Spontaneous Parkinsonism Is Associated With Cognitive Impairment in Antipsychotic-Naive Patients With First-Episode Psychosis: A 6-Month Follow-up Study

Manuel J. Cuesta,*1 Ana M. Sánchez-Torres1, Elena García de Jalón1, Maria S. Campos1, Berta Ibáñez2, Lucía Moreno-Izco1, and Víctor Peralta1

1Psychiatric Unit B, Complejo Hospitalario de Navarra, Pamplona, Spain; 2Methodology Unit, Biomedical Research Center, Fundación Miguel Servet, Pamplona, Spain

*To whom correspondence should be addressed; Psychiatric Unit B, Complejo Hospitalario de Navarra, c/Irunlarrea 4, 31008 Pamplona, Spain; tel: 34 848 422488, fax: 34 848 422488, e-mail: mcuestaz@cfnavarra.es

There is now growing evidence that parkinsonism and other extrapyramidal signs are highly prevalent in patients with first-episode psychosis who have never been exposed to antipsychotic drugs. However, the neurocognitive correlates of parkinsonism in this population remained to be clarified. A sample comprising 100 consecutive drug-naive patients with first-episode psychosis were enrolled on the study and followed up for 6 months. Seventy-seven completed assessments at 3 time points (baseline, 1 mo, and 6 mo), involving clinical and cognitive examinations and a specific assessment of motor abnormalities. The Simpson-Angus Scale (SAS) was used for the assessment of extrapyramidal signs, and each motor domain was evaluated with a standard assessment scale. Linear mixed models were built to explore the longitudinal relationships between parkinsonism scores and cognitive impairment. Parkinsonism scores showed significant strong longitudinal associations with deficits in memory, executive functioning, and attention. Spontaneous parkinsonism (total SAS score and hypokinesia and rigidity subscores at baseline) showed high 6-month predictive values for cognitive impairment. In addition, they also had high predictive values for neurologic soft-sign abnormalities but not for dyskinesia, akathisia, and pure cata tonic abnormalities. No predictive value was found for glabella-salivation or tremor subscores on the SAS scale. These results emphasize the relevance of the assessment of parkinsonism signs prior to starting to administer antipsychotic drugs, as core manifestations of psychotic illness with a high predictive value for cognitive impairment.

Key words: schizophrenia/neuropsychological impairment/cognition/extrapyramidal signs/abnormal movements

Introduction

The ubiquity of motor signs and symptoms in patients with schizophrenia and other psychoses has been recognized from the early writings of psychiatrists. Changing paradigms over the last century, however, relating motor disorders to either disease processes or to psychopathological phenomena, have hampered advances in our understanding.

Motor abnormalities (MAs) comprise a wide variety of signs and behaviors with different levels of complexity, which can be evidenced by observation or elicitation in the clinical examination. MAs can be clustered into 4 different domains on the basis of both different historical and conceptual backgrounds and different hypothetical pathophysiological underpinnings. These separate domains include catatonic signs, neurologic hard and soft signs, and extrapyramidal signs. Nonetheless, structured investigations of MAs by means current standardized instruments has demonstrated that a substantial proportion of patients show a great overlap of different kinds of MAs, with the exception of parkinsonism in patients never treated with antipsychotic drugs.

There is now growing evidence that parkinsonism and other extrapyramidal signs, such as dyskinesia and akathisia, have been consistently identified in patients who have never taken antipsychotic drugs. This led to the coining of the term spontaneous parkinsonism (SP), also described as spontaneous extrapyramidal signs. Parkinsonism is not only highly prevalent in the early stages of schizophrenia but is also the most common extrapyramidal abnormality in drug-naive psychotic individuals and, in consequence, could be considered a core manifestation of the disease process.
Studies focusing on neurocognitive correlates of motor phenomena have been fruitful regarding neurologic soft signs (NSSs). Psychosis patients not only obtain higher NSSs scores under examination than control subjects but also NSSs are strongly related to neuropsychological performance, suggesting that they reflect neurocognitive dysfunction.\textsuperscript{14,15} In contrast, there has been little research into neurocognitive underpinnings of catatonic abnormalities.\textsuperscript{16} And, to the best of our knowledge, the neurocognitive correlates of SP have not been studied in populations of patients with psychosis never exposed to antipsychotic treatment.

This study had 2 goals: the first, to examine the association between SP and cognitive impairment in antipsychotic-naive state patients with first-episode psychosis and the second, to ascertain whether this relationship is stable over time after patients start to take antipsychotic drugs. The hypothesis was that patients exhibiting SP in the antipsychotic-naive state have more severe cognitive impairment and that this will endure over a 6-month follow-up.

**Methods**

A sample comprising 100 consecutive drug-naive patients with first-episode psychosis were enrolled on the study. The inclusion criteria were the following: (a) being aged 16–65 years, (b) having an acute episode on admission to the study that met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)-Text Revision criteria for schizophrenia or other nonpurely affective psychotic disorders, (c) no previous exposure to antipsychotics, and (d) providing written informed consent to participate in the study and being sufficiently cooperative to be neuropsychologically assessed. Patients with a history of serious medical or neurologic disease, head injury, intellectual disability, or drug dependence were excluded from the study.

This was a longitudinal study lasting 6 months, and it was carried out in a naturalistic setting. Patients were extensively examined for neuromotor signs (extrapyramidal, catatonic, and NSSs) and neurocognitive functioning at baseline, ie, in an antipsychotic-naive state, 1 month, and 6 months after starting the antipsychotic treatment. Sample attrition during the follow-up reduced the final sample to 77 patients, and the analysis presented refers to these patients who completed the follow-up. A detailed description of the sample and procedures has been presented elsewhere.\textsuperscript{18}

Patients signed a written consent form after the study aims and procedures had been fully explained to them and their families. The Clinical Research Ethical Committee of our hospital approved the study.

Psychopathological status and diagnoses were assessed by means of a semistructured interview (Comprehensive Assessment of Symptoms and History interview).\textsuperscript{19} Duration of untreated psychosis (DUP) was evaluated by means of the Symptom Onset in Schizophrenia inventory.\textsuperscript{20} The DUP symptom score of general symptoms was chosen for this study.\textsuperscript{21}

Once we completed the baseline assessment, patients were assigned alternated to risperidone or olanzapine drugs under the recommendation that they continue their monotherapy regimen. Afterward, patients were followed up in their natural treatment setting, and their community psychiatrists made all treatment decisions. Final drug allocation groups were as follows: risperidone group (n = 29), olanzapine group (n = 22), mixed group (patients whose treatment was changed during the follow-up period) (n = 16), and no-antipsychotic group (n = 10).

To assess extrapyramidal signs, the Simpson-Angus Scale (SAS)\textsuperscript{22} was used. The SAS is made up of 10 items, each rated on a scale from 0 to 4. Akathisia and dyskinesia were evaluated using the global clinical assessment item of the Barnes Akathisia Rating Scale (BARS)\textsuperscript{23} and the first 7 items from the Abnormal Involuntary Movement Scale,\textsuperscript{24} respectively. The presence of any other extrapyramidal adverse events, eg, dystonic reactions, was determined on the basis of reports from patients and family members as well as ward records.

Catatonic signs were evaluated using the Modified Rogers Scale (MRS)\textsuperscript{25} (36 items, each scored from 0 to 2). Because the MRS was devised to rate both extrapyramidal and catatonic abnormalities, as well as those classified as either, 2 sub(scores were calculated: MRS extrapyramidal score and MRS catatonic score or “pure catatonic abnormalities.”\textsuperscript{25} NSS were assessed by means of the Neurological Evaluation Scale (NES)\textsuperscript{26} (26 items, each scored from 0 to 2), respectively. Total global scores of the BARS and NES and the total global score of the MRS and its 2 subcomponent scores were used in this study as complementary measures of neuromotor abnormalities.

Two junior psychiatrists carried out the assessments in such a way that each was masked to the opinions of the other and to the treatment received by patients. Good interrater reliability coefficients (k = 0.80–0.98) were obtained for psychopathological assessments by these 2 psychiatrists.

The criterion for SP was set a priori, before the analysis of the data. The summary score of all 10 SAS items was used as a continuous measure of global parkinsonism. The cutoff of ≥4 on the total SAS score was used to define parkinsonism based on previous studies addressing parkinsonism related to antipsychotic drugs because it seems arguable that this cutoff score is a sufficiently sensitive threshold to identify a high rates of caseness.\textsuperscript{27,28}

In addition to the parkinsonism global rating and cutoff points mentioned above, we obtained scores for the 4 main extrapyramidal domains in the SAS, namely hypokinesia (1 item), rigidity (sum of 6 items), tremor (1 item), and glabella-salivation (2 items).

General intelligence quotient (IQ) was ascertained by means of the Spanish version of a nonverbal IQ
Neuropsychological assessment covered attention, executive function, information processing, and memory. A detailed description of the neuropsychological battery has been published elsewhere. Briefly, the neuropsychological tests included Verbal Fluency (number of animals named in 1 min), the Trail Making Test-Part B, the Wechsler Memory Scale (WMS), and 4 tasks of the CogLab computerized neuropsychological battery: a reaction time task, a vigilance and span of apprehension task (Asarnow’s test, including the Total False Alarms and Total Perseverative Alarms), a visual backward-masking task, and the Wisconsin Card Sorting Test (WCST; considering the number of Perseverative Errors and Total Trials). In addition, an Executive Efficiency Index was calculated from results of the CogLab version of the WCST and a Vigilance-Span of Apprehension total score by combining scores on the Asarnow tasks as described by Gurpegui et al. Cognitive scores were transformed in such a way that higher scores reflected better performance.

Statistical Analysis

First, a descriptive analysis was performed to explore patient characteristics, including demographic, clinical, neuromotor, and cognitive data. Differences in these variables were examined between patients with SP comparing those with and without parkinsonism signs at baseline. Because many variables were not normally distributed, the nonparametric Kruskal-Wallis and Fischer’s exact tests were used when appropriate.

To investigate the relationship between parkinsonism and neurocognitive and other neuromotor scores and its evaluation over time, linear mixed models were fitted, one per each parkinsonism-neurocognitive/neuromotor combination. Each model had, as response variable, the cognitive or the neuromotor variable at each evaluation time (t = baseline, 1 mo, and 6 mo) and, as fixed effects, both the corresponding evaluation time (baseline, 1 mo, and 6 mo) and the parkinsonism score at that time. A random effect to account for intrindividual correlation due to the longitudinal structure of the data was also included. The interaction term between the parkinsonism scores and evaluation time was also included to assess whether the association between parkinsonism scores and neuropsychological performance changed over time. Where high scores indicated impairment, scores were transformed (direction reversed) for the linear mixed model so that high scores always indicated better cognitive functioning.

The possible confounding effect of other variables, such as age at onset, sex, and educational level, was also assessed. Additional models were built to account for differences in the main antipsychotic treatment received during the follow-up period and the DSM-IV 5-month diagnosis (schizophrenia and schizoaffective disorders vs other psychoses); both these variables entered as covariates (separately) in the aforementioned mixed linear models. Finally, to assess the ability of the SP in its categorical form (SAS < 4 vs SAS ≥ 4) in predicting neuropsychological and other neuromotor variables at 6-month time, we also compared the results (both at 6 mo and change during the follow-up) between both groups with the Mann-Whitney test.

The significance level was set at α = .05, and the statistical analyses were carried out using the SPSS package (v.18).

Results

Seventy-seven antipsychotic-naive patients with first-episode psychosis were assessed at baseline and reevaluated at 1 month and 6 months. Most of these patients were male (n = 53, 69%). Their age (mean ± SD) was 30.09 ± 10 years at enrolment and 27.83 ± 9.78 years at the first episode of psychosis. Most had completed primary education, with a mean of 13.92 ± 4.04 years of education.

The breakdown of DSM-IV diagnoses at 6 months of follow-up was as follows: schizophrenia (n = 33, 43%), schizophreniform disorder (n = 12, 16%), schizoaffective disorder (n = 6, 8%), brief psychotic disorder (n = 18, 23%), delusional disorder (n = 6, 8%), and psychosis not otherwise specified (n = 2, 3%).

Clinical, Neurologic, and Cognitive Variables at Baseline

Table 1 displays the descriptive characteristics of the final sample dichotomized by the presence of SP (cutoff for parkinsonism at baseline: SAS total score ≥ 4). Statistical comparisons between the 2 groups did not identify any significant differences either in demographic characteristics (age, sex, number of years of education, and age at onset) or in illness-related characteristics (positive, negative, disorganization, mania, and depression scores; global functioning over the previous year; and DUP general prodrome symptoms). However, the large SDs of DUPs parameters were suggestive of the presence of outlying values in the 2 groups.

SP patients did not differ significantly in premorbid IQ and neuropsychological performance at baseline except for significantly lower scores on the WMS Verbal Paired Associates subtests (table 1).

Raw scores of neuromotor scales and neurocognitive examinations at the 3 points of assessments clustered by predominant antipsychotic treatment are displayed, respectively, in online supplementary tables 1 and 2.

Associations of Parkinsonism Scores With Cognitive Performance Over Time: Results From Linear Mixed Models

Parkinsonism total score was significantly associated with impairment in memory (as reflected in WMS total,
Table 1. Results of Psychopathological, Neuromotor, and Neurocognitive Examinations at Baseline

<table>
<thead>
<tr>
<th></th>
<th>SAS &lt; 4 at Baseline</th>
<th>SAS ≥ 4 at Baseline</th>
<th>Kruskal-Wallis Test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 62 (80.5%)</td>
<td>n = 15 (19.5%)</td>
<td>( \chi^2 )</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>( P )</td>
<td></td>
</tr>
<tr>
<td>Sociodemographic variables</td>
<td></td>
<td></td>
<td>( \leq 0.05 )</td>
</tr>
<tr>
<td>Age</td>
<td>29.11 ± 8.89</td>
<td>34.13 ± 12.38</td>
<td>1.328</td>
</tr>
<tr>
<td>Sex (n, %)</td>
<td>53.68%</td>
<td>24.31.2%</td>
<td>1.069</td>
</tr>
<tr>
<td>Age at onset</td>
<td>27.33 ± 8.82</td>
<td>29.88 ± 13.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Years of education (parents)</td>
<td>13.90 ± 4.16</td>
<td>14.00 ± 3.60</td>
<td>0.008</td>
</tr>
<tr>
<td>Years of education (parents)</td>
<td>8.07 ± 2.79</td>
<td>8.07 ± 3.39</td>
<td>0.190</td>
</tr>
<tr>
<td>Functioning past year (GAF)</td>
<td>78.71 ± 15.64</td>
<td>73.00 ± 22.25</td>
<td>0.221</td>
</tr>
<tr>
<td>DUP general prodrome (mo)</td>
<td>11.83 ± 20.25</td>
<td>4.86 ± 5.98</td>
<td>0.997</td>
</tr>
<tr>
<td>Psychopathological variables*</td>
<td></td>
<td></td>
<td>( \leq 0.05 )</td>
</tr>
<tr>
<td>Positive</td>
<td>3.29 ± 1.08</td>
<td>3.43 ± 0.96</td>
<td>0.191</td>
</tr>
<tr>
<td>Negative</td>
<td>1.28 ± 1.19</td>
<td>1.22 ± 1.28</td>
<td>0.720</td>
</tr>
<tr>
<td>Disorganization</td>
<td>1.62 ± 1.05</td>
<td>1.86 ± 1.36</td>
<td>0.570</td>
</tr>
<tr>
<td>Manic</td>
<td>0.29 ± 0.87</td>
<td>0.13 ± 0.35</td>
<td>0.007</td>
</tr>
<tr>
<td>Depression</td>
<td>1.10 ± 1.52</td>
<td>0.33 ± 0.72</td>
<td>0.093</td>
</tr>
<tr>
<td>Neuromotor variables</td>
<td></td>
<td></td>
<td>( \leq 0.05 )</td>
</tr>
<tr>
<td>SAS total</td>
<td>1.21 ± 1.01</td>
<td>6.40 ± 3.39</td>
<td>37.347</td>
</tr>
<tr>
<td>Hypokinesia</td>
<td>0.05 ± 0.16</td>
<td>0.27 ± 0.45</td>
<td>6.873</td>
</tr>
<tr>
<td>Rigidity</td>
<td>0.09 ± 0.13</td>
<td>0.86 ± 0.59</td>
<td>35.007</td>
</tr>
<tr>
<td>Tremor</td>
<td>0.42 ± 0.56</td>
<td>0.73 ± 0.45</td>
<td>4.903</td>
</tr>
<tr>
<td>Glabella-salivation</td>
<td>0.08 ± 0.23</td>
<td>0.13 ± 0.29</td>
<td>0.304</td>
</tr>
<tr>
<td>AIMS total</td>
<td>1.77 ± 3.30</td>
<td>2.00 ± 1.72</td>
<td>3.021</td>
</tr>
<tr>
<td>BARS total</td>
<td>0.21 ± 0.51</td>
<td>0.27 ± 0.45</td>
<td>0.547</td>
</tr>
<tr>
<td>MRS total</td>
<td>2.55 ± 3.07</td>
<td>2.53 ± 1.35</td>
<td>1.378</td>
</tr>
<tr>
<td>MRS catatonic score</td>
<td>1.08 ± 1.44</td>
<td>0.60 ± 0.91</td>
<td>1.315</td>
</tr>
<tr>
<td>MRS extrapyramidal score</td>
<td>1.50 ± 1.82</td>
<td>1.93 ± 1.03</td>
<td>0.779</td>
</tr>
<tr>
<td>NES total</td>
<td>16.06 ± 8.66</td>
<td>21.33 ± 11.1</td>
<td>2.824</td>
</tr>
<tr>
<td>Neuropsychological variables</td>
<td></td>
<td></td>
<td>( \leq 0.05 )</td>
</tr>
<tr>
<td>TONI-2</td>
<td>31.65 ± 8.95</td>
<td>26.93 ± 8.81</td>
<td>3.415</td>
</tr>
<tr>
<td>Verbal Fluency</td>
<td>17.15 ± 7.52</td>
<td>16.13 ± 4.70</td>
<td>0.259</td>
</tr>
<tr>
<td>Trail Making Test-Part B</td>
<td>155.48 ± 107.91</td>
<td>187.63 ± 119.62</td>
<td>1.462</td>
</tr>
<tr>
<td>Wechsler Memory Scale total</td>
<td>48.59 ± 13.14</td>
<td>42.83 ± 12.69</td>
<td>2.170</td>
</tr>
<tr>
<td>Logical Memory</td>
<td>5.94 ± 3.50</td>
<td>4.60 ± 3.65</td>
<td>2.101</td>
</tr>
<tr>
<td>Digit Memory</td>
<td>9.16 ± 2.22</td>
<td>9.06 ± 1.79</td>
<td>0.001</td>
</tr>
<tr>
<td>Visual Reproduction</td>
<td>8.51 ± 3.62</td>
<td>7.40 ± 4.38</td>
<td>0.889</td>
</tr>
<tr>
<td>Verbal Paired Associates</td>
<td>10.45 ± 4.59</td>
<td>7.43 ± 4.34</td>
<td>5.831</td>
</tr>
<tr>
<td>Reaction Time</td>
<td>301.55 ± 80.02</td>
<td>332.87 ± 109.57</td>
<td>0.732</td>
</tr>
<tr>
<td>Backward Masking</td>
<td>37.52 ± 13.34</td>
<td>37.93 ± 12.12</td>
<td>0.002</td>
</tr>
<tr>
<td>VSA</td>
<td>14.93 ± 3.54</td>
<td>14.78 ± 3.28</td>
<td>0.083</td>
</tr>
<tr>
<td>Asarnow False Alarms</td>
<td>0.80 ± 2.67</td>
<td>1.14 ± 1.61</td>
<td>1.344</td>
</tr>
<tr>
<td>Asarnow Perseverative Alarms</td>
<td>0.52 ± 1.45</td>
<td>0.21 ± 0.57</td>
<td>0.813</td>
</tr>
<tr>
<td>WCST Perseverative Errors</td>
<td>11.49 ± 7.48</td>
<td>14.13 ± 8.28</td>
<td>1.354</td>
</tr>
<tr>
<td>Executive Efficiency Index total</td>
<td>2.35 ± 0.79</td>
<td>2.17 ± 0.87</td>
<td>0.873</td>
</tr>
</tbody>
</table>

Note: DUP, duration of untreated psychosis; GAF, Global assessment of functioning; SAS, Simpson-Angus Scale; AIMS, Abnormal Involuntary Movement Scale; BARS, Barnes Akathisia Rating Scale; MRS, Modified Rogers Scale; NES, Neurological Evaluation Scale; TONI-2, Test of Nonverbal Intelligence-2; VSA: Vigilance-Span of Apprehension; WCST: Wisconsin Card Sorting Test. Values highlighted in bold are \( P \) < .05.

*Psychopathological scores derived from Comprehensive Assessment of Symptoms and History interview.

as well as Logical Memory and Visual Reproduction subtest scores, executive functioning (WCST Perseverative Errors and Executive Efficiency Index), and attention (reaction time and backward-masking task) (table 2). Asarnow False Alarms displayed a failure to obtain a positive definite solution for the Hessian matrix (table 2) and hereafter, it was removed from the subsequent analyses.

Because for the subscores we considered, hypokinesia showed similar significant associations with impairment in cognitive functioning to SAS total score (except for \( P \) values not being significant for the WMS Logical Memory subtests and backward-masking task). Rigidity was significantly associated with impaired executive functioning (WCST Perseverative Errors and Executive Efficiency Index) and showed a trend to an association...
with poorer WMS total and Logical Memory scores but not with performance on attention tasks. Tremor did not show any significant association with cognitive performance. Lastly, the glabella-salivation score was significantly associated with performance on reaction time and backward-masking tasks and WMS Digit Memory and Visual Reproduction subtests, as well as the Executive Efficiency Index.

Most significant associations between parkinsonism scores and cognitive tests were maintained over time in the models and consistently demonstrated that the greater severity of parkinsonism, the higher cognitive impairment.

No interaction term between parkinsonism scores and time was found significant for neither SAS total nor rigidity. For hypokinesia, the negative association with Verbal Paired Associates found at baseline disappears as time goes by (interaction \( P = .010 \)), and the negative association with Backward Masking is only observed at 1 month (interaction \( P = .005 \)). For tremor, the negative association observed with Reaction Time disappears with time (interaction \( P = .005 \)), and the same occurred with the negative correlation observed between glabella-salivation and Executive Efficiency Index (interaction \( P = .026 \)).

### Table 2. Results From Linear Mixed Models for Examining the Relationships Between Parkinsonism and Neurocognitive and Other Neuromotor Scores Over Time

<table>
<thead>
<tr>
<th></th>
<th>SAS Total</th>
<th>Hypokinesia</th>
<th>Rigidity</th>
<th>Tremor</th>
<th>Glabella-Salivation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \beta )</td>
<td>( P )</td>
<td>( \beta )</td>
<td>( P )</td>
<td>( \beta )</td>
</tr>
<tr>
<td>Verbal Fluency</td>
<td>0.09</td>
<td>.460</td>
<td>0.33</td>
<td>.724</td>
<td>0.26</td>
</tr>
<tr>
<td>Trail Making Test-B</td>
<td>-1.37</td>
<td>.779</td>
<td>-19.5</td>
<td>.123</td>
<td>-4.86</td>
</tr>
<tr>
<td>Wechsler Memory Scale total</td>
<td>-0.59</td>
<td>.008</td>
<td>-3.84</td>
<td>.011</td>
<td>-3.00</td>
</tr>
<tr>
<td>Logical Memory</td>
<td>-0.19</td>
<td>.006</td>
<td>-0.92</td>
<td>.069</td>
<td>-0.97</td>
</tr>
<tr>
<td>Digit Memory</td>
<td>-0.42</td>
<td>.244</td>
<td>-0.11</td>
<td>.635</td>
<td>-0.12</td>
</tr>
<tr>
<td>Visual Reproduction</td>
<td>-0.16</td>
<td>.026</td>
<td>-1.05</td>
<td>.051</td>
<td>-0.81</td>
</tr>
<tr>
<td>Verbal Paired Associates</td>
<td>-0.11</td>
<td>.190</td>
<td>-0.80a</td>
<td>.220a</td>
<td>-0.86</td>
</tr>
<tr>
<td>Backward Masking</td>
<td>-0.49</td>
<td>.037</td>
<td>-3.16a</td>
<td>.090a</td>
<td>-2.07</td>
</tr>
<tr>
<td>VSA</td>
<td>0.06</td>
<td>.278</td>
<td>0.58</td>
<td>.197</td>
<td>0.34</td>
</tr>
<tr>
<td>Asarnow False Alarmsb</td>
<td>0.01</td>
<td>.999</td>
<td>0.01</td>
<td>.999</td>
<td>0.01</td>
</tr>
<tr>
<td>Asarnow Perseverative Alarms</td>
<td>-0.01</td>
<td>.759</td>
<td>0.30</td>
<td>.108</td>
<td>0.12</td>
</tr>
<tr>
<td>WCST Perseverative Errors</td>
<td>-0.34</td>
<td>.023</td>
<td>-3.04</td>
<td>.016</td>
<td>-2.41</td>
</tr>
<tr>
<td>Executive Efficiency Index total</td>
<td>-0.04</td>
<td>.013</td>
<td>-0.29</td>
<td>.026</td>
<td>-0.24</td>
</tr>
<tr>
<td>AIMS total</td>
<td>0.04</td>
<td>.861</td>
<td>0.23</td>
<td>.600</td>
<td>0.08</td>
</tr>
<tr>
<td>BARS total</td>
<td>0.03</td>
<td>.031</td>
<td>0.17</td>
<td>.203</td>
<td>0.11</td>
</tr>
<tr>
<td>MRS score</td>
<td>0.14</td>
<td>.001</td>
<td>1.01</td>
<td>.005</td>
<td>0.94</td>
</tr>
<tr>
<td>MRS catatonic score</td>
<td>0.01</td>
<td>.797</td>
<td>0.11</td>
<td>.592</td>
<td>0.01</td>
</tr>
<tr>
<td>MRS extrapyramidal score</td>
<td>0.17</td>
<td>.517</td>
<td>0.39</td>
<td>.111</td>
<td>0.13</td>
</tr>
<tr>
<td>NES total</td>
<td>0.60</td>
<td>.001</td>
<td>1.76</td>
<td>.141</td>
<td>2.82</td>
</tr>
</tbody>
</table>

**Note:** Abbreviations are explained in the first footnote to table 1. Values highlighted in bold are \( P < .05 \).

\(^a\)Interaction term between parkinsonism score and time was significant. For hypokinesia, \( P = .010 \) and \( P = .005 \) for Verbal Paired Associates and Backward Masking, respectively; for tremor, \( P = .005 \) and for glabella-salivation, \( P = .026 \) (see online supplementary table 3 for details).

\(^b\)The final Hessian matrix was not positive definite although it fulfilled the convergence criteria.

### Associations of Parkinsonism Scores With Other Neuromotor Abnormalities Over Time: Results From the Linear Mixed Models

Parkinsonism total score was associated strongly with global catatonic abnormalities and NSSs and moderately with akathisia (BARS total score), whereas no significant association was found with dyskinesia. However, parkinsonism total score did not reveal significant associations with the 2 subcomponents of the MRS scale (“pure catatonic” and extrapyramidal scores) (table 2).

Regarding parkinsonism subscores, the data revealed strong relationships of hypokinesia with catatonic signs; rigidity with global catatonic and neurological soft signs; and glabella-salivation items with akathisia and neurological soft signs; as well as a moderate association of hypokinesia with catatonic signs; as well as a moderate association of tremor with dyskinesia, akathisia, and neurological soft signs. Parkinsonian subscores were not significantly associated with the 2 MRS subscors (“pure catatonic” and extrapyramidal scores) (table 2).

### SP Features and Cognitive Functioning at 6 Months

Patients exhibiting SP were found to have poorer WMS total, Logical Memory, and Verbal Paired Associates scores than those without parkinsonism signs. Further,
patients classed as having SP on the basis of an SAS at baseline of ≥4 showed significant impairment in Backward Masking and WCST Perseverative Errors at follow-up (table 3).

Regarding other neuromotor signs at 6-month follow-up, “extrapyramidal score” but not “catatonic score” from the MRS was strongly associated with SP; neurological soft signs were also strongly associated with patients with SAS total scores ≥4. On the other hand, SP was not significantly associated with akathisia and dyskinesia.

All these significant results found in the comparison of the scores at 6 months disappear when the response variable is the change between 6 months and baseline because differences between groups, when exists, are at least marginally depicted at the beginning, and they are not modified significantly at time goes by. Figure 1 portrays the results over time of the Trail Making Test-B for patients with and without SP, as example of the outcome pattern of most cognitive measures of this study.

Effect of the Main Treatment on the Follow-up and Diagnosis of Schizophrenia or Schizoaffective Disorder

To explore the possible effect of the main antipsychotic treatment and receiving the diagnosis of schizophrenia or schizoaffective disorder, both variables were entered separately into mixed linear models as covariates.

No effect of main antipsychotic treatment was found except on Reaction Time: olanzapine and risperidone groups had significantly poorer performance than patients not receiving treatment (β = −57.91, P ≤ .012; β = −40.91, P ≤ .059, respectively). Regarding the effect of diagnosis, schizophrenia or schizoaffective disorder, scores only tended to be lower among these patients than those with other psychoses on the WMS Visual Reproduction subtests (β = 1.32, P ≤ .057).

Patients taking regularly anticholinergic drugs during the follow-up were infrequent because at baseline, no patients were receiving any drug; only 1 patient at 1-month follow-up and 3 patients at the 6-month follow-up were taking low doses of benzotropine drugs. Due to the low frequency of adjunctive antiparkinsonian drugs in our sample, this variable was not included in the statistical analyses.

Discussion

The results of this study add evidence supporting the view that SP is a primary MA in a substantial proportion of psychosis patients.13,33 SP not only preceded the beginning of the antipsychotic drug treatment in a substantial proportion of patients but also had strong associations with cognitive impairments.

Three main conclusions can be drawn. First, patients with and without parkinsonism signs at baseline did not

| Table 3. Differences in Cognitive and Neuromotor Outcomes at the 6-Mo Follow-up by Spontaneous Parkinsonism (Cutoff Point SAS ≥ 4 at Baseline) and Differences in Change Score Over the Follow-up Between Both Groups |
|---------------------------------------------------------------------------------------------------------------|-------------------|-----------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
|                                                                                                               | 6-Mo Outcome Scores by Spontaneous Parkinsonism                                                                 |                                                                 | Change in the 6-Mo Outcome Scores by Spontaneous Parkinsonism                                                                 |
|                                                                                                               | SAS < 4                           | SAS ≥ 4               | Comparison                      | SAS < 4                           | SAS ≥ 4               | Comparison                      |
|                                                                                                               | Mean (SD)                         | Mean (SD)             | χ²   | P             | Mean (SD)                         | Mean (SD)             | χ²   | P             |
| Verbal Fluency                                                                                                 | 20.71 ± 6.69                      | 18.87 ± 5.39          | 0.76 | .381          | 3.56 (6.87)                      | 2.73 (4.71)          | 0.12 | .728          |
| Trail Making Test-Part B                                                                                       | 84.97 ± 30.72                     | 148.53 ± 157.29       | 1.29 | .255          | −70.5 (95.6)                     | −39.1 (113.3)        | 0.38 | .537          |
| WMS total                                                                                                     | 62.67 ± 10.44                     | 54.10 ± 13.49         | 5.49 | .019          | 13.8 (11.0)                      | 11.3 (13.4)          | 0.67 | .411          |
| Logical Memory                                                                                                | 9.70 ± 3.74                       | 7.06 ± 3.43           | 6.86 | .009          | 3.76 (3.48)                      | 2.47 (3.99)          | 1.06 | .303          |
| Digit Memory                                                                                                   | 10.16 ± 2.00                      | 9.66 ± 2.19           | 0.46 | .494          | 1.00 (1.74)                      | 0.60 (1.40)          | 0.87 | .348          |
| Visual Reproduction                                                                                           | 11.64 ± 2.80                      | 9.73 ± 4.31           | 2.48 | .115          | 3.13 (3.73)                      | 2.33 (4.19)          | 0.85 | .352          |
| Verbal Paired Associates                                                                                       | 14.43 ± 3.90                      | 11.96 ± 4.52          | 4.41 | .036          | 3.97 (4.63)                      | 4.53 (5.76)          | 0.01 | .913          |
| Reaction Time                                                                                                 | 261.19 ± 47.57                    | 303.67 ± 102.29       | 3.24 | .072          | −40.4 (75.8)                     | −29.2 (61.2)         | 0.64 | .421          |
| Backward Masking                                                                                               | 49.82 ± 7.20                      | 42.93 ± 12.38         | 4.25 | .039          | 12.3 (13.2)                      | 5.36 (11.1)          | 3.30 | .069          |
| VSA                                                                                                           | 17.45 ± 2.20                      | 15.93 ± 4.18          | 1.62 | .202          | 2.49 (3.15)                      | 1.00 (1.96)          | 3.21 | .073          |
| Asarnow Perseverative Alarms                                                                                    | 0.48 ± 0.76                       | 0.53 ± 0.99           | 0.95 | .734          | −0.21 (1.48)                     | −0.21 (0.69)         | 1.19 | .274          |
| WCST Perseverative Errors                                                                                      | 7.35 ± 4.86                       | 10.67 ± 5.46          | 4.75 | .029          | −4.11 (8.89)                     | −3.47 (7.51)         | 0.04 | .829          |
| Executive Efficiency Index                                                                                     | 2.80 ± 0.62                       | 2.53 ± 0.59           | 3.18 | .074          | 0.44 (0.92)                      | 0.36 (0.89)          | 0.01 | .969          |
| AIMS total                                                                                                     | 1.44 ± 1.81                       | 2.20 ± 2.33           | 1.62 | .202          | −0.34 (3.21)                     | 0.20 (2.73)          | 0.02 | .886          |
| BARS total                                                                                                    | 0.32 ± 0.64                       | 0.47 ± 0.64           | 1.28 | .258          | 0.11 (0.83)                      | 0.20 (0.77)          | 0.11 | .733          |
| MRS total                                                                                                     | 1.26 ± 1.07                       | 2.13 ± 1.12           | 6.92 | .009          | −1.29 (3.00)                     | 0.60 (1.40)          | 1.30 | .253          |
| Catatonic score                                                                                                | 0.40 ± 0.56                       | 0.53 ± 0.64           | 0.63 | .427          | −0.64 (1.41)                     | −0.06 (1.27)         | 2.56 | .109          |
| Extrapyramidal score                                                                                           | 0.85 ± 0.78                       | 1.60 ± 0.82           | 9.18 | .002          | −0.64 (1.84)                     | −0.33 (1.39)         | 0.68 | .436          |
| NES total                                                                                                     | 8.85 ± 5.35                       | 14.13 ± 10.24         | 4.41 | .036          | −7.16 (8.19)                     | −7.20 (11.4)         | 0.01 | .892          |

Note: Abbreviations are explained in the first footnote to table 1. WMS, Wechsler Memory Scale. Values highlighted in bold are P < .05.
differ significantly in terms of sociodemographic and psychopathological characteristics. Likewise, there were no significant differences between the 2 groups at baseline in other non-extrapyramidal neuromotor abnormalities or in most cognitive variables. Second, parkinsonism scores showed significant longitudinal associations with impairment in memory, executive functioning, and attention over time, from baseline assessment to 1 month and 6 months of follow-up. These associations were strong in magnitude and significant for total parkinsonism score as well as for subscores for hypokinesia, rigidity, and glabella-salivation but nonsignificant for tremor. And third, SP in the antipsychotic-naive state had a high 6-month predictive value for cognitive impairment and NSS abnormalities but not for other neuromotor abnormalities, such as dyskinesia, akathisia, and MRS catatonic disturbances after extracting the extrapyramidal component from the MRS scale.

Our study found that nearly 1 in 5 drug-naive patients with psychosis fulfilled criteria for SP (19.48%). This prevalence is within the range of figures reported in literature. In the most comprehensive review to date, Pappa and Dazzan concluded that SP is the most common extrapyramidal abnormality in drug-naive psychotic patients, and its prevalence varies across studies from 2.3% to 26.9% with a median prevalence of 17%. Despite our SP rate being within the range of the aforementioned review, it should be noted that the cutoff point of the scales used as threshold criteria for case identification varied across the 11 studies reviewed. In particular, the criteria applied were generally less stringent than ours, meaning that their results include subtle or mild cases of parkinsonism. Prevalence rates of parkinsonism in antipsychotic-treated patients in the neuroleptic era for chronic schizophrenia varied from 15% to 30%.

No significant differences were detected between SP and non-SP patients in demographic or psychopathological characteristics. While a lack of significant differences in age and sex has also been noted in other studies, in our patients, there were also no differences in negative symptoms and previous findings regarding this variable have not been consistent.

A key characteristic of studies analyzing extrapyramidal signs of psychosis is the choice of the scale used to assess these signs. Although there is some variation in scales and items across studies, the most widely used is the SAS, which paradoxically was originally designed to assess the side effects of neuroleptic treatments. This scale has been criticized due to the high weight of items assessing rigidity compared those for other parkinsonian signs and regarding a need for modifications in its procedure. Notwithstanding these concerns, the SAS seems to be a reliable and valid instrument. It allows 2 main subcomponents to be identified, namely akinetic manifestations, including akinesia and rigidity, and nonkinetic manifestations, covering other signs namely tremor, glabella tap, and salivation. Scores on these 4 subcomponents of the SAS scale might need different explanations in terms of the underlying the anatomical and functional basis and have been shown to differ before and after exposure to antipsychotic treatment.

Our patients with SP were significantly more likely to have a deteriorating cognitive course at 6 months, including after controlling for significant differences at baseline (these only being observed on the WMS Verbal Paired Associates subtests). In addition, the presence of SP was a clear predictor of impairment in attention, memory, and executive performance. These cognitive impairments seem to represent core manifestations and be the most critical determinants of functioning and quality of life in schizophrenia and other psychoses, and it has been hypothesized that they may have common psychological and neurobiological substrates.

In addition, the strong associations between SP and cognitive impairments could not be attributed to premorbid intellectual inferiority of SP patients because there were no differences between patients with and without SP in their number of years of education or the educational background of their parents.

Cross-sectional studies with a single-point assessment might obscure the clinical and cognitive correlates of SP because it has been demonstrated that the level of abnormal movements and parkinsonism fluctuates over time. Moreover, the starting of antipsychotic treatment introduces a great source of confusion in the interpretation of the relationships between SP and cognitive performance.
because parkinsonism at baseline might be either increased
or modified by the side effects of antipsychotic treatment.44

Diagnostic Issues
We included first-episode patients in our study popula-
tion, not limiting the focus to schizophrenia only due to
the lack of any definitive validity of any psychotic disor-
der. Both parkinsonism and cognitive impairment have
been extensively studied across psychosis subtypes and
both have been found to be more common in schizo-
phrenia than other psychoses. Specifically, Chong et al45
reported higher rates of SP in nonaffective psychosis
than patients with affective psychosis and schizoaffective
disorder.

Further, regarding cognitive dysfunction, there is wide
agreement that the degree of cognitive impairment is
more severe in schizophrenia than in affective psychi-
sis. However, psychosis subtypes seem to share a similar
profile of neuropsychological impairment, varying only
in the severity but not in the profile affected cognitive
domains.46,47

To further explore the possible differences due to
diagnosis, we introduced a new variable describing the
6-month DSM-IV diagnosis as a covariate in the linear
mixed models, 54 patients having been diagnosed with
schizophrenia or schizoaffective disorder (70%) and 23
(30%) with other psychoses at this stage. In our patients,
the significant associations between SP and cognitive
impairment remained statistically significant after con-
trolling for the schizophrenia diagnosis.

Relationships With Other MAs
A burgeoning literature supports the view that there are
complex relationships between MAs. While SP patients
did not show significant differences from non-SP patients
in dyskinesia, akathisia, catatonia, or NSSs at baseline,
those with SP did have more severe akathisia and NSSs
but not more dyskinesia and “pure” catatonic score, over
the follow-up period. These findings are in agreement
with the overlap between MAs reported in literature,6,7,13,48
as well as with reports of different patterns of correlates
in parkinsonism and dyskinesia8 and differences in pre-
morbid correlates between parkinsonism, akathisia, and
tardive dyskinesia.49

Antipsychotic Treatment
Antipsychotic drugs may both improve preexisting abnor-
malities and cause “de novo” neurologic syndromes,44
making it unclear to what extent motor disorders in
schizophrenia can be interpreted as medication-related
phenomena. To explore the effect of antipsychotic treat-
ment, we considered the main antipsychotic treatment
received during the follow-up as a potential confounding
variable in the analysis, but the significant associations
between SP and cognitive impairment remained stable in
almost all associations studied.

Pathophysiological Issues
The basal ganglia are essential components of the cen-
tral circuitry controlling voluntary movement as well as
sensorimotor integration, motor, and nonmotor learn-
ing and a number of higher cognitive functions.49 These
nuclei are intimately connected to the frontal cortex via 5
frontostriatal circuits mainly based on underlying dopa-
minergic and other monoaminergic modulation mech-
anisms.31 In addition, they seem to have a prominent role
in the attentional control of the early stages of learning
and reward system via dopaminergic pathways.

The dopamine hypothesis of schizophrenia (DAS)
has been the most prominent etiologic theory for the last
30 years. The DAS was well substantiated in the pharma-
cological action of neuroleptic drugs, but most efforts to
empirically validate it failed. The current view of the phys-
opathology of schizophrenia holds that psychosis might
be mediated by dopamine overactivity in the mesolimbic
system.52 Howes and Kapur53 revisited the DAS emphasizing
the following 3 facts. First, the elevation of presynap-
tic striatal dopaminergic function might be the substrate
of the final common pathway. Second, dopamine dysregu-
lation is linked to “psychosis” rather than schizophrenia.
And third, frontal/cognitive changes are not necessarily
primary but rather could arise from striatal dysfunction.

To integrate our findings within the frame of the dopa-
mine hypothesis and basal ganglia functioning, psychotic
patients with prominent SP might have a coexistence of
presynaptic striatal hyperdopaminergia to explain psy-
chosis with some kind of striatal or subcortical hypodo-
paminergia that would express parkinsonian signs such as
hypokinesia and cognitive dysfunction. In keeping with
the later, most of the significant associations with cogni-
tive impairment were related to the akinetic symptoms
of SP, particularly to hypokinesia and rigidity, which are
usually linked to striatal dysfunction. In line with this,
a recent study focusing on the early stages of Parkinson’s
disease before the intake of dopaminergic medication
found that parkinsonian signs were closely related to cog-
nitive impairment.54

Limitations
The results of this study should be understood in the con-
text of certain limitations. First, caution is warranted in
generalizing our findings to all individuals with psychosis
because our study focused on first-episode patients requir-
ing admission. Further and longer longitudinal studies
should be carried out in larger samples of patients with
schizophrenia and other psychoses in different phases of
their illness.

The attrition rate in our study was moderate (23%).
We note, however, that despite this attrition, we found no
significant differences in epidemiological or clinical characteristics between patients who declined to continue participating and those who completed the study.\textsuperscript{18} Low rates of dyskinesia and dystonia were found in our sample, but similar figures have also been reported by other authors.\textsuperscript{6} In this regard, baseline examinations prior to prescribing antipsychotic drugs may help to focus treatment on patients susceptible to developing parkinsonism.

Finally, there is considerable evidence suggesting that cognitive improvement in schizophrenia should be due to either placebo or practice effect.\textsuperscript{55} However, we reported elsewhere that cognitive improvement persisted even after allowing for the practice effect by means of reliable change index methods.\textsuperscript{18}

\section*{Supplementary Material}


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