Spontaneous parkinsonism is associated with cognitive impairment in antipsychotic-naïve patients with first-episode psychosis: A 6-month follow-up study.

Journal:	*Schizophrenia Bulletin*
Manuscript ID:	SZBLTN-ART-13-0087.R3
Manuscript Type:	Regular Article
Date Submitted by the Author:	n/a
Complete List of Authors:	Cuesta, Manuel; COMPLEJO HOSPITALARIO DE NAVARRA, PSYCHIATRIC UNIT B; Sanchez-Torres, Ana; Complejo Hospitalario de Navarra, Psychiatric Unit B Garcia-Jalon, Elena; Complejo Hospitalario de Navarra, Psychiatric Unit B Campos, Maria; Complejo Hospitalario de Navarra, Psychiatric Unit B Ibañez, Berta; Fundación Miguel Servet, Methodology Unit, Biomedical Research Center, Moreno-Izco, Lucia; Complejo Hospitalario de Navarra, Psychiatric Unit B Peralta, Victor; Complejo Hospitalario de Navarra, Psychiatric Unit B
Keywords:	Schizophrenia, neuropsychological impairment, cognition, extrapyramidal signs, abnormal movements

This is a pre-copyedited, author-produced version of an article accepted for publication in Schizophrenia Bulletin following peer review. The version of record Manuel J. Cuesta, Ana M. Sánchez-Torres, Elena García de Jalón, Maria S. Campos, Berta Ibáñez, Lucía Moreno-Izco, Víctor Peralta, Spontaneous Parkinsonism Is Associated With Cognitive Impairment in Antipsychotic-Naive Patients With First-Episode Psychosis: A 6-Month Follow-up Study, Schizophrenia Bulletin, Volume 40, Issue 5, September 2014, Pages 1164–1173, https://doi.org/10.1093/schbul/sbt125 is available online at: https://doi.org/10.1093/schbul/sbt125

Cuesta, MJ; Sánchez-Torres, AM; de Jalón, EG; Campos, MS; Ibañez, B; Moreno-Izco, L; Peralta V. (2014) Spontaneous parkinsonism is associated with cognitive impairment in antipsychotic-naive patients with first-episode psychosis: a 6-month follow-up study. Schizophr Bull. 40(5):1164-73. doi: 10.1093/schbul/sbt125.

Spontaneous parkinsonism linked to cognitive impairment

TITLE

Spontaneous parkinsonism is associated with cognitive impairment in antipsychotic-naïve patients with first-episode psychosis: A 6-month follow-up study.

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KEYWORDS: Schizophrenia, neuropsychological impairment, cognition, extrapyramidal signs, abnormal movements.

WORD COUNT:

Abstract: 226

Manuscript: 4258

ABSTRACT

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-naïve patients with first-episode psychosis were enrolled on the study and followed-up for 6 months. Seventy-seven completed assessments at three time points (baseline, 1 month and 6 months), involving clinical and cognitive examinations and a specific assessment of motor abnormalities. The Simpson-Angus Scale (SAS) was used for the assessment of extra-pyramidal 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. Spontaneuos 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 catatonic 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.

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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[1, 2] or to psychopathological phenomena[3] have hampered advances in our understanding[4, 5].

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 four 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[4, 6, 7], with the exception of parkinsonism in patients never treated with antipsychotic drugs[8].

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[9-12]. 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[11] but is also the most common extrapyramidal abnormality in drug-naïve psychotic individuals[13] and, in consequence, could be considered a core manifestation of the disease process.

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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[14, 15]. In contrast, there has been little research into neurocognitive underpinnings of catatonic abnormalities[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 two goals: the first, to examine the association between SP and cognitive impairment in antipsychotic-naïve 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-naïve state have more severe cognitive impairment and that this will endure over a 6-month follow-up.

METHODS

A sample comprising 100 consecutive drug-naïve patients with first-episode psychosis were enrolled on the study. The inclusion criteria were: (a) being aged 16–65 years; (b) having an acute episode on admission to the study that met DSM–IV–TR criteria for schizophrenia or other non-purely affective psychotic disorders[17]; (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.

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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 neurologic soft signs) and neurocognitive functioning at baseline, that is in an antipsychotic-naïve state, and 1- 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[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 semi-structured interview (Comprehensive Assessment of Symptoms and History interview)[19]. Duration of untreated psychosis (DUP) was evaluated by means of the Symptom Onset in Schizophrenia (SOS) inventory[20]. The DUP symptom score of general symptoms was chosen for this study[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).

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To assess extrapyramidal signs the Simpson-Angus Scale (SAS)[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)[23] and the first seven items from the Abnormal Involuntary Movement Scale (AIMS)[24], respectively. The presence of any other extrapyramidal adverse events, e.g., 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)[25] (36 items, each scored from 0 to 2). As the MRS was devised to rate both extrapyramidal and catatonic abnormalities, as well as those classified as either, two subscores were calculated: MRS extrapyramidal score and MRS catatonic score or 'pure catatonic abnormalities'[25]. NSS were assessed by means of the Neurological Evaluation Scale (NES)[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 two 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 two psychiatrists.

The criterion for spontaneous parkinsonism 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 cut-off of ≥ 4 on the total SAS score was used to define parkinsonism based on previous studies addressing parkinsonism related to antipsychotic drugs since it seems arguable that this cut-off score is a sufficiently

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sensitive threshold to identify a high rates of caseness[27-30]. In addition to the parkinsonism global rating and cut-off points mentioned above, we obtained scores for the four main extrapyramidal domains in the SAS, namely hypokinesia (one item), rigidity (sum of 6 items), tremor (one item) and glabella-salivation (two items).

General IQ was ascertained by means of the Spanish version of a non-verbal IQ test (TONI-2 Test)[31]. Neuropsychological assessment covered attention, executive function, information processing, and memory. A detailed description of the neuropsychological battery has been published elsewhere[18]. 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 four 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 (VSA) total score by combining scores on the Asarnow tasks as described by Gurpegui et al[32]. 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 spontaneous parkinsonism comparing those with and without parkinsonism signs at baseline. As many variables were not

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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 model were fitted, one per each parkinsonisim – neurocognitive/neuromotor combination. Each model had as response variable the cognitive or the neuromotor variable at each evaluation time (t= baseline, 1 month and 6 months), and as fixed effects both the corresponding evaluation time (baseline, 1 month and 6 months), and the parkinsonism score at that time. A random effect to account for intra-individual 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 versus 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-months time, we also compared the results (both at 6-

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months and change during the follow-up) between both groups with the Mann-Withney test.

The significance level was set at α=0.05, and the statistical analyses were carried out using the SPSS package (v.18).

RESULTS

Seventy seven antipsychotic naïve patients with first episode psychosis were assessed at baseline and re-evaluated at 1- 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 (NOS) (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 (cut-off for parkinsonism at baseline: SAS total score ≥4). Statistical comparisons between the two 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

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year; and DUP general prodrom symptoms. However, the large standard deviations of DUPs parameters were suggestive of the presence of outlying values in the two 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 three points of assessments clustered by predominant antipsychotic treatment are displayed respectively in Supplementary Table 1 and Supplementary Table 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, as well as Logical Memory and Visual Reproduction subtest scores), executive functioning (WCST Perseverative Responses 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.

As 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

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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 either for SAS total nor for rigidity. For hypokinesia, the negative association with Verbal Paired Associates found at baseline disappear as times goes by (interaction p=0.010), and the negative association with Backward Masking is only observed at 1 month (interaction p=0.005). For tremor, the negative association observed with Reaction time disappears with time (interaction p=0.005), and the same occurred with the negative correlation observed between glabella-salivation and Executive Efficiency Index (interaction p=0.026) (Supplementary Table 3).

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 two subcomponents of the MRS scale ('pure catatonic' and extrapyramidal scores) (Table 2).

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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 tremor with dyskinesia, akathisia and neurological soft signs. Parkinsonian subscores were not significantly associated with the two MRS subsocres ('pure catatonic' and extrapyramidal scores) (Table 2).

Spontaneous parkinsonism 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-months follow-up, 'extrapyramidal score' but not 'catatonic score' from the MRS was strongly associated with spontaneous parkinsonism; and neurological soft signs were also strongly associated with patients with SAS total scores ≥4. On the other hand, spontaneous parkinsonism 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 times goes by. Figure 1 portrays the results over time of the Trail Making Test B for patients with and without

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spontaneous parkinsonism, as example of the outcome pattern of most cognitive measures 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≤0.012; β= -40.91, p≤0.059, 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≤0.057).

Patients taking regularly anticholinergic drugs during the follow-up were infrequent since at baseline no patients were receiving any drug; and only 1 patient at 1-month and 3 patients at the 6 month follow-up were taking low doses of benztropine drugs. Due to the low frequency of adjunctive anti-parkinsonian 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 spontaneous parkinsonism is a primary motor abnormality in a substantial proportion of psychosis patients[9, 13, 33]. SP not only preceded the beginning of the antipsychotic drug treatment

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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 differ significantly in terms of sociodemographic and psychopathological characteristics. Likewise, there were no significant differences between the two 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 non-significant for tremor. And third, SP in the antipsychotic-naïve state had a high 6-month predictive value for cognitive impairment and NSS abnormalities but nor 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-naïve 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[13] concluded that SP is the most common extrapyramidal abnormality in drug-naïve 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 cut-off point of the scales used as threshold criteria for case identification varied across the 11 studies reviewed. In particular, the criteria

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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%[34].

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[35, 36].

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[22], 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[37]. Notwithstanding these concerns, the SAS seems to be a reliable and valid instrument[38, 39]. It allows two main subcomponents to be identified, namely akinetic manifestations, including akinesia and rigidity, and non-akinetic manifestations, covering other signs namely tremor, glabella tap and salivation[40]. Scores on these four subcomponents of the SAS scale might need different explanations in terms of the underlying the anatomical and functional basis[41] and have been shown to differ before and after exposure to antipsychotic treatment[40, 42].

Our patients with SP were significantly more likely to have a deteriorating cognitive course at six months, including after controlling for significant differences at

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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[43].

In addition, the strong associations between SP and cognitive impairments could not be attributed to premorbid intellectual inferiority of SP patients since 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, since it has been demonstrated that the level of abnormal movements and parkinsonism fluctuate over time[12]. Moreover, the starting of antipsychotic treatment introduce a great source of confusion in the interpretation of the relationships between SP and cognitive performance since 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 population, not limiting the focus to schizophrenia only due to the lack of any definitive validity of any psychotic disorder. Both parkinsonism and cognitive impairment have been extensively studied across psychosis subtypes and both have been found to be more common in schizophrenia than other psychoses. Specifically, Chong et al.[45] reported higher rates

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of SP in non-affective 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 psychosis. However, psychosis subtypes seems to share a similar profile of neuropsychological impairment varying only in the severity but no 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 being 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 controlling 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 neurologic soft signs 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 dyskinesia[8] and differences in premorbid correlates between parkinsonism, akathisia and tardive dyskinesia[49].

Antipsychotic treatment

Cuesta, MJ; Sánchez-Torres, AM; de Jalón, EG; Campos, MS; Ibáñez, B; Moreno-Izco, L; Peralta V. (2014) Spontaneous parkinsonism is associated with cognitive impairment in antipsychotic-naive patients with first-episode psychosis: a 6-month follow-up study. Schizophr Bull. 40(5):1164-73. doi: 10.1093/schbul/sbt125.

Antipsychotic drugs may both improve pre-existing abnormalities 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 treatment, 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 central circuitry controlling voluntary movement as well as sensorimotor integration, motor and non-motor learning, and a number of higher cognitive functions[50]. These nuclei are intimately connected to the frontal cortex via five fronto-striatal circuits mainly based on underlying dopaminergic and other monoaminergic modulation mechanisms[51]. 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 pharmacological action of neuroleptic drugs but most efforts to empirically validate it failed. The current view of the physiopathology of schizophrenia holds that psychosis might be mediated by dopamine overactivity in the mesolimbic system[52]. Howes and Kapur[53] revisited the dopamine hypothesis of schizophrenia emphasizing the following three facts. First, the elevation of presynaptic striatal dopaminergic function might be the substrate of the final common pathway. Second, dopamine dysregulation is linked

Cuesta, MJ; Sánchez-Torres, AM; de Jalón, EG; Campos, MS; Ibáñez, B; Moreno-Izco, L; Peralta V. (2014) Spontaneous parkinsonism is associated with cognitive impairment in antipsychotic-naive patients with first-episode psychosis: a 6-month follow-up study. Schizophr Bull. 40(5):1164-73. doi: 10.1093/schbul/sbt125.

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 dopamine hypothesis and basal ganglia functioning, psychotic patients with prominent SP might have a coexistence of presynaptic striatal hyperdopaminergia to explain psychosis with some kind of striatal or subcortical hypodopaminergia that would express parkinsonian signs such as hypokinesia and cognitive dysfunction. In keeping with the later, most of the significant associations with cognitive impairment were related to the akinetic symptoms of SP, particularly to hypokinesia and rigidity, which are usually linked to striatum 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 cognitive impairment[54].

Limitations

The results of this study should be understood in the context of certain limitations. First, caution is warranted in generalizing our findings to all individuals with psychosis since our study focused on first-episode patients requiring 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[18].

Low rates of dyskinesia and dystonia were found in our sample, but similar figures have also been reported by other authors[6]. In this regard, baseline

Cuesta, MJ; Sánchez-Torres, AM; de Jalón, EG; Campos, MS; Ibáñez, B; Moreno-Izco, L; Peralta V. (2014) Spontaneous parkinsonism is associated with cognitive impairment in antipsychotic-naive patients with first-episode psychosis: a 6-month follow-up study. Schizophr Bull. 40(5):1164-73. doi: 10.1093/schbul/sbt125.

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[55]. However, we reported elsewhere that cognitive improvement persisted even after allowing for the practice effect by means of reliable change index methods[18].

Cuesta, MJ; Sánchez-Torres, AM; de Jalón, EG; Campos, MS; Ibáñez, B; Moreno-Izco, L; Peralta V. (2014) Spontaneous parkinsonism is associated with cognitive impairment in antipsychotic-naive patients with first-episode psychosis: a 6-month follow-up study. Schizophr Bull. 40(5):1164-73. doi: 10.1093/schbul/sbt125.

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FUNDING

This work was supported by the Department of Health of the Government of Navarra (grants 55/2007 and 11/101), the Carlos III Health Institute (FEDER Funds) from the Spanish Ministry of Economy and Competitivity (grant 08/I/1026) and the Spanish Ministry of Science and Innovation (grant SAF2008-05674-C03-02).

CONFLICT OF INTEREST

None.

Cuesta, MJ; Sánchez-Torres, AM; de Jalón, EG; Campos, MS; Ibáñez, B; Moreno-Izco, L; Peralta V. (2014) Spontaneous parkinsonism is associated with cognitive impairment in antipsychotic-naive patients with first-episode psychosis: a 6-month follow-up study. Schizophr Bull. 40(5):1164-73. doi: 10.1093/schbul/sbt125.

Table 1. Results of psychopathological, neuromotor and neurocognitive examinations at baseline

	SAS < 4 at baseline n=62 (80.5%)	SAS ≥ 4 at baseline n=15 (19.5%)	Kruskal-Wallis test	
	Mean (S.D.)	Mean (S.D.)	x^2	p≤
Sociodemographic variables				
Age	29.11 ± 8.89	34.13± 13.28	1.328	0.249
Sex (n, %)	53, 68.8%	24, 31.2%	1.069	0.301
Age at onset	27.33 ± 8.82	29.88 ± 13.2	0.001	0.990
Years of education (patients)	13.90 ± 4.16	14.00 ± 3.60	0.008	0.663
Years of education (parents)	8.07 ± 2.79	8.07 ± 3.39	0.190	0.892
Functioning past year (GAF)	78.71 ± 15.64	73.00 ± 22.25	0.221	0.638
DUP General prodrome (months)	11.83 ± 20.25	4.86 ± 5.98	0.997	0.318
Psychopathological variables[1]				
Positive	3.29± 1.08	3.43 ± 0.96	0.191	0.128
Negative	1.28 ± 1.19	1.22 ± 1.28	0.720	0.128
Disorganization	1.62 ± 1.05	1.86 ± 1.36	0.570	0.323
Manic	0.29 ± 0.87	0.13 ±0.35	0.007	0.936
Depression	1.10 ± 1.52	0.33 ± 0.72	0.093	2.820
Neuromotor variables				
SAS total	1.21 ± 1.01	6.40 ± 3. 39	37.347	**0.000**
Hypokinesia	0.05 ± 0.16	0.27 ± 0.45	6.873	**0.009**
Rigidity	0.09± 0.13	0.85 ± 0.59	35.905	**0.000**
Tremor	0.42 ± 0.56	0.73 ± 0.45	4.903	**0.027**
Glabella-Salivation	0.08 ± 0.23	0.13± 0.29	0.304	0.581
AIMS total	1.77 ± 3.30	2.00 ± 1.72	3.021	0.082
BARS total	0.21 ± 0.51	0.27 ± 0.45	0.547	0.460
MRS total	2.55 ± 3.07	2.53 ± 1.35	1.378	0.240
MRS catatonic score	1.05 ± 1.44	0.60 ± 0.91	1.315	0.255
MRS extrapyramidal score	1.50 ± 1.82	1.93 ± 1.03	0.779	0.380
NES total	16.06 ± 8.66	21.33 ± 11.1	2.824	0.093
Neuropsychological variables				
TONI-2	31.65 ± 8.95	26.93 ± 8.81	3.415	0.065
Verbal Fluency	17.15 ± 7.52	16.13 ± 4.70	0.259	0.611
Trail Making Test – part B	155.48± 107.91	187.63 ±119.62	1.462	0.227
Wechsler Memory Scale total	48.59 ± 13.14	42.83 ± 12.69	2.170	0.141
Logical Memory	5.94 ± 3.50	4.60 ± 3.65	2.101	0.147
Digit Memory	9.16 ± 2.22	9.06 ± 1.79	0.001	0.976
Visual Reproduction	8.51 ± 3.62	7.40 ± 4.38	0.889	0.346
Verbal Paired Associates	10.45 ± 4.59	7.43 ± 4.34	5.831	**0.016**
Reaction Time	301.55 ± 80. 02	332.87± 109.57	0.732	0.392
Backward Masking	37.52 ± 13.34	37.93 ± 12.12	0.001	0.984
VSA	14.93 ± 3.54	14.78 ± 3.28	0.083	0.774
Asarnow False Alarms	0.80 ± 2.657	1.14 ± 1.61	1.344	0.246
Asarnow Perseverative Alarms	0.52 ± 1.45	0.21± 0.57	0.813	0.367
WCST Perseverative Errors	11.49 ± 7.48	14.13 ± 8.28	1.354	0.245
Executive Efficiency Index Total	2.35 ± 0.79	2.17 ± 0.87	0.873	0.350

DUP: Duration of untreated psychosis; SAS: Simpson-Angus scale; AIMS; Abnormal involuntary movement scale; BARS: Barnes Akathisia Rating Scale; MRS: Modified Rogers Scale; NES: Neurological Examination Schedule; VSA: Vigilance Span of Apprehension; WCST: Wisconsin Card Sorting Test.

[1] = Psychopathological scores derived from Comprehensive Assessment of Symptoms and History interview

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Table 2. Results from linear mixed models for examining the relationships between parkinsonism and neurocognitve and other neuromotor scores over time

	SAS total		Hypokinesia		Rigidity		Tremor		Glabella-salivation	
	β	p	β	p	β	p	β	p	β	p
Verbal Fluency	0.09	.460	0.33	.724	0.26	.781	0.17	.786	1.15	.224
Trail Making Test B	-1.37	.779	-19.5	.123	-4.86	.694	1.77	.839	-10.9	.390
Wechsler Memory Scale total	-0.59	**.008**	-3.84	**.011**	-3.00	.057	-0.84	.434	-2.42	.119
Logical Memory	-0.19	**.006**	-0.92	.069	-0.97	.053	-0.49	.157	-0.88	.084
Digit Memory	-0.42	.244	-0.11	.635	-0.12	.623	-0.08	.628	-0.58	**.021**
Visual Reproduction	-0.16	**.026**	-1.05	**.051**	-0.81	.117	-0.04	.906	-1.09	**.044**
Verbal Paired Associates	-0.11	.190	-0.80[2]	.220[2]	-0.86	.175	-0.43	.340	0.57	.380
Reaction Time	-3.12	**.034**	-25.0	**.016**	-18.8	.069	10.96[2]	.125[2]	-22.1	**.036**
Backward Masking	-0.49	**.037**	-3.16[2]	.090[2]	-2.07	.212	-1.10	.367	-4.47	**.012**
VSA	-0.06	.278	-0.58	.197	-0.34	.433	-0.01	.971	-0.35	.416
Asarnow False Alarms[1]	0.01	.999	- 0.01	.999	-0.01	.999	-0.01	.999	-0.01	.999
Asarnow Perseverative Alarms	-0.01	.759	-0.30	.108	0.12	.399	0.01	.868	-0.17	.302
WCST Perseverative Errors	-0.34	**.023**	-3.04	**.016**	-2.41	**.022**	0.96	.236	-1.09	.368
Executive Efficiency Index Total	-0.04	**.013**	-0.29	**.026**	-0.24	**.029**	0.06	.462	-0.24[2]	**.054**[2]
AIMS total	0.04	.861	0.23	.600	0.08	.820	0.62	**.030**	0.28	.506
BARS total	0.03	**.031**	0.17	.203	0.11	.302	0.20	**.021**	0.36	**.006**
MRS score	0.14	**.001**	1.01	**.005**	0.94	**.003**	0.14	.533	0.28	.428
MRS catatonic score	0.01	.797	0.11	.592	0.01	.905	0.06	.604	0.03	.591
MRS extrapyramidal score	0.17	.517	0.39	.111	0.13	.460	0.01	.926	0.18	.430
NES total	0.60	**.001**	1.76	.141	2.82	**.015**	1.67	**.042**	3.75	**.002**

[1]= The final Hessian matrix was not positive definite although it fulfilled the convergence criteria.
[2]= Interaction term between parkinsonism score and time was significant. For Hypokinesia, p=0.010 and p=0.005 for Verbal Paired Associates and Backward Masking respectively, for Tremor, p=0.005, and forGlabella-salivation, p=0.026 (see online supplementary table for details).

SAS: Simpson-Angus scale; VSA: Vigilance Span of Apprehension; WCST: Wisconsin Card Sorting Test; AIMS; Abnormal Involuntary Movement Scale; BARS: Barnes Akathisia Rating Scale; MRS: Modified Rogers Scale; NES: Neurological Examination Schedule

Cuesta, MJ; Sánchez-Torres, AM; de Jalón, EG; Campos, MS; Ibáñez, B; Moreno-Izco, L; Peralta V. (2014) Spontaneous parkinsonism is associated with cognitive impairment in antipsychotic-naive patients with first-episode psychosis: a 6-month follow-up study. Schizophr Bull. 40(5):1164-73. doi: 10.1093/schbul/sbt125.

Table 3. Differences in cognitive and neuromotor outcomes at the 6-months follow-up by Spontaneous parkinsonism (cut-off point SAS ≥ 4 at baseline) and differences in change score over the follow-up between both groups.

	6-months outcome scores by Spontaneous parkinsonism				Change in the 6-months outcome scores by Spontaneous parkinsonism			
	SAS<4 (n=62)	SAS≥4 (n=15)	Comparison		SAS<4 (n=62)	SAS≥4 (n=15)	Comparsion	
	Mean(sd)	Mean(sd)	X^2	p	Change	Change	X^2	p
Verbal Fluency	20.71±6.69	18.87±5.39	0.76	0.381	3.56(6.87)	2.73(4.71)	0.12	0.728
Trail Making Test – part B	84.97±30.72	148.53±157.29	1.29	0.255	-70.5(95.6)	-39.1(113.3)	0.38	0.537
WMS Total	62.67±10.44	54.10± 13.49	5.49	**0.019**	13.8(11.0)	11.3(13.4)	0.67	0.411
Logical Memory	9.70± 3.74	7.06± 3.43	6.86	**0.009**	3.76(3.48)	2.47(3.99)	1.06	0.303
Digit Memory	10.16± 2.00	9.66± 2.19	0.46	0.494	1.00(1.74)	0.60(1.40)	0.87	0.348
Visual Reproduction	11.64± 2.80	9.73± 4.31	2.48	0.115	3.13(3.73)	2.33(4.19)	0.85	0.352
Verbal Paired Associates	14.43± 3.90	11.96±4.52	4.41	**0.036**	3.97(4.63)	4.53(5.76)	0.01	0.913
Reaction Time	261.19±47.57	303.67±102.29	3.24	**0.072**	-40.4(75.8)	-29.2(61.2)	0.64	0.421
Backward Masking	49.82±7.20	42.93±12.38	4.25	**0.039**	12.3(13.2)	5.36(11.1)	3.30	0.069
VSA	17.45±2.20	15.93±4.18	1.62	0.202	2.49(3.15)	1.00(1.96)	3.21	0.073
Asarnow Persev. Alarms	0.48±0.76	0.53±0.99	0.95	0.734	-0.21(1.48)	-0.21(0.69)	1.19	0.274
WCST Persevev. Errors	7.35±4.86	10.67±5.46	4.75	**0.029**	-4.11(8.89)	-3.47(7.51)	0.04	0.829
Executive Efficiency Index	2.80±0.62	2.53±0.59	3.18	0.074	0.44(0.92)	0.36(0.89)	0.01	0.969
AIMS total	1.44±1.81	2.20±2.33	1.62	0.202	-0.34(3.21)	0.20(2.73)	0.02	0.886
BARS total	0.32±0.64	0.47±0.64	1.28	0.258	0.11(0.83)	0.20(0.77)	0.11	0.733
MRS total	1.26±1.07	2.13±1.12	6.92	**0.009**	-1.29(3.00)	0.60(1.40)	1.30	0.253
Catatonic score	0.40±0.56	0.53±0.64	0.63	0.427	-0.64(1.41)	-0.06(1.27)	2.56	0.109
Extrapyramidal score	0.85±0.78	1.60±0.82	9.18	**0.002**	-0.64(1.84)	-0.33(1.39)	0.68	0.436
NES total	8.85 ±5.35	14.13±10.24	4.41	**0.036**	-7.16(8.19)	-7.20(11.4)	0.01	0.892

SAS: Simpson-Angus scale; VSA: Vigilance Span of Apprehension; WMS: Wechsler Memory Scale; WCST: Wisconsin Card Sorting Test; AIMS; Abnormal Involuntary Movement Scale; BARS: Barnes Akathisia Rating Scale; MRS: Modified Rogers Scale; NES: Neurological Examination Schedule

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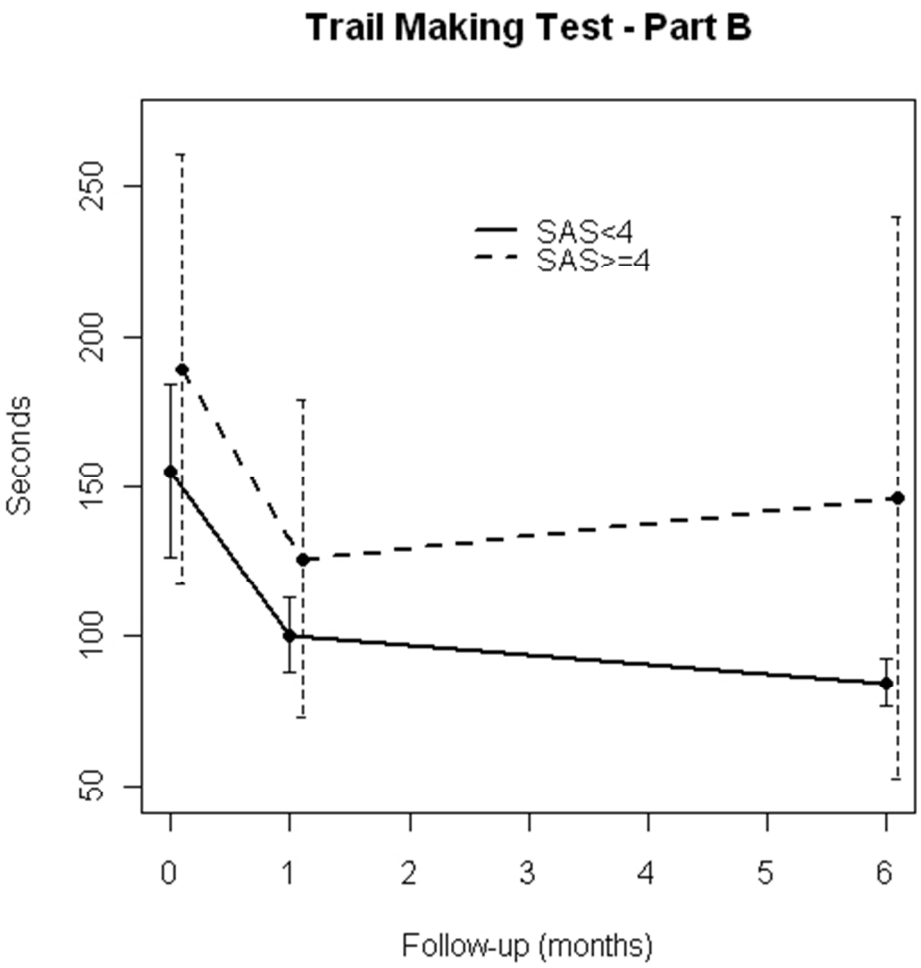

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Supplementary Table 1. Results of neuromotor scales at baseline, 1 -month and 6–month of follow-up by predominant antipsychotic drug

	Risperidone N=29 Mean (S.D)			Olanzapine N=22 Mean (S.D)			Mixed drugs group N=16 Mean (S.D)			No treatment group N=10 Mean (S.D)		
Neuromotor scales	Baseline	1-month	6-months	Baseline	1-month	6-months	Baseline	1-month	6-months	Baseline	1-month	6-months
SAS	2.24±2.88	5.14±3.62	3.14±3.30	2.14±3.37	2.41±2.66	2.32±2.85	2.38±1.70	4.69±4.27	4.06±3.80	2.10±1.91	3.00±2.86	1.90±1.44
AIMS	2.48±3.55	1.76±2.04	1.97±2.12	.95±1.43	1.32±1.35	.68± .83	2.31±4.11	2.06±3.41	2.00±1.86	1.00±1.41	1.30±1.25	1.80±2.70
BARS	.28± .64	1.10±1.14	.34± .48	.18± .39	.14± .35	.09± .29	.06± .25	.63±1.02	.69±1.01	.40± .51	.50± .70	.40± .69
MRS	3.00±3.05	2.24±2.16	1.62±1.26	1.95±1.36	1.18± .85	1.14± .88	2.75±4.02	2.25±2.17	1.50± .81	2.20±2.20	1.60± .96	1.40±1.57
NES	18.31±10.13	11.59±7.10	9.93±4.90	14.09±8.04	11.18±7.65	8.77±6.45	19.38±10.05	13.69±7.02	10.56±5.02	16.20±8.03	12.60±11.90	11.10±13.22

SAS: Simpson-Angus scale; AIMS: Abnormal Involuntary Movement Scale; BARS: Barnes Akathisia Rating Scale; MRS: Modified Rogers Scale; NES: Neurological Examination Schedule

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Supplementary Table 2. Results of neurocognitive examinations at baseline, 1-month, 6-months of follow up by predominant antipsychotic treatment.

	Risperidone N=29 Mean (S.D)			Olanzapine N=22 Mean (S.D)			Mixed drugs group N=16 Mean (S.D)			No treatment group N=10 Mean (S.D)		
	Baseline	1-month	6-months	Baseline	1-month	6-months	Baseline	1-month	6-months	Baseline	1-month	6-months
Neurocognitive tests												
Verbal Fluency	16.24±6.61	20.38±5.21	19.86±5.83	19.27±7.30	22.14±6.81	21.95±7.94	15.69±7.37	17.81±6.94	19.56±5.91	15.90±6.99	21.80±7.48	19.50±5.77
Trail Making Test	161.00±108.02	94.48±39.85	83.86±27.82	148.23±96.13	111.91±70.56	109.73±110.59	194.75±150.62	116.88±46	97.13±34.46	140.90±63.44	109.60±85.36	109.60±127.48
WMS	45.70±14.16	57.64±10.44	60.08±9.36	51.15±11.24	60.61±11.05	63.54±12.91	44.21±14.85	55.58±12.65	57.81±10.58	49.70±10.52	60.35±13.32	62.90±15.13
Logical Memory	5.82±4.26	7.77±3.48	8.51±3.44	6.22±3.10	9.38±3.07	10.18±4.74	4.84±3.17	7.09±3.14	8.68±2.73	5.40±2.91	9.15±4.17	9.75±4.00
Digit Memory	9.06±1.81	9.62±1.82	9.96±1.72	9.13±2.23	9.72±2.22	10.04±2.10	8.81±2.56	9.68±1.99	9.75±2.51	9.90±2.28	10.80±2.04	10.90±2.02
Visual Reproduction	7.55±4.27	11.00±3.46	11.37±3.02	8.86±3.10	11.13±3.21	11.54±3.36	8.93±3.31	9.93±4.44	10.37±3.32	8.20±4.41	11.30±3.16	11.80±3.45
Verbal Paired Associates	9.18±5.09	13.79±4.37	13.31±3.91	11.97±3.56	13.68±3.80	15.31±4.03	7.50±4.64	12.75±4.07	13.31±3.75	11.00±3.85	13.30±4.76	13.85±5.27
Reaction Time	314.31±81.73	284.10±50.32	259.38±39.02	283.73±50.86	257.95±41.13	254.95±43.61	298.76±100.89	292.13±45.44	283.38±54.02	355.20±124.15	305.90±119.07	308.40±130.87
Backward Masking	36.69±14.36	45.97±9.56	51.00±6.09	37.86±13.82	46.19±9.42	46.68±10.71	35.73±11.73	44.07±11.51	45.75±9.27	43.00±8.15	49.50±7.01	49.50±9.20
VSA	15.31±3.42	16.72±2.47	17.68±2.10	14.86±2.74	15.76±3.47	16.90±2.38	14.00±4.17	16.80±1.89	17.25±2.11	15.22±4.29	15.80±4.56	16.00±5.09
Asarnow False Alarms	.66±1.23	.69±1.56	.41± .78	1.59±4.22	.67±1.278	.55± .85	.47±1.06	.60± .98	.50± .63	.44±1.01	.60±1.07	.60±1.07
Asarnow Persev. Alamrs	.24± .57	.41± .82	.34± .85	.59±2.13	.48± .68	.36± .58	.53±1.060	.27± .594	.19± .54	.78±1.09	.10± .31	.40± .51
WCST Persev. Errors	13.72±7.93	9.66±6.13	7.17±3.51	9.59±7.81	10.76±9.88	9.45±7.72	12.38±7.74	8.60±6.243	8.38±3.20	11.78±5.49	9.20±6.79	6.60±4.11
EEI	2.19± .86	2.55± .60	2.75± .62	2.56± .88	2.59± .88	2.64± .71	2.15± .61	2.60± .76	2.72± .54	2.43± .68	2.68± .73	3.05± .53

WMS: Wechsler Memory Scale; VSA: Vigilance Span of Apprehension; EEI: Executive Efficiency Index

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Supplementary Table 3: Model results for those relationships between parkinsonism and neurocognitive scores that are not constant along time

Models: Response variable with Covariate	Parameter estimates (slopes)			Covariate signification test		Interaction term test	
	β (95% CI)	e.e.	p-value	F-statistic	p-value	F-statistic	p-value
M1: Verbal Paired Associates with Hypokinesia							
Hypokinesia slope at baseline (Reference)	-3.58(-6.21,-0.95)	1.333	0.008				
Hypokinesia slope at 1-month of follow up	1.13(-0.73,2.98)	0.940	0.232	4.328	0.039	4.703	0.010
Hypokinesia slope at 6-month of follow up	-1.74(-4.16,0.68)	1.226	0.157				
Comparison slope 1-month vs baseline β	4.70(1.54,7.88)	1.606	0.004				
Comparison slope 6 months vs baseline β	1.84(-1.78,5.46)	1.838	0.318				
M2: Backward Masking with Hypokinesia							
Hypokinesia slope at baseline (Reference)	3.78(-3.84,11.40)	3.864	0.329				
Hypokinesia slope at 1-month of follow up	-9.33(-14.49,-4.18)	2.613	<0.001				
Hypokinesia slope at 6-month of follow up	1.46(-5.06,7.99)	3.307	0.659	0.518	0.473	5.512	0.005
Comparison slope 1-month vs baseline β	-13.12(-22.2,-4.07)	4.581	0.005				
Comparison slope 6 months vs baseline β	-2.32(-12.47,7.82)	5.145	0.653				
M3: Reaction Time with Tremor							
Tremor slope at baseline (Reference)	-33.7(-55.3,-12.0)	10.97	0.002				
Tremor slope at 1-month of follow up	-16.69(-39.6,-8.01)	11.60	0.152				
Tremor slope at 6-month of follow up	11.94(-7.87,31.73)	10.03	0.236	3.330	0.070	5.495	0.005
Comparison slope 1-month vs baseline β	17.0(-12.7,46.7)	15.03	0.260				
Comparison slope 6 months vs baseline β	45.6(17.8,73.4)	14.08	0.001				
M4: Executive Efficiency Index Total with Glabella-salivation							
Glabella-saliv slope at baseline (Reference)	-0.72(-1.33,-0.11)	0.311	0.022				
Glabella-saliv slope at 1-month of follow up	-0.31(-0.61,-0.02)	0.149	0.038	2.691	0.102	3.736	0.026
Glabella-saliv slope at 6-month of follow up	0.29(-0.21,0.79)	0.256	0.253				
Comparison slope 1-month vs baseline β	0.41(-0.26,1.08)	0.340	0.230				
Comparison slope 6 months vs baseline β	1.02(0.25,1.78)	0.390	0.010				

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