discriminant Analysis: Standardized Canonical Coefficients of Patient Groups vs Control Subjects for 11 Cognitive and Motor Tests*

<table>
<thead>
<tr>
<th>Gestures</th>
<th>Patients With PD (n=14 [7 M/7 F])</th>
<th>Patients With MSA (n=19 [7 M/12 F])</th>
<th>Patients With PSP (n=15 [9 M/6 F])</th>
<th>Controls (n=18 [4 M/14 F])</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single</td>
<td>34.9±1.8†§#</td>
<td>33.7±2.8†§</td>
<td>32.7±3.2†§</td>
<td>35.7±0.7§</td>
<td>.002</td>
</tr>
<tr>
<td>Sequence</td>
<td>29.6±4.1†§§</td>
<td>28.5±6.3†§§</td>
<td>25.7±6.2†§§</td>
<td>34.0±2.7§§</td>
<td>.0001</td>
</tr>
<tr>
<td>Total Score</td>
<td>64.5±5.2†§§</td>
<td>62.2±8.4†§§</td>
<td>58.4±8.9†§§</td>
<td>69.7±3.2†§§</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

* PD indicates Parkinson disease; MSA, multiple system atrophy; and PSP, progressive supranuclear palsy. All values are presented as mean±SD.
† With P values, Kruskal-Wallis 1-way analysis of variance was used; means of sequence tapping were adjusted for simple tapping.
‡ Post hoc comparisons (P<.05): controls vs patients with PD.
§ Post hoc comparisons (P<.05): controls vs patients with MSA.
# Post hoc comparisons (P<.05): patients with PD vs patients with MSA.
¶ Post hoc comparisons (P<.05): patients with PD vs patients with PSP.
* Post hoc comparisons (P<.05): patients with MSA vs patients with PSP.

Unlike the 2 previous studies that compared cognitive performance in patients with MSA, PD, and PSP and normal control subjects,6,7 our patients with MSA and PSP were not selected for cognitive deterioration, but were referred consecutively to our center as outpatients or inpatients. The patients with PD were then selected as having motor impairment similar to that of patients with MSA and PSP.

In this population with parkinsonian syndromes, we found that patients with MSA and PSP were compromised compared with control subjects in all cognitive functions, ie, abstract reasoning (Raven test), learning and memory (Short Tale Test), visuospatial orientation (Benton test), attention and visuomotor ability (visual search), and executive functions (verbal fluency and Nelson test). The low cognitive test scores in patients with PSP highlight the pervasiveness of cognitive impairment in this unselected sample of patients. The patients with PD were impaired compared with control subjects in all cognitive tests and the Nelson test.

Our findings on the Nelson and verbal fluency tests reproduce those of a recent article by Pillon et al.67 comparing patients with MSA, PD, and PSP and control subjects, and they confirm the presence of frontal dysfunction in basal ganglia diseases. Pillon et al.67 concluded that patients with MSA were impaired in spontaneous flexibility, those with PD were impaired in reactive flexibility, and patients with PSP were compromised in both.

A qualitatively different pattern of impairment of executive functions among patients with PD, MSA, and PSP was also found by Robbins et al.12 and Owen and Robbins31 but again with more extensive compromise in PSP. Furthermore, Robbins et al.12 and Pillon et al.67 found that the executive functions that are controlled by the striatofrontal circuits are the earliest and most compromised functions in patients with parkinsonian syndromes.6,7

The cognitive test results in our patients with PD and MSA were similar to those found previously,6,34 whereas the patients with PSP had greater cognitive impairment, which is probably related to the greater striatal damage com...
bined with pervasive pallidal degeneration that characterizes this disease compared with PD and MSA.35

The patients with PSP also performed worse than the other groups on the Benton visuospatial test and the Visual Search Test. The superior colliculi and periaqueductal gray matter are severely damaged in PSP and are likely to be implicated in the pathogenesis of the dysfunction in visual search and scanning ability in PSP, as indicated in early neuropsychological articles on this disease.36

In the simple tapping test, the performance of patients with PSP and MSA, but not of those with PD, was significantly worse than that of control subjects. Although patients with PD were selected as having the same Hoehn and Yahr stage as the other 2 disease groups at the time of testing, patients with PSP and MSA were more bradykinetic because they were not treated with or responded poorly to levodopa. However, when we covaried sequential tapping for simple tapping as a measure of bradykinesia, we still obtained a significant difference between patients with PSP and MSA and control subjects, to the advantage of the control subjects; but this time, patients with PD were also significantly worse than control subjects. Impairment in the execution of motor sequences was well documented in PD. Benecke et al37 found impairments of simultaneous and sequential movements in patients with PD,37 which they attributed to a dysfunction of the SMA. In addition, many reports have emphasized the importance of the SMA in memorizing, generating, and possibly learning sequential movements.9

The 3 disease groups were significantly worse than control subjects in the apraxia test, when imitating both single and sequence gestures, with patients with PSP being especially compromised. The definition of ideomotor apraxia includes the requirement that gesture disorders are not due to akinesia.10 The finding that, in all patients, most of the errors on the test for ideomotor apraxia were due to clumsiness testifies to the difficulty of diagnosing apraxia in patients with basal ganglia diseases. On the other hand, it is noteworthy that patients’ performance was particularly bad in the sequence of gestures and that the most common errors of patients with MSA and PSP, after errors due to clumsiness, were sequence defects.

The substantial impairment in the sequence of tapping and gestures in our patients with MSA and PSP is consistent with the results of Pillon et al86 and Cambier and colleagues,30 whose patients with PSP were particularly compromised in sequential gestures that were part of a frontal score.

In the study by Benecke et al,37 the longer reaction times in sequential movements for patients with PD included an extra time not explained by the increase in single-movement reaction times. Therefore, sequence impairment does not appear to be explained by bradykinesia alone but seems to be a higher-order motor disturbance possibly due to involvement of the premotor areas.

Freund40 proposed that derangements in the premotor cortex (SMA and lateral premotor cortex) could give rise to what he called “frontal” or “executorial” apraxias; these included limb-kinetic apraxia, disorders of motor learning, and rhythm production. We presume that a compromised ability to produce rhythm would also impair sequencing. In the present study, 3 patients with PSP and 2 with MSA had De Renzi scores in the apraxia range. The errors made by the 2 patients with MSA and 1 patient with PSP were mostly due to clumsiness and sequencing errors, whereas the 2 other patients with PSP also made orientation and localization errors. Because of these orientation and localization errors, we considered the latter group of patients more securely apraxic. Following Freund’s paradigm,40 however, the others would also be considered apraxic because when sequencing impairment is so severe as to render the whole gesture, it is a mark of “true” apraxia.

Two types of ideomotor apraxia have been hypothesized41: a posterior type caused by lesions in the left parietal cortex where visuokinesthetic motor engrams are stored, and an anterior type caused by lesions anterior to the supramarginal gyrus that disconnect motor engrams from the premotor areas. In the former type, patients cannot execute skilled movements on command or imitation and cannot recognize or discriminate gestures because they have lost the representations; in the second type, patients cannot execute gestures on command or imitation but can recognize a motor act and can tell whether it is well performed. All our patients were able to recognize meaningful gestures and, therefore, had the anterior type of ideomotor apraxia, consistent with the known premotor area dysfunction in parkinsonian syndromes.

Goldenberg et al42 found that patients with PD were impaired on apraxia tests, which they attributed to defective motor memory, while a recent report by Leiguarda et al43 found that 13 of 45 patients with PD were apraxic. None of our patients with PD scored in the apraxia range. We propose 2 explanations for this. First, the PD group of Leiguarda et al had a lower mean MMSE score than our PD group and probably included patients with greater mental decay, some of whom may have had borderline dementia; it is well known that apraxia is common in cortical dementing pathologies. Second, the apraxia test used by these investigators43 has a narrow range, with a cutoff for apraxia at 33 and a maximum score of 36 for normal subjects. The De Renzi test of ideomotor apraxia that we used (validated on 200 normal subjects) has a cutoff for apraxia at 53 and a maximum score of 72; borderline apraxia is between 53 and 62, and the normal range is wide. This test is, therefore, more exacting for the diagnosis of apraxia than that of the previous study43; furthermore, it includes a greater number of sequence gestures, which are more sensitive in revealing impairments in patients with MSA and PSP than single gesture tasks.

The finding that our patients with PSP performed poorly on the apraxia test raises the problem of differentiating the diagnosis from corticobasal degeneration in which apraxia is one of the most important signs. A recent clinicopathological article underlined the difficulty of clinically differentiating corticobasal degeneration from PSP and even showed that the 2 conditions could coexist pathologically.44 We selected our PSP patients according to the clinical criteria of Litvan et al,19 which in all cases were correlated with pathological findings; thus, all our PSP patients had supranuclear gaze palsy and frequent falls, and none had an asymmetric akinetic-rigid syndrome. All underwent magnetic resonance imaging, and none displayed asymmetric frontoparietal atrophy characteristic of corticobasal degeneration.45

On the other hand, the presence of apraxia in PSP is consistent with cortical damage (involving the motor and premotor cortex) in this condition, as re-emphasized recently.46,47 In a pathological study of PSP,46
it was noted that neurofibrillary tangles were frequent in the frontal cortex, especially the precentral gyrus, and that density was related to the severity of neuronal loss. These pathological findings are also supported by positron emission tomographic studies showing a symmetric loss of frontal metabolism in PSP. 48

Direct cortical involvement has also been found in MSA: the premotor areas show neural and oligodendroglial, basophilic, argyrophil, cytoplasmic inclusions that are relatively specific for this disease and point to a cortical origin of the motor disorganization in MSA. 49

CONCLUSIONS

The more extensive impairment of cognitive functions in patients with PSP than in those with MSA or PD and the more substantial alteration in motor organization in patients with PSP and MSA compared with patients with PD are not explained by varying extents of frontal deafferentation related to striatal dysfunction,50 but indicate direct involvement of the cortical premotor areas in PSP and MSA. Our discriminant analysis showed that the tests that best identified the patient groups compared with control subjects were the sequential tapping test and the ideomotor apraxia tests, i.e., those requiring motor planning and sequence production. In fact, the extent of the motor disorganization in patients with MSA and PSP indicates a cumulative effect due to both striatal damage and premotor cortical involvement.

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