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ORIGINAL PAPER

Antipsychotic-induced parkinsonism is associated with working memory deficits in schizophrenia-spectrum disorders

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Abstract In view of the significant cognitive deficits in schizophrenia and their impact on patients' social and occupational functioning, and considering that the influence potential influence of antipsychotic-induced extrapyramidal symptoms on cognition in schizophrenia remains poorly understood, the current study sought to identify the clinical, socio-demographic and neurologic predictors of the cognitive performance of schizophrenia patients. Eighty-two schizophrenia-spectrum (DSM-IV criteria) outpatients were recruited. Psychiatric symptoms were evaluated with the *Positive And Negative Syndrome Scale* and the *Calgary Depression Scale for Schizophrenia*. Extrapyramidal symptoms were evaluated with the *Extrapyramidal Symptoms Rating Scale*, while spatial working, planning abilities and visual paired associates learning were evaluated with the *CAmbridge Neuropsychological Tests Automated Battery*. The Stroop test was also administered. Multivariate hierarchic linear regression analyses were performed. We found that negative symptoms were associated with cognitive flexibility, planning, visual learning and working memory performance in schizophrenia. Age, sex, number of hospitalizations and antipsychotic type also emerged as significant predictors. More importantly, we found a significant association between antipsychotic-induced parkinsonism and working memory performance. The fact that negative symptoms and socio-demographic variables predicted cognitive performance in schizophrenia is consistent with the previous literature on the topic. The finding of an association between parkinsonism and working memory may have clinical implications, since working memory deficits are considered putative endophenotypes of schizophrenia and are known to impair patients' social and occupational functioning. Our results will need to be replicated in longitudinal studies involving larger samples of patients.

Keywords Schizophrenia · Parkinsonism · Working memory · Cognitive flexibility · Negative symptoms

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Introduction

Neuropsychological studies have shown that 70–75 % of patients with schizophrenia have significant cognitive deficits [1]. The deficits encompass attention, reasoning and problem solving, speed of processing, verbal memory, visual memory and working memory [2]. Cognitive performance of patients with schizophrenia is 1–1.5 standard deviations below the performance of the general population [3]. Importantly, cognitive deficits are better predictors of social and occupational functioning than positive (delusions, hallucination) and negative symptoms (social withdrawal, blunting of affect, etc.) [4].

In view of the importance of cognitive dysfunctions in schizophrenia, research has been actively pursued in order to identify clinical factors that may predict patients' cognitive performance. Thus far, one of the most well-established relationships is the association between negative

symptoms and cognition. Negative symptoms are more strongly associated with cognition in schizophrenia than positive or depressive symptoms, and it has been estimated by meta-analysis that a small-to-moderate portion of the variance in cognitive performance can be attributed to negative symptoms [5]. Apart from psychiatric symptoms, various socio-demographic variables (such as age, sex and number of hospitalizations) have also been shown to be correlated with the cognitive deficits of schizophrenia, although these factors seem to explain a smaller portion of variance [6, 7].

Antipsychotics are the mainstay of schizophrenia treatment, but they can unfortunately cause a broad range of side effects, including sedation, hypotension, weight gain, sexual dysfunctions and neurologic symptoms [8]. First-generation antipsychotics (FGAs) are more likely than second-generation ones (SGAs) to produce extrapyramidal symptoms (EPS) [8], such as akathisia (subjective and observed restlessness), dystonia (muscular cramps), parkinsonism (resting tremor, bradykinesia and rigidity), and tardive dyskinesia (repetitive and involuntary movements) [9]. The emergence of EPS may lead, in return, to poor-treatment compliance [10]. Importantly, these neurologic side effects are overlooked factors that may contribute to cognitive deficits in schizophrenia. In Parkinson's disease patients without any psychotic disorder, significant cognitive deficits have been described. Parkinson's disease patients are at increased risk of developing dementia [11, 12], and in those who did not develop dementia yet, it has been shown that their performance is impaired on various frontal lobe functions, such as working memory, attention, verbal fluency, cognitive flexibility and concept formation [13]. Milder deficits in episodic memory have also been described, albeit less consistently [13]. A recent met-analysis of 18 neuropsychological studies performed in Parkinson's disease patients (without dementia) produced moderate-to-large effect size estimates for frontal lobe deficits [14].

In schizophrenia, the potential associations between drug-induced EPS and cognition have not been extensively studied. Moreover, most studies on the topic have examined the link between EPS and subjective cognitive complaints. For instance, Kim and Byun [15] showed, in a group of 91 outpatients with schizophrenia, a significant and positive correlation between drug-induced parkinsonism and subjective complaints, as measured with the *Frankfurt Complaint Questionnaire* (FCQ) [16]. Similarly, Krausz et al. [17] showed, in 86 schizophrenia inpatients, that high levels of EPS were associated increased subjective complaints on 6 of the 10 FCQ subscales. Other groups have examined the relationships between *objective* cognition and EPS. While Tanaka et al. [18] found that higher EPS were associated with poorer attention and poorer global cognitive performance, Palmer et al. [19] found that higher EPS were associated with deficits in verbal learning and motor skills. While looking more specifically at tardive dyskinesia (TD), Pantelis et al. [20] found that schizophrenia patients have increased deficits in spatial working memory, whereas Wu et al. [21] found that TD is associated with more prominent deficits in visuo-spatial abilities and attention in schizophrenia. Importantly, however, the seminal CATIE examined the relationship between TD and cognition in 1,310 schizophrenia patients, and after controlling for various socio-demographic confounding variables (age, antipsychotic type, etc.), the study found no association between TD and worsening of cognition [22]. In the end, the current state of knowledge provides preliminary though non-conclusive evidence of the influence of EPS on cognition in schizophrenia, without specifying which EPS is the most likely to exacerbate cognitive impairment. It is also uncertain whether the influence of EPS on cognition remains significant after controlling for the presence of other factors known to influence cognition in schizophrenia.

The objective of the current study was to identify the psychiatric, socio-demographic and neurologic predictors of cognitive impairments in schizophrenia, using a multivariate statistical approach. Our a priori hypothesis was that antipsychotic-induced EPS would be associated with cognitive deficits and that the influence of EPS on cognition would be small, once other clinical factors would be included in the statistical modeling.

Methods

Participants

Patients aged 18–60 years and having a DSM-IV diagnosis of schizophrenia-spectrum disorder were included. Patients presenting with a major physical disability, comorbid substance use disorder, mental retardation and/or cognitive deficits of organic origin (such as dementia) were excluded. Participants were all outpatients in a stable state without any major change in medication for at least 2 months prior to the study. All participants signed a detailed consent form. The study was approved by the local ethics committee from the Centre Hospitalier de l'Université de Montréal and Louis-H Lafontaine Hospital and was therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Clinical evaluation

The psychiatric and depressive symptoms of schizophrenia were evaluated, with the *Positive And Negative Syndrome*

Scale (PANSS) [23] and the *Calgary Depression Scale for Schizophrenia* (CDSS), respectively [24]. EPS were evaluated with the *Extrapyramidal Symptoms Rating Scale* (ESRS), which has high inter-rater reliability [25]. The ESRS is one of the most utilized scales to measure antipsychotic-induced EPS [26], and it provides a score for the patients' subjective appraisal of his symptoms, objective scores for parkinsonism, dystonia and dyskinesia and a global evaluation of EPS. For the purpose of the current study, we used the objective scores for parkinsonism, dystonia and dyskinesia. Psychiatric symptoms and EPS were assessed by a well-trained physician with a unique expertise in psychiatry and neurology who was blind to the study objective.

Neuro-cognition was assessed using the *Cambridge Neuropsychological Test Automated Battery* (CANTAB, Eclipse version 2.0) [27, 28], a series of computerized tasks. The tests were run on computers with touch-sensitive color monitors. Four CANTAB subtests were administered, and specific indexes were used: the *Motor Screening* task (MOT), which measures visuo-motor coordination by mean latency time; the *Paired Associates Learning* task (PAL), where recall is measured with the first-trial memory score and learning is measured by the total errors adjusted score; the *Stockings of Cambridge* task (SOC), which measures planning with the number of problems solved in minimum moves; the *Spatial Working Memory* task (SWM), which measures visuo-SWM with the number of errors made between searches as well as with a strategy score that indicates the use of a more systematic strategy. The Color-Word and the interference scores of the *Stroop Color-Word Test* (Golden version) were used to assess selective attention [29].

Statistical analysis

Statistical analyses were performed using the Predictive Analytics SoftWare (PASW; version 18). For all continuous variables, the Kolmogorov–Smirnov one-sample test for normality was applied. Root transformations were used in order to remove skews when appropriate. Multiple hierarchical linear regression analyses were used to explore associations between cognition and EPS, while considering the influence of psychopathology and socio-demographic variables. Multiple hierarchical linear regression analyses provide finer information than correlation analyses by generating models in which one or several significant predictors are hierarchically sorted according to the amount of variance they account for a given dependent variable. Analyses of variance and Pearson's correlations were used to screen potential confounders, including socio-demographic (age, sex, education level, hospitalizations, psychiatric diagnosis, antipsychotic type, duration of illness, antidepressants and anticholinergics) and psychiatric (positive, negative and depressive symptoms) variables. Confounders that were significantly related with our variables of interest (cut-off: $p < 0.1$) were subsequently entered into the multi-variate regression models. In the multivariate analyses, cognitive variables were the dependent variables, the predictors (regressors) were EPS, and the confounders identified in the correlation analyses. For the multivariate analyses, the level of significance for the regression models was set at $p < 0.05$, and we applied Bonferroni correction (thus, 0.05/8 cognitive scores $\rightarrow$ $p < 0.00625$).

A post hoc power analysis showed that the recruitment of 82 patients (see below) would allow to detect a moderate association ($r = 0.3$) between cognitive functioning and EPS in schizophrenia with a statistical power higher than 80 %.

Results

Description of population

Our sample of participants included 82 outpatients with schizophrenia-spectrum disorders living independently in the community. As illustrated in Table 1, our sample was composed of so-called "chronic" patients who had mild-to-moderate levels of psychiatric symptoms. Most patients were male, single, unemployed Caucasians, who were treated with second-generation antipsychotics (SGAs). Noteworthy, 29.3 % of patients were treated with clozapine. Based on CANTAB's normative data (age- and sex-adjusted), the patients' cognitive performance was 0.6–1.5 standard deviations below the performance of the general population. Finally, the most prevalent EPS diagnosis was parkinsonism, followed by dyskinesia and dystonia.

Relationships between clinical variables and cognition

As shown in Table 2, MOT meant latency was predicted by antipsychotic type, which explained 12.5 % of the variance. The PAL first-trial memory score was predicted by education level, which explained 13.0 % of the variance. For PAL total errors, the multiple regression analyses produced a model including three significant predictors (age, education level and negative symptoms), which accounted for 29.0 % of the variance. For SWM between errors, the multiple regression analysis produced a model including two significant predictors (age and parkinsonism), which accounted for 22.7 % of the variance. For SWM strategy, it was predicted by a model including three regressors (age, sex and negative symptoms), which accounted for 26.1 % of the variance. SOC performance

Table 1 Population characteristics

Variable	Description
Age	41.7 ± 10.0 years
Sex	52 males, 30 females
Education levels	11.7 ± 2.9 years
Number of hospitalizations	5.5 ± 5.7
Duration of illness	16.0 ± 9.4 years
Ethnicity	75 Caucasian; 4 African; 1 Asian; 2 Haitian
Marital status	72 single
Occupation	57 unemployed
Psychiatric diagnoses	Schizophrenia ($n = 53$)
	Schizo-affective disorder ($n = 20$)
	Other non-affective psychotic disorders ($n = 9$)
Neurologic diagnoses[a]	Dyskinesia ($n = 18$)
	Dystonia ($n = 5$)
	Parkinsonism ($n = 29$)
Antipsychotics[b]	First-generation antipsychotics ($n = 7$)
	Second-generation antipsychotics ($n = 58$)
	Mixed antipsychotics ($n = 16$)
	Drug free ($n = 1$)
Adjuvants	Anticholinergics ($n = 24$)
	Antidepressants ($n = 25$)
	Mood stabilizers ($n = 4$)
PANSS	
Positive	19.0 ± 5.4
Negative	20.2 ± 7.4
General	38.5 ± 8.6
Total	76.0 ± 18.1
CDSS	2.2 ± 1.8
CANTAB	
MOT mean latency	1,226.2 ± 260.9 (z score = −1.1)
PAL first-trial memory score	15.7 ± 4.5 ($z = -1.5$)
PAL total errors	35.9 ± 37.8 ($z = -1.4$)
SOC problems solved in minimal moves	7.6 ± 2.1 ($z = -0.6$)
SWM between errors	37.5 ± 20.2 ($z = -0.7$)
SWM strategy	35.4 ± 5.9 ($z = -0.6$)
Stroop Color-Word	37.1 ± 15.2
Stroop Interference	−2.7 ± 9.0

CANTAB Cambridge Neuropsychological Tests Automated Battery, *CDSS* Calgary Depression Scale for Schizophrenia, *MOT* motor screening, *PAL* paired associates learning, *PANSS* Positive And Negative Syndrome Scale, *SOC* Stockings of Cambridge, *SWM* spatial working memory

[a] Neurologic diagnoses were based on cutoff scores defined by Chouinard and Margolese [24]

[b] 24 patients were treated with clozapine

Table 2 Clinical and neurologic predictors of cognitive deficits in schizophrenia

Predictors	r^2	β	Significance
Dependent variable: MOT			
Antipsychotic type	0.125	117.4	$F = 10.6$; $p = 0.002$
Dependent variable: PAL first-trial memory score			
Education level	0.130	0.538	$F = 11.6$; $p = 0.001$
Dependent variable: PAL total errors			
Model	0.290		$F = 10.5$; $p = 0.0001$
Age		1.497	$t = 4.0$; $p = 0.0001$
Education level		−3.915	$t = -3.0$; $p = 0.003$
PANSS negative symptoms		1.213	$t = 2.4$; $p = 0.017$
Dependent variable: SWM between search errors			
Model	0.227		$F = 11.5$; $p = 0.0001$
Age		0.669	$t = 3.2$; $p = 0.002$
Parkinsonism		5.219	$t = 3.1$; $p = 0.003$
Dependent variable: SWM strategy			
Model	0.261		$F = 8.8$; $p = 0.0001$
Age		0.210	$t = 3.4$; $p = 0.001$
Sex		3.216	$t = 2.6$; $p = 0.012$
PANSS negative symptoms		0.211	$t = 2.6$; $p = 0.012$
Dependent variable: SOC problems solved in minimum moves			
Model	0.169		$F = 5.8$; $p = 0.005$
PANSS negative symptoms		−0.090	$t = -2.8$; $p = 0.008$
Hospitalizations		−0.424	$t = -2.0$; $p = 0.045$
Dependent variable: Stroop Color-Word			
Model	0.377		$F = 15.5$; $p = 0.001$
Age		−2.627	$t = -4.3$; $p = 0.0001$
PANSS negative symptoms		−0.606	$t = -3.1$; $p = 0.003$
Parkinsonism		−0.636	$t = -2.0$; $p = 0.045$

MOT motor screening, *PAL* paired associates learning, *PANSS* Positive and Negative Syndrome Scale, *SOC* Stockings of Cambridge, *SWM* spatial working memory

(problems solved in minimum moves) was predicted by a model including two regressors (negative symptoms and hospitalizations), which explained 16.9 % of the variance. Finally, for the Stroop Color-Word, the multiple regression analysis produced a model including three significant

predictors (age, negative symptoms and parkinsonism), explaining 37.7 % of the variance. Finally, parkinsonism emerged as significant predictor, which accounted for 4.8 % of the variance the Stroop-Interference dependent variable. However, this result ceased to be significant after applying Bonferroni correction.

Discussion

In view of the significant cognitive deficits in schizophrenia and their impact on patients' social and occupational functioning, and considering that the potential influence of antipsychotic-induced EPS on cognition in schizophrenia remains poorly understood, the current study sought to identify the clinical, socio-demographic and neurologic predictors of the cognitive performance of 82 schizophrenia-spectrum patients. Here, we found that negative symptoms were associated with increased deficits in cognitive flexibility, planning, visual PAL and working memory in schizophrenia. Such results are consistent with the vast literature highlighting small-to-moderate associations between negative symptoms and all of the core cognitive domains impaired in schizophrenia, namely attention, reasoning and problem solving, speed of processing, verbal/visual memory and working memory [5]. Apart from negative symptoms, various socio-demographic variables (age, education level, number of hospitalizations and sex) also emerged as significantly related with cognitive impairment in schizophrenia in the current study. Again, these results are consistent with the available evidence. Although the notion of progressive cognitive decline in schizophrenia is controversial, various groups have reported that age and hospitalization number (or duration of illness) are associated with cognitive impairment in schizophrenia, while education is a typical confounding variable of cognitive studies performed in schizophrenia [7, 30]. As for the association between sex and working memory in schizophrenia, it is supported by preliminary results suggesting that cognitive performance in schizophrenia is influenced by subtle sex-differences, both normal and possibly inverted [6, 31]. Here, we found that being female was a predictor of increased working memory errors. This finding is consistent with the results a large cross-sectional study performed by Torniainen et al. [32] in 218 schizophrenia patients, 438 unaffected first-degree relatives and 123 healthy volunteers, which showed that males outperformed females on visual working memory across groups.

The most important result of the current study is the association between antipsychotic-induced parkinsonism and working memory deficits in schizophrenia. As such, this result is consistent with cognitive literature showing that Parkinson's disease patients without any psychotic disorder have moderate impairments in working memory [13]. It is also consistent with a recent study from Cuesta et al. [33], which showed that *spontaneous* parkinsonism is associated with increased frontal lobe deficits in first-episode psychosis patients. On biological grounds, positron emission tomography (PET) studies have shown that EPS occur when antipsychotics occupy more than 80 % of dopamine-D_2 receptors in the striatum [34]. Antipsychotics therefore cause dopaminergic alterations similar to those observed in Parkinson's disease, which is primarily caused by loss of dopaminergic neurons in the nigrostriatal pathway [35]. In Parkinson's disease, it has been proposed that secondary dopamine alterations may occur in other dopaminergic pathways, including the mesocortical system [36], which could give rise to the relatively well-documented deficits in executive functions associated with the disease. In schizophrenia, executive dysfunctions have long been assumed to be related to prefrontal hypo-dopaminergic functioning, although the formal demonstration of this hypothesis has been difficult to achieve [37]. Still, functional magnetic resonance imaging studies have repeatedly shown that schizophrenia patients have abnormal activations of the dorsolateral prefrontal cortex during working memory performance [38]. By blocking frontal D_2 receptors, antipsychotics may thus exacerbate the working memory deficits of schizophrenia patients. Interestingly, in a recent PET study, aripiprazole (antipsychotic) was administered to healthy volunteers and the results showed that greater striatal D_2 receptor occupancy was associated with greater decreases in frontal lobe metabolism, and longer reaction times on a working memory task [39].

Even though our results are consistent with was has been shown in Parkinson's disease, this association may not be related to common dopaminergic alterations. It may be related, instead, to the use of anticholinergic drugs that are prescribed to schizophrenia patients experiencing EPS and known to cause mnesic problems [40]. However, we examined the potential influence of anticholinergics and found no effect of these drugs on our results. Another possible explanation is that the association between parkinsonism and working memory may reflect time-related issues. In a population of chronic patients, working memory deficits were predicted not only by drug-induced parkinsonism but also by patients' age. However, we found no association between duration of illness and cognitive performance in schizophrenia. Still, our study is a cross-sectional not a longitudinal one. Due to this study design, it is difficult to confirm or disprove the role of time-related issues on our results. The cross-sectional nature of study makes it also difficult to determine the directionality of the observed association. While drug-induced parkinsonism may contribute to working memory deficits in

schizophrenia, it is also possible that schizophrenia patients having the worst cognitive and occupational functioning are those who are the most likely to receive the drug regimen increasing the risk of having neurologic side effects.

In the current study, we found no relationship between cognition and dystonia as well as dyskinesia. In the latter case, the absence of relationship is surprising since it has previously been shown that TD is associated with increased cognitive deficits in schizophrenia [20, 21], although the CATIE study did not find this association [22]. One of the potential reasons for this lack of effect is that only 18 patients (e.g. 22 %) of our whole sample responded to a dyskinesia diagnosis, whereas more than 50 % of patients had TD in the studies from Pantelis et al. [20] and Wu et al. [21]. Another reason may be related to the fact that we used a multivariate statistical approach, but this is an unlikely explanation since the studies from Pantelis et al. [20] and Wu et al. [21] both paid attention to potential confounding factors. Finally, we found an association between antipsychotic type and speed of processing (e.g., MOT task). More precisely, we found a linear relationship where the worse performance was associated with multiple antipsychotic treatment (SGAs and FGAs), and the best performance, with SGA treatment. Although the phenomenon has not been frequently studied, there is preliminary evidence showing that *multiple* antipsychotics may slightly impair cognitive performance in some cases in schizophrenia [41]. In addition, researchers are growingly acknowledging that deficits in speed of processing play a critical role in schizophrenia. For instance, a recent study from Ojeda et al. [42] used confirmatory factor analysis in 100 schizophrenia and 53 healthy volunteers and found that the patients' deficits in attention, executive functions, verbal memory, visual memory and working memory were substantially smaller after controlling for processing speed. Importantly, no other cognitive domain had similar effects on results.

The results of the current study may have clinical implications. Although EPS were not found to exert a broad influence on cognition in schizophrenia, a more specific relationship between parkinsonism and working memory was observed. This association is noteworthy since this study was naturalistic and did not purposely recruit patients with increased levels of EPS. Working memory is generally considered as a putative endophenotype of schizophrenia [43]. Working memory deficits have been shown in unaffected first-degree relatives, as well as in individuals at clinical high risk for psychosis, including those who later develop psychosis [44]. In addition, working memory deficits are known to significantly impair social and occupational functioning in schizophrenia [45]. If confirmed, the association reported here could imply that by treating antipsychotic-induced parkinsonism, it may be possible to improve working memory performance in schizophrenia.

Our study had a few limitations that need to be discussed. First, we did not have access to antipsychotic dosages; thus, chlorpromazine equivalents could not be calculated. The emergence of EPS may signal that antipsychotic treatment is prescribed at doses that are too high and may therefore impair cognition by mechanisms other than drug-induced parkinsonism. Without calculating chlorpromazine equivalents, this interpretation of our results cannot be ruled out. However, it is important to remind that there is currently no gold standard widely accepted by the scientific community to calculate antipsychotic equivalents [46]. Moreover, the calculation of chlorpromazine equivalents is more problematic in the case of clozapine and quetiapine. The curb distribution of chlorpromazine equivalents is typically skewed in studies involving a significant number of patients treated with these drugs, such as in the current study (clozapine, 24; quetiapine, 18) [47]. In addition, we entered antipsychotic type (FGAs, SGAs, and both) into the statistical modeling and it emerged as being only significantly associated with speed of processing performance (e.g. MOT task). Another limitation of this study is the lack of measurement of verbal learning and memory, which is one of the core cognitive domains known to be impaired in schizophrenia [48]. However, our cognitive battery comprised comprehensive assessments of attention, reasoning and problem solving, speed of processing, visual learning and working memory. Moreover, akathisia was not measured with a specific scale in the current study. However, the current state of knowledge does not seem to suggest that akathisia is the EPS the most likely to impair cognition in schizophrenia [49]. Finally, the study did not have a control group of healthy controls. As an alternative, we used CANTAB's normative data to determine the magnitude of patients' cognitive deficits.

The current study showed that antipsychotic-induced parkinsonism is associated with increased working memory deficits in schizophrenia, while replicating the previously reported influence of negative symptoms, age, sex, number of hospitalizations and education on the cognitive performance of these patients. In the future, longitudinal and large-scaled studies will need to be performed in order to better understand the complex relationships between EPS and cognition in schizophrenia. Attention will also need to be paid to other side effects of antipsychotics, such as sedation, which may also contribute to cognitive dysfunctions in schizophrenia.

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Conflict of interest None.

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