Procedural Learning in Schizophrenia Can Reflect the Pharmacologic Properties of the Antipsychotic Treatments

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Background: Conventional and atypical antipsychotics have different affinities for D_2 receptors, and these receptors are principally located in the striatum. Given that this cerebral structure was previously found to play a major role in procedural learning, the antipsychotic treatment in schizophrenia may be determinant for the procedural learning profile of these patients.

Objective: The current study was aimed at verifying whether procedural learning differs in patients with schizophrenia treated with conventional antipsychotics and patients treated with atypical antipsychotics.

Method: Forty-five patients with schizophrenia were divided into 3 different groups according to their pharmacologic treatment: (1) haloperidol, a classical neuroleptic with high D_2 receptor affinity; (2) clozapine, an atypical neuroleptic with practically no D_2 receptor affinity; and (3) risperidone, an atypical neuroleptic that nevertheless shows high D_2 receptor affinity. Patients were compared to 35 control subjects on a visuomotor procedural learning task (mirror drawing).

Results: All patients were able to learn the task. However, those treated with haloperidol showed some degree of learning impairment, while those treated with clozapine or risperidone did not show this impairment. In addition, performance per se, regardless of the learning, was found to be affected in the haloperidol and risperidone, but not in the clozapine groups.

Conclusion: Procedural learning in schizophrenia may be differentially affected, depending on the pharmacologic profiles of the antipsychotics used for the treatment of this illness.

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Cognitive deficits in schizophrenia are now well established. Dysfunctions in the area of attention, memory, language, and executive functions have been described and are now recognized as core features of the illness.[1–3] Moreover, it has recently been established that cognitive measures have a better predictive value for the social adaptation of patients with schizophrenia than psychiatric scales.[4,5] However, until now, cognitive dysfunctions in schizophrenia have been documented mostly in chronically medicated patients. It is therefore difficult to determine the dysfunctions that may be attributed to the illness itself and those that may be more specifically related to the neuroleptic-induced effects. This question has gained in importance during the past decade with the emergence of the new generation of neuroleptics, which were found to be less deleterious than the classical neuroleptics on multiple cognitive functions,[6,7] including procedural learning.[8,9]

Procedural learning may be defined as the development of skills in which the strategy of execution cannot be explicitly described (learning by doing). Cognitive or motor procedural skills are learned progressively with practice until there is an automatization of the optimal performance. This function is usually assessed with tasks that require unfamiliar motor or cognitive skills. For instance, the subject may be required to learn and replicate an arbitrarily defined visuospatial sequence or to learn to track a moving target along a predictable path. These types of learning were reported to be impaired first in neurologic illnesses involving the striatum, such as Huntington or Parkinson disease.[10–12] The striatum was then suggested as a critical structure involved in procedural learning. Other cerebral structures such as the cerebellum, the prefrontal cortex, and the supplementary motor area have also been found to be involved, although their specific contributions vary considerably depending on the different learning stages examined and on the specific cognitive or motor processes involved in

the task.[13,14] For instance, Positron emission tomography studies performed on normal subjects have shown that frontal structures were activated during the initial stages of a psychomotor procedural acquisition, while striatal and cerebellar structures were found to be active throughout the learning process.[13]

Previous studies have shown that patients with schizophrenia are able to learn new cognitive or motor procedures.[1,15–18] However, the learning profile in these patients seems to be distinct from normal subjects. In particular, low learning rates[15,19] and large inter-trial fluctuations[8,9,20] seem to characterize the procedural learning of patients with schizophrenia. Given that such disturbances have been observed in neurologic populations with striatal lesions, in schizophrenia, these abnormal procedural learning profiles have been also associated with striatal dysfunction.[8,9,16,19] Striatal dysfunction in schizophrenia has been recently demonstrated by imaging methods, even in drug naive patients.[21,22] On the other hand, the contribution of antipsychotic drugs may not be excluded given that these substances are known to affect striatal functioning and that acute administration of antipsychotics such as chlorpromazine have been found to induce procedural learning disturbances in normal subjects.[23,24]

In recent years, there has been a growing interest in the use of atypical antipsychotic agents since contrary to the classical agents, these substances have been found efficient on the negative symptoms of the illness. In addition, striatal functioning remains almost unaffected when these substances are administered in therapeutic doses,[25–27] and the prevalence of extrapyramidal symptoms in schizophrenia was found to be lower with atypical than with classical antipsychotics.[28,29] However, it should be stressed that among the atypical antipsychotics, there seems to be a large spectrum of effects that does not allow one to consider these substances as homogeneous.[30] For instance, clozapine may be considered the prototype of the atypical antipsychotics, while risperidone, which is also considered an atypical one, may show pharmacologic features of both classical and atypical antipsychotics.

Results obtained previously in our laboratory[8,9] have shown that patients with schizophrenia exhibit different profiles with respect to procedural learning, depending on whether they are treated with a classical or an atypical antipsychotic (haloperidol and clozapine, respectively). Patients treated with clozapine showed normal progressive learning across trials, while patients treated with haloperidol had significant learning difficulties. This result might be attributed to the differential pharmacologic effects of these substances in the striatum. The present study was an attempt to further investigate this question by studying the effects on a procedural learning task of a classical (haloperidol) and 2 atypical antipsychotics, one that is considered as the prototype of atypicality (clozapine) and the other that remains questionable regarding its atypicality (risperidone). Two specific hypotheses were formulated: (1) Given its effect on the striatum, the conventional neuroleptic should be more deleterious on procedural learning than the atypical neuroleptics. (2) Given that risperidone has some features of conventional neuroleptics, namely its high D_2 receptor affinity, this substance should have a different effect than clozapine on procedural learning.

METHODS

Subjects

Forty-five institutionalized patients with chronic schizophrenia and 35 control subjects were included in the study. All were right handed. A written informed consent was obtained from all the subjects after a complete description of the study. Control subjects were healthy volunteers taken from the general population and specifically enrolled to participate in this study. Neurologic and psychiatric conditions were ruled out in each participant during a screening interview performed by a trained neuropsychiatrist before the enrollment. However, extrapyramidal symptoms were not a priori exclusion criteria in patients with schizophrenia, although all of them were devoid of such motor manifestation at the moment of the testing session. The diagnosis of schizophrenia was based on the fourth edition of *The Diagnotic and Statistical Manual for Mental Disorders*. Criteria for paranoid, residual, undifferentiated, or disorganized schizophrenia were used. None of the patients had diagnosable neurologic diseases, and none suffered from substance abuse (with the exception of cigarette smoking).

Patients were selected on the basis of their antipsychotic treatment and the evidence that they were stable with this medication. At the time of testing, all patients were treated with only 1 antipsychotic since at least 3 months without interruption and without dose changes. Three antipsychotic medications were selected on the basis of their classification as conventional and atypical substances. These included (1) haloperidol, the prototype of the conventional antipsychotics; (2) clozapine, the prototype of the atypical antipsychotics; and (3) risperidone, an atypical antipsychotic that shows some pharmacologic features of the conventional ones.[26,30] There were 15 patients in each of the 3 groups. Given that the clinical conditions of all patients were stabilized with their current antipsychotic treatments and that it is not ethically possible to administer clozapine to non-refractory patients, a double-blind crossover design with placebo was not possible in this study. Thus, the design of the study was naturalistic; there was no readjustment of doses or change in medication. In addition to their antipsychotic medication, patients did not receive concurrent psychotropic medication such as lithium or benzodiazepine. However, some patients may have been treated with anti-Parkinsonian medications (Table 1).

The 3 patient groups were matched with the control group for age, sex, and education. In order to make the 3

TABLE 1. Sociodemographic and Clinical Features for Each Group

	Controls (n = 35)	Haloperidol (n = 15)	Clozapine (n = 14)	Risperidone (n = 15)	*F*	*df*	*p*
Age (yr)	38.0 (9.2)	37.1 (8.7)	36.5 (8.7)	38.1 (9.3)	0.23	3,77	NS
Education (yr)	11.1 (2.5)	12.3 (3.4)	12.1 (3.1)	11.1 (2.3)	0.90	3,77	NS
Illness duration (yr)	—	9.9 (10.0)	11.2 (6.3)	9.9 (6.8)	0.10	2,43	NS
PANSS (positive score)	—	15.1 (6.2)	14.6 (4.8)	13.2 (6.5)	0.14	2,41	NS
PANSS (negative score)	—	19.5 (6.4)	19.4 (6.6)	20.2 (8.8)	0.25	2,41	NS
PANSS (general score)	—	33.8 (10.8)	34.6 (9.8)	33.6 (12.2)	0.00	2,41	NS
ESRS (parkinsonim)	—	8.7 (8.3)	4.6 (2.5)	8.7 (5.1)	1.27	2,39	NS
ESRS (dystonia)	—	0.1 (.25)	0.0 (0.0)	0.2 (0.6)	0.97	2,40	NS
ESRS (dyskinesia)	—	1.1 (2.28)	0.8 (2.7)	0.5 (1.4)	0.26	2,40	NS
Doses (mg/day)	—	13.3 (11)	348 (188)	5.2 (2.7)	—	—	—
Equivalent chlorpromazine doses (mg/day)	—	638.2 (541.6)	418.8 (226.8)	606.2 (365.2)	1.91	2,41	NS
Diagnosis	—	10 Paranoid 4 Undifferentiated 1 Disorganized	12 Paranoid 2 Undifferentiated	13 Paranoid 1 Residual 1 affective	—	—	—
Anti-Parkinsonian (occurrence)	—	7 Benztropine 6 Procyclidine	0 Benztropine 0 Procyclidine	5 Benztropine 4 Procyclidine	22.9*	2	<0.01

Values are means and standard deviations (in parentheses).
*Chi-square on the occurrence of antiparkinsonian medication.
PANSS, Positive and Negative Syndrome Scale; NS, not significant; ESRS, Estra Pyramidal Symptoms Rating Scale.

groups of patients comparable on the basis of equivalent antipsychotic doses, daily chlorpromazine dose equivalents were computed for each patient within all groups, using the equivalence table of the American Psychiatric Association guidelines.[31]

Psychiatric symptoms in schizophrenic patients were assessed using the Positive and Negative Syndrome Scale (PANSS).[32] Extrapyramidal symptoms were assessed with the "Extrapyramidal Symptoms Rating Scale (ESRS).[33] Table 1 shows the sociodemographic and clinical features of each group. Neuroleptic doses were comparable to those observed in other studies on the cognitive functions of patients with chronic schizophrenia.[7,34]

Procedural Learning Task

The mirror drawing task was administered to all participants. This task has previously been used to assess visuomotor procedural learning in multiple clinical populations,[35,36] including schizophrenia.[9] The task requires the subjects to learn to move their hand in a transformed visuospatial context (mirror inversion). More specifically, subject must draw the outline of a picture (a 5-arm star) by looking only at its mirror reflection. Participants were required to trace the star as quickly as possible in a clockwise direction, from a set starting position, using their preferred hand. The task includes 10 successive trials divided in 2 blocks of 5 trials. A 5-minute pause was inserted between the first and second block of trials. For each trial, scores included the time to completion (seconds) and the number of errors (oversteps of more than 5 mm beyond the guidelines of the star to be drawn). Given that a speed–accuracy tradeoff was present (fast completion time with numerous errors in some trials and slow completion time without errors in other trials), statistics were performed on the scores computed from the following equation: [completion time] × [number of errors + 1]. Although this puts a greater emphasis on the number of errors than on execution, such a score has the advantage of comparing all subjects on the basis of the same performance criterion. Figure 1 illustrates learning curves of individual subjects taken from the different groups.

Statistical Methods

Within the clinical variables, raw scores of the PANSS-positive symptoms subscale and ESRS Parkinsonism subscale were not normally distributed and were therefore transformed into their natural logarithm before statistical analysis. All other clinical and sociodemographic variables were normally distributed. One-way analyses of variance (ANOVAs) were performed on these variables. Before statistical analyses, homogeneity of variance among groups was verified for each variable using the Levene statistic. Chi-square analyses were used to compare the use of anti-Parkinsonian ancillary treatment in the 3 groups of patients.

In the mirror drawing task, group differences at the beginning and end of the task were assessed by using ANOVAs performed separately on the scores of the first and last trials.

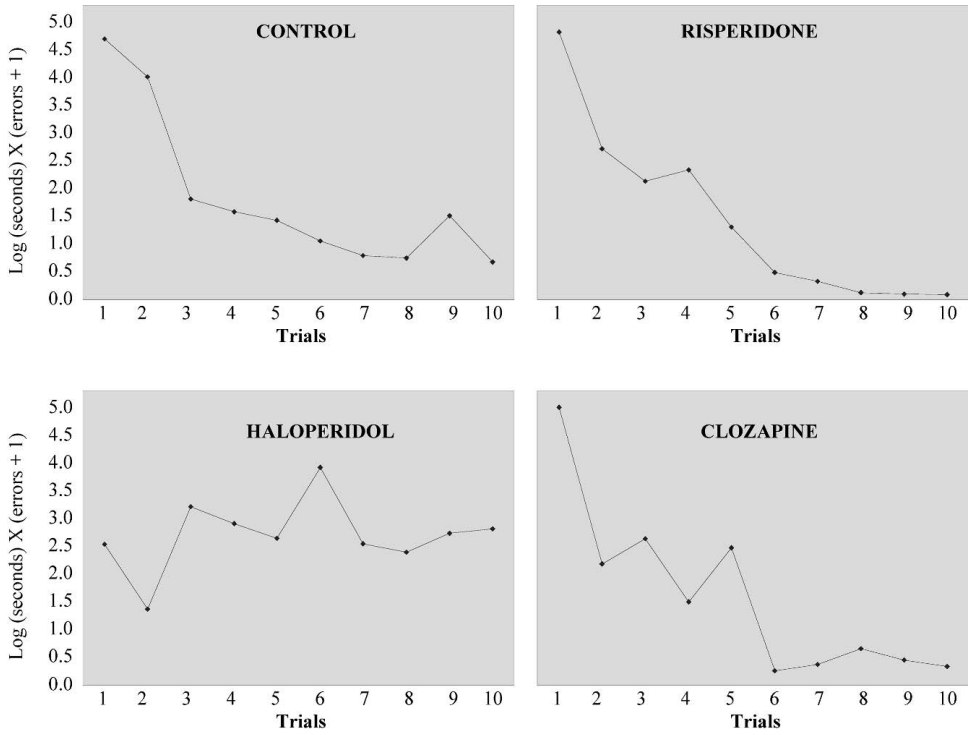

FIGURE 1. Learning curves of individuals taken from each group. Performance of the haloperidol-treated patient illustrates the lack of improvement from the beginning to the end of the task and the performance fluctuations from trial to trial.

Learning profiles along the 10 trials and across the 4 groups were analyzed using a 10 × 4 ANOVA for repeated measures. Interactions suggesting different learning profiles among groups were further contrasted using Tukey HSD post hoc comparisons. The learning profile was further analyzed qualitatively through the coefficient of determination (r^2) computed for each subject over the 10 trials, a measure called "inter-trial fluctuations." The higher the coefficient of determination (values ranging from 0 to 1), the more consistent the improvement from trial to trial. Large inter-trial fluctuations were therefore reflected by a low coefficient of determination. This variable of inter-trial fluctuations was normalized for statistical analyses using the Fisher Transformation. Another variable corresponding to the mean score for all trials was also created in order to estimate the "average performance" of each subject in the overall test. Average performance was not normally distributed so that raw data had to be normalized into natural logarithm. The third qualitative variable of learning profile was the "learning rate," corresponding to the slope (values ranging from 0 to 1), which was computed over the 10 trials. High slope values indicate fast learning rates. Groups were compared on these 3 qualitative variables of learning profile, using analysis of covariance (ANCOVA) with performance at the first trial as covariate. This ANCOVA allowed comparing groups without interfering with the initial difference of basic motor performances.

In addition to the preceding variables, "oscillations"—previously described in patients with frontal lobe lesions[34,35]—were also compiled. These were defined as "zigzag" shaped movements occurring during a trial and corresponding to a temporary incapacity to move in the correct direction. The number of oscillations in each trial was counted by 2 independent blind scorers. In case of disagreement between scorers for a given trial, the mean of the 2 scores was used. Given that oscillations usually occurred at the initial stages of learning[35,36] this score was computed separately for the first (initial stage of learning) and the second (automatization) block of trials. The oscillation score could not be normalized, so a dichotomization score was created (low vs. high oscillation frequency), by using Fisher Exact test (2 tailed), to determine a cutoff point between the minimum and the maximum number of oscillations (0 and 20) in our total sample (all groups taken together). A value of 9 oscillations was obtained as the cutoff point. A between-groups Kruskal-Wallis chi-square analysis was performed on the oscillation variable. Wilcoxon tests were performed to further contrast individual groups.

In order to assess the effect of the anti-Parkinsonian ancillary treatment (benztropine and procyclidine) on procedural learning, patients from the haloperidol, risperidone, and clozapine groups were pooled together, and Student t tests were performed between those receiving (n = 20) and those not receiving (n = 24) such medication.

RESULTS

The Sociodemographic And Clinical Variables

Comparisons among groups did not show any difference in age or education (Table 1). Also, the 3 groups of patients did not differ on any clinical scale or subscale of the PANSS or ESRS. Mean daily chlorpromazine dose equivalents did not differ among the 3 groups. Chi-square analyses revealed a greater use of anti-Parkinsonian medication in the haloperidol group than in the 2 other patient groups [x^2 (2,44) = 22.9, $p <$ 0.01] and a greater use in the risperidone than in the clozapine group [x^2 (1,27) = 8.6, $p < 0.01$]. There was no difference between the risperidone and the haloperidol groups regarding the occurrence of both benztropine and procyclidine.

The Mirror Drawing Task

Given that the 3 groups of patients were not different on the chlorpromazine dose equivalents, no analysis of covariance was performed with this variable as covariate. A one-way ANOVA performed on the first and the last trial, and comparing the 4 groups, showed no difference at the beginning of the test (first trial) [F (3,72) = 2.07, $p = 0.112$], but a significant difference was detected at the end (last trial) [F (3,72) = 6.443, $p < 0.001$]. Post hoc comparisons revealed that at the last trial, the haloperidol group, was significantly poorer than the other groups [(haloperidol vs. risperidone: mean difference = 0.84, $p < 0.05$), (haloperidol vs. clozapine: mean difference = .96, $p <$ 0.05), (haloperidol vs. controls*:* mean difference = 0.82, $p <$ 0.05)]. No other post hoc comparison was significant [(risperidone vs. clozapine*:* mean difference= 0.12, $p = 0.982$), (risperidone vs. control: mean difference = 0.15, $p = 0.967$), (clozapine vs. control: mean difference = 0.12, $p = 0.982$)]. A 4 × 10 ANOVA (groups × trials) for repeated measures revealed a trial effect [F (2.05,145.8) = 14.14, $p < 0.01$], a group effect [F (3,72) = 3.57, $p < 0.02$], and a group-by-trial interaction [F (6.07,145.8) = 2.91, $p < 0.05$]. Post hoc comparisons showed that performances across trials (learning profile) were different between haloperidol-treated patients and normal controls (mean difference = 135.18, $p < 0.05$) (Figure 1). However, the other patients groups (risperidone and clozapine) did not differ from normal controls [(risperidone vs. control: mean difference = 112.18, $p = 0.147$), (clozapine vs. control: mean difference = 122.71, $p = 0.111$)], nor from each other [(risperidone vs. clozapine: mean difference = 0.53, $p = 1.00$) (haloperidol vs. risperidone: mean difference = 13.00, $p = 0.997$) (haloperidol vs. clozapine: mean difference = 12.47, $p =$ 0.997)], with respect to their learning profile. The difference of learning profile in the haloperidol group was not produced by a difference of the learning rate given that the between-group ANCOVA was not significant on the slope [F (3,72) = 0.728, $p = 0.538$] (Figure 2). However, such an ANCOVA performed on the inter-trial fluctuations revealed significant between-groups differences [F (3,72) = 3.44, $p < 0.05$]. Post hoc comparisons indicated that the haloperidol group (mean difference = −0.206, $p < 0.05$), but neither the risperidone (mean difference = −0.04, $p = 0.70$) nor the clozapine groups (mean difference = −0.06, $p < 0.75$), significantly differed from controls. Other post hoc comparisons did not reveal significant differ ences in inter-trial fluctuations [(risperidone vs. clozapine: mean difference = 0.96, $p = 0.904$), (haloperidol vs. risperidone: mean difference = 0.521, $p = 0.856$), (haloperidol vs. clozapine: mean difference = −0.836, $p = 0.773$)]. ANCOVA on the average performance also showed the presence of group differences [F (3,72) = 5.285, $p < 0.005$]. Post hoc comparisons revealed that both haloperidol (mean difference = 0.553, $p <$ 0.001) and risperidone (mean difference = 0.428, $p < 0.05$) groups, but not the clozapine group (mean difference = 0.304, $p = 0.212$), performed worse than controls. Other post hoc comparisons did not reveal any significant difference [(risperidone vs. clozapine: mean difference = 0.836, $p = 0.773$), (haloperidol vs. risperidone: mean difference = −0.314, $p = 0.910$),

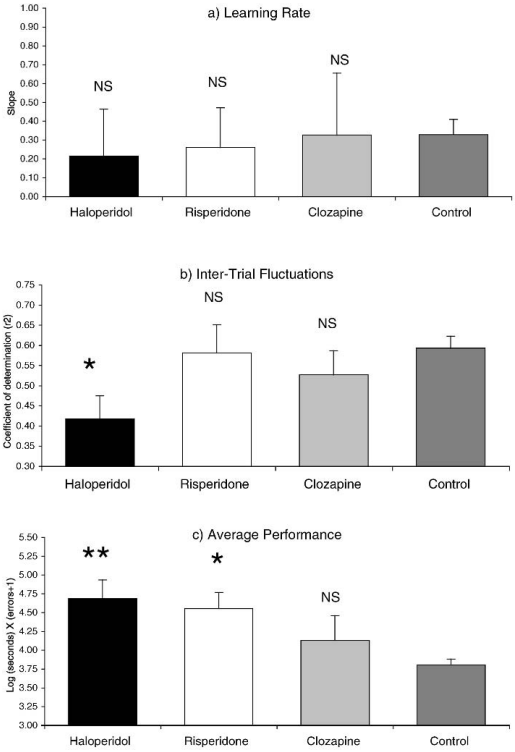

FIGURE 2. Control subjects were compared with each group of patients. The first graph (**A**) shows that learning rate was similar in the 4 groups. Comparisons of the inter-trial fluctuations, as illustrated in the second graph (**B**), show that the haloperidol group is the only group of patients that differs from the control subjects (the lower the coefficient of determination, the greater the fluctuations). The last graph (**C**) shows that both haloperidol- and risperidone-treated patients, but not clozapine-treated patients, showed poorer average performances than control subjects. NS, not significant; *= $p <$ 0.05; ** = $p < 0.001$

(haloperidol vs. clozapine: mean difference = 0.521, p = 0.856)].

In patients as well as in controls, oscillations were observed only during the first block of trials. The percentage of control subjects with a number of oscillations greater than the cutoff of 9 was 22.8%, while in patients with schizophrenia, the percentage was 46.7%, a significant difference ($x^2 = 4.83$, $p < 0.05$). However, there was no difference in the oscillations variable among the 3 groups of patients. Comparisons between patients receiving and those not receiving the anti-Parkinsonian medications (irrespective of the haloperidol, risperidone, or clozapine groups) did not show differences on the average performance [t (2,42) = 1.11, p = 0.272], the inter-trial fluctuations [t (2,42) = 1.11, p = 0.272], the learning rate [t (2,42) = 1.26, p = 0.522], or the oscillations [t (2,42) = 1.58, p = 0.751].

DISCUSSION

The results of this study indicate that patients with schizophrenia may show different procedural learning profiles depending on their antipsychotic medication. Even if procedural learning was observed in all groups of patients, those treated with haloperidol showed abnormal inter-trial fluctuations throughout the testing session, while those treated with clozapine or risperidone showed procedural learning profile comparable with control subjects.

One may ask how significant inter-trial fluctuations are from a clinical perspective. Patients treated with haloperidol may not benefit as much as the other subjects from the immediately preceding trial. In other words, their learning is less efficient (2 steps forward and 1 step back) than that of controls (who generally start each new trial at a level better than the preceding one). From a practical point of view, one might visualize learning fluctuations as in the example of learning to ride a bicycle. After some trials, performance would certainly improve in both normal subjects and in patients treated with haloperidol. However, while normal subjects would progressively improve their riding from one trial to the next, the patients treated with haloperidol may occasionally fall and hurt themselves, even if the preceding trials were well performed. They both can learn, but their learning smoothness is not the same.

Given that age, education, disease duration, and all the clinical symptom scales were similar among the groups of patients included in the current study, these factors cannot account for the procedural learning differences observed. It seems, therefore, that the pharmacologic profile of the neuroleptics may constitute the principal factor contributing to these group differences. This hypothesis may help account for the discrepancies observed in the literature regarding procedural learning in schizophrenia. Some authors[15,17,18] argued that despite the fact that patients with schizophrenia show poor performance per se or problem-solving deficit in some procedural tasks, they generally present an acquisition rate (learning) similar to controls. However, others[8,9,19] have found clear learning disturbances in other procedural tasks. Although the tasks themselves must be taken into account, the pharmacologic profile of the antipsychotics taken by the patients included in these studies may have played a role in such discrepancies.

It should be stressed that the 2 groups of patients that did not show procedural learning disturbances in the present study were treated with atypical neuroleptics, while the group of patients showing disturbances is the one treated with the conventional neuroleptic. This confirms our first hypothesis suggesting that conventional neuroleptics, but not atypical neuroleptics, would affect procedural learning. Our second hypothesis (risperidone associated with a deleterious effect greater than clozapine but lower than haloperidol) is also confirmed by the demonstration that haloperidol-treated patients showed both a disturbed procedural learning and a poor average performance, while risperidone-treated patients showed only poor average performance without disturbance of the learning profile and clozapine-treated patients were comparable with controls. These results might be explained by the greater striatal D_2 receptor occupancy associated with haloperidol and risperidone than with clozapine.[26,27,37,38] However, risperidone has a D_2 affinity as high as that of haloperidol,[26,39,40] and therefore, the D_2 occupancy hypothesis may not fully account for the differential effects observed in the present study between haloperidol and risperidone.

Atypical neuroleptics, like clozapine and risperidone, can be distinguished from conventional neuroleptics by their greater serotonin 5-HT_2 than dopamine D_2 receptor affinity.[26,27,38,39,42] This pharmacologic profile of atypical neuroleptics has been found to be related to the reduced incidence of extrapyramidal symptoms.[28] Although the mechanism of this effect is not fully understood, it may involve 5-HT_2 blockade of the inhibiting serotoninergic terminals arising from the raphe and projecting to the dopaminergic terminals in the striatum.[26,27,39,43] This 5-HT_2 receptor blockade would increase dopaminergic firing, compensating then for the D_2 receptor blockade. Another hypothesis may be that at therapeutic doses, atypical neuroleptics have lower D_2 receptor occupancy in the nigrostriatal system (associated with extrapyramidal symptoms) and higher 5-HT_2 receptor occupancy in the mesolimbic and mesocortical systems (associated with schizophrenic symptoms). In the present study, difference between atypical (risperidone and clozapine) and the conventional (haloperidol) antipsychotics on procedural learning may be related to the greater 5-HT_2 than D_2 affinity of the atypicals. Greater D_2 than 5-HT_2 receptor occupancy by haloperidol would in contrast induce striatal dysfunctions and procedural learning disturbances. Correlation between procedural learning performances and striatal D_2 receptor occupancy as measured by in vivo imaging methods in treated patients and in normal sub-

jects would certainly help elucidate the mechanism of action of the antipsychotics on procedural learning.

Cholinergic mechanisms may also be involved in the effects of antipsychotic medication on procedural learning. Benztropine and procyclidine were administered to several of our patients, and although the specific mechanism of action of these substances is not well known, it is usually assumed that they have anticholinergic activity that may counterbalance the anti-D_2 activity of the antipsychotics in the striatum. This is the theoretical premise for administering anticholinergics to reduce neuroleptic-induced extrapyramidal symptoms in schizophrenia. If we assume that the procedural learning disturbance observed in the present study may be related to a striatal dopaminergic dysfunction, one may suggest that the protective effect of clozapine could be related to its potent M_2 cholinergic receptor blocking properties,[40] while in patients treated with risperidone, such a protective effect could also be obtained by the concurrent administration of procyclidine and benztropine. However, this explanation cannot account for the deleterious effect of haloperidol with the concurrent administration of procyclidine and benztropine. Since clinical scales of extrapyramidal symptoms did not differ among our 3 groups of patients, it is unlikely that anticholinergic treatment in the haloperidol group was insufficient in compensating for the neuroleptic-induced dopamine dysfunctions in the striatum. Alternatively, it is possible that the anticholinergic substances administered to both groups (haloperidol and risperidone) were sufficient to alleviate the extrapyramidal symptoms, but not the procedural learning disruption. In other words, the procedural learning tests may be more sensitive than the extrapyramidal symptoms scale to detect the antipsychotic-induced striatal dysfunction. Conversely, it is possible that the procedural learning deficits may be related to the direct action of procyclidine or benztropine medication, given that these substances were more frequently used in the haloperidol group than in the other 2 patient groups. However, our results show that when comparing patients with and without such anticholinergic medication (irrespective of their neuroleptic treatments), there was no difference on any procedural learning measures.

One may suggest that the procedural learning problems observed with haloperidol may be related to a mechanism that does not involve the striatum. The cerebellum has been found to play a role in some procedural learning tasks.[1,13] However, this structure contains practically no D_2 receptors. Even without considering their neurochemical mechanisms, neuroleptics in general have never been associated with any deleterious effect on the cerebellum, so this structure is unlikely to be involved in the present results. Frontal cortex has also been found to be involved in procedural learning.[13,14,35,36] Given that this region receives rich dopamine innervation from the ventral tegmental area (mesocortical system), which in turn is known to be modulated by D_2 receptors, one may suggest that conventional neuroleptics may affect procedural learning by altering frontal cortex activity. However, unicellular recordings in animals[25,37] have revealed that dopamine-containing fibers from the ventral tegmental area are equally affected by conventional and atypical antipsychotics, while there is a difference between the effects of the 2 types of antipsychotics on the dopaminergic fibers arising from the substantia nigra and projecting to the striatum (nigrostriatal system). In other words, conventional antipsychotics would affect the dopaminergic cellular firing both in mesocortical and nigrostriatal systems, while atypical antipsychotics seem to affect the former without affecting the latter.[25,42] This reinforces the suggestion of a primary role of the striatum in the haloperidol-induced procedural learning disruption.

Several of the patients in the haloperidol group received more than 20 mg per day. These doses are comparable with previous studies on the cognitive functions of patients with schizophrenia.[7] However, such high doses could have contributed to the deleterious effects observed with haloperidol. Positron emission tomography studies have shown that 80% of D_2 receptors are saturated at a daily dose of 5 mg of haloperidol and that greater saturation of these receptors is usually associated with extrapyramidal symptoms.[26,27] More research will be needed to determine the highest D_2 receptor occupancy that can be achieved without producing procedural learning problems.

Another possible explanation for the differences in procedural learning among the 3 groups of patients is that the social and clinical factors that influence the choice of an antipsychotic substance for a given patient may also directly affect procedural learning. Factors such as history of treatment response, history of recent relapses or occupational functioning, and history of successes in the community could influence the choice of conventional or atypical antipsychotics, thus indirectly contributing to the results. In addition, patients treated with clozapine usually differ from other patients in that they are usually resistant to other neuroleptics. Although such an explanation remains possible, all of our patients were institutionalized and recruited from the same psychiatric community. In addition, at the time of testing, there were no differences among groups in the duration of illness, in sociodemographic variables, or in any clinical psychiatric as well as extrapyramidal scales.

Oscillations in the mirror drawing task were more frequent in patients with schizophrenia taken as a whole than in normal controls. There were no differences among patients treated with the different antipsychotics, suggesting that the phenomenon could be attributed to the illness itself rather than to the treatment. Such oscillations have been described first in patients with frontal lobe lesions.[35,36] Frontal dysfunction can affect the control of movements in novel visuospatial contexts. These oscillations appear as the inability to resolve a conflict between a highly internalized and automatized motor program (movements produced in the natural visuospatial environment)

and a new external requirement (mirror inversion of the visual feedback). In patients with schizophrenia, as in patients with frontal lobe lesions, frequent oscillations were present in the initial stage of learning (first block of trials), even if the learning took place, suggesting a difficulty in adapting to a new context. Frontal lobe dysfunctions have been well described in schizophrenia by post mortem studies,[45] imaging techniques,[46,47] and neuropsychological assessments,[2,15] and it is possible that this dysfunction may account for the oscillations observed in the initial stages of learning. Positron emission tomography studies conducted in normal subjects confirm such an assumption by showing that the frontal cortex is more active at the initial stages than at the final stage of motor procedural learning.[13,48]

CONCLUSION

The neuroleptics examined in the present study show different effects on procedural learning in patients with schizophrenia. Even though all groups showed clear procedural learning capacities, some learning disturbances can be observed in those treated with haloperidol, but not in those treated with clozapine or risperidone. This dissociation could be linked to the pharmacology of these substances on the dopaminergic and the serotonergic systems of the striatum.

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