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ORIGINAL RESEARCH

Risperidone improves interpersonal perception and executive function in patients with schizophrenia

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Objective: To investigate whether risperidone improves social cognitive impairments and executive dysfunction in people with schizophrenia.

Methods: Fifty-six patients who met the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition, diagnostic criteria for schizophrenia were allocated to a risperidone treatment group (RTG, n=28) and a typical antipsychotic treatment group (TATG, n=28). Twenty-eight healthy volunteers were recruited as the normal control group (NCG). The Positive and Negative Syndrome Scale, Interpersonal Perception Task-15 (IPT-15), and Wisconsin Card Sorting Test (WCST) were rated at baseline and after 4 and 12 weeks of treatment with risperidone or typical antipsychotics.

Results: Risperidone and typical antipsychotics decreased Positive and Negative Syndrome Scale scores for total psychopathology and positive and negative symptoms. At baseline, in the IPT-15, total scores and five factor scores, as well as the number of categories completed and the percentage of conceptual level responses, were significantly lower in the RTG and TATG than in the NCG, whereas total response errors, perseverative errors, and failure to maintain set were significantly higher in the patient groups than in the NCG. Repeated measures analysis of variance revealed a significant main effect of time period (baseline, 4 weeks, and 12 weeks) for IPT-15 scores and WCST performances, and significant interactions for time period × group (RTG and TATG). Multivariate analysis of variance showed no significant differences between the RTG and TATG on IPT-15 scores at 4 weeks, but there were significant differences between these two groups at 12 weeks. Significant differences were also found between the RTG and TATG on WCST performances at 4 and 12 weeks.

Conclusion: Individuals with schizophrenia have impairments in social cognitive and executive function, which might be improved by risperidone.

Keywords: schizophrenia, executive function, social cognition, Interpersonal Perception Task-15, Wisconsin Card Sorting Test

Introduction

Schizophrenia is a mental disorder that often begins during adolescence or early adulthood and is characterized by abnormal thoughts, perceptions, affective responses, and behaviors.[1] Cognitive impairment is as important as positive and negative symptoms in the clinical assessment and management of patients with schizophrenia[2] and includes impairments in executive function, perceptual and motor processing, attention, vigilance, verbal learning, memory, and social cognition.[3] Cognitive symptoms are a core feature of schizophrenia and are correlated with functional impairment. Furthermore, cognitive deficits should be recognized as a major element in the social and professional

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integration of patients with schizophrenia, and assessment of cognitive function should become part of the standard assessment approach in clinical practice.[2]

Executive functions are a set of higher-level cognitive skills including attentional regulation, inhibitory control, reasoning, problem solving, working memory, cognitive flexibility, and planning. These functions are responsible for monitoring behaviors that facilitate the attainment of chosen goals and, as such, are necessary for the cognitive control of behavior.[4] Executive dysfunction in schizophrenia mainly affects forward planning, concept formation, initiation, self-monitoring, and the ability to direct attention and memory; in addition, executive impairment, specifically social cognition, predicts functional outcome across multiple domains in people with schizophrenia.[5–8]

Social cognition is the ability to analyze and comprehend social psychological phenomena. Social cognitive processes encompass the perception and judgment of social and affective stimuli and the behavioral and interpersonal consequences of cognitive processes.[9,10] Many studies have shown that patients with schizophrenia have impairments in social cognitive processes, and that social cognitive dysfunction is distinct from other hallmark neurocognitive and clinical features of schizophrenia.[11,12]

Antipsychotic medication is still the main therapeutic approach for schizophrenia. Although its efficacy against certain symptoms of schizophrenia cannot be denied, the overall outcome is generally unsatisfactory.[13] For example, in some patients, cognitive or negative symptoms can be refractory to antipsychotic medication.[14] Many studies have indicated that although atypical antipsychotics are superior to typical antipsychotics in improving specific types of cognitive function in treatment-responsive schizophrenia, both typical and atypical antipsychotics can improve neurocognitive functions in patients with the disorder. For example, in a study comparing the neurocognitive effects of olanzapine and low-dose haloperidol in patients with first-episode schizophrenia, schizoaffective disorder, or schizophreniform disorder, both treatments significantly improved neurocognitive function composite score.[15] Another study demonstrated that over short periods of time, neuropsychological disturbances in schizophrenia were moderately responsive to both typical and atypical neuroleptics.[16]

There is considerable evidence that many atypical antipsychotics, including olanzapine, quetiapine, aripiprazole, and clozapine,[17–20] improve social cognitive dysfunction in patients with schizophrenia; indeed, many more studies have shown these effects with atypical antipsychotics than with typical antipsychotics. However, the effects of the atypical antipsychotic risperidone remain unclear; a few studies support the notion that risperidone improves social cognitive dysfunction in schizophrenia,[21,22] whereas others have indicated that it does not.[19,23,24] Confirming the effects of risperidone on social cognitive impairment in schizophrenia is essential for the identification of an effective clinical therapeutic strategy.

In the present study, we recruited patients with schizophrenia and healthy volunteers. Of the patients, some were treated with risperidone and others with typical antipsychotics. The Interpersonal Perception Task-15 (IPT-15) was used to assess social cognitive function (interpersonal perception), and the Wisconsin Card Sorting Test (WCST) was used to measure executive function. The purpose of this study was to determine whether risperidone improves social cognitive impairment in people with schizophrenia.

Materials and methods

All research procedures were approved by the Ethics Committee on Human Studies, Wuxi Mental Health Center, Nanjing Medical University, People's Republic of China, and were conducted in accordance with the Declaration of Helsinki. All participants gave written informed consent to participate, and all were compensated for their participation in this study. Because the patients' capacity to consent was considered to be compromised, written informed consent on the behalf of each participant was also obtained from their next of kin, caregiver(s), or guardian(s), who were also provided with details of all research procedures.

Diagnostic approaches and subjects

Fifty-six patients meeting the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth edition (DSM–5) criteria for schizophrenia were allocated to a risperidone treatment group (RTG, n=28) and a typical antipsychotic treatment group (TATG, n=28). In the RTG, 19 patients were neuroleptic-naive and nine were neuroleptic-free (five for at least 6 months and four for at least 1 month). The mean (±standard deviation) dose of risperidone was 4±1.5 mg/d. In the TATG, 17 patients were neuroleptic-naive and 11 were neuroleptic-free (eight for at least 6 months and five for at least 1 month). Patients received haloperidol (n=12), fluphenazine (n=8), chlorpromazine (n=6), or trifluoperazine (n=2). The mean chlorpromazine-equivalent dose was 502.0±198.3 mg/d. No concomitant medication was used in either patient group. Twenty-eight healthy volunteers were recruited as the normal control group (NCG). No controls had any personal or family

history of schizophrenia. Patients were recruited from Wuxi Mental Health Center, Nanjing Medical University, Jiangsu Province, People's Republic of China; controls were citizens of Wuxi City, Jiangsu Province, People's Republic of China, recruited through local advertisement. Patients and controls were excluded from the study if they were smokers, had a diagnosis of alcohol or substance dependence, had neurological disorders, had suffered any kind of head injury or systemic disease that might affect the central nervous system, or had received electroconvulsive therapy in the past 6 months. All participants were Chinese.

Clinical assessment

All participants underwent clinical assessment by psychiatric residents to collect information on medication and sociodemographic data and to confirm or exclude a DSM-5 diagnosis. Psychopathology was rated with the Positive and Negative Syndrome Scale (PANSS) at baseline and after 4 and 12 weeks of treatment.

Social perception assessment

Interpersonal Perception Task-15 (IPT-15)

The IPT-15 consists of a 20-minute video containing 15 naturalistic scenes, each 28–122 seconds in duration, with one to four roles in each scene. All scenes were professionally dubbed into Chinese. There were three scenes for each of five categories: kinship, intimacy, deception, competition, and status. All participants were asked a question about the role in each scene and chose one of two or three answers on a standardized answer sheet, with no additional description given.

Executive function assessment

Wisconsin Card Sorting Test

The WCST (computerized version VI), described in detail previously,[25] was used for assessment of executive function. We analyzed five main measures: 1) total response errors; 2) percentage of conceptual level responses; 3) perseverative errors; 4) number of categories completed; and 5) failure to maintain set.

Statistical analyses

Data were analyzed using the Statistical Package for the Social Sciences, version 17.0 (SPSS, Chicago, IL, USA). Sex ratios in RTG, TATG, and NCG were analyzed using the χ^2 test. One-way analyses of variance (ANOVAs) were used to compare baseline IPT-15 and WCST scores between groups (RTG, TATG, and NCG). Repeated measures and multivariate ANOVAs were used for group (RTG and TATG) comparisons of PANSS, IPT-15, and WCST scores. Partial eta squared (η^2) was used as the reporting measure of effect size for significant effects. Statistical significance was defined as $P<0.05$.

Results

Demographics

The demographic characteristics of the participants are listed in Table 1.

Comparisons of PANSS scores before and after antipsychotic treatment in RTG and TATG

Time point (baseline, and after 4 or 12 weeks of treatment) was the within-subject factor, and time point × group (RTG and TATG) was the between-subject factor, in a repeated measures ANOVA, which revealed a highly significant main effect of time period for total PANSS score (F=420, df=2, P=0.000), positive symptom score (F=213, df=2, P=0.000, η^2=0.30), negative symptom score (F=186, df=2, P=0.000, η^2=0.23), and total psychopathology score (F=167, df=2, P=0.000, η^2=0.19). There was no time period × group interaction (F=1.695, 1.786, 2.453, and 1.875; all df=2; P=0.193, 0.213, 0.112, and 0.236; η^2=0.021, 0.012, 0.025, and 0.029). These results indicate that risperidone and typical antipsychotic treatment decreased PANSS scores for total psychopathology, positive symptoms, and negative symptoms, but that there were no significant differences in treatment effect between RTG and TATG (Table 2).

Table 1 Demographic characteristics and clinical data of subjects and controls

	RTG	TATG	NCG	Test statistic	Post hoc analyses
Sex ratio (M/F), n	28 (16/12)	28 (17/11)	28 (15/13)	χ^2=5.95, P=0.16, NS	NA
Mean age (SD), years	38 (12)	38 (13)	38 (12)	F(2,83)=3.92, NS	NA
Age range, years	18–52	19–53	18–54	NA	NA
Education (SD), years	8 (3)	8 (3)	9 (3)	F(2,83)=3.21, NS	NA

Abbreviations: RTG, risperidone treatment group; TATG, typical antipsychotic treatment group; NCG, normal control group; M, male; F, female; NA, not applicable; SD, standard deviation; NS, not significant.

Table 2 PANSS scores (presented as mean [SD]) before and after risperidone and typical antipsychotic treatments between RTG (n=28) and TATG (n=28)

	Baseline		After 4 weeks of treatment		After 12 weeks of treatment	
	RTG	TATG	RTG	TATG	RTG	TATG
PANSS total score	100.0 (5.5)	99.3 (4.1)	72.7 (6.4)	71.0 (5.5)	67.3 (8.1)	66.8 (5.3)
Positive symptom scale	25.0 (8.1)	25.8 (7.0)	13.5 (5.0)	13.8 (6.6)	13.5 (5.2)	13.0 (5.0)
Negative symptom scale	28.0 (5.3)	27.7 (6.6)	20.4 (7.9)	20.2 (8.2)	18.8 (7.3)	18.9 (7.7)
Total psychopathology scale	47.1 (7.1)	46.8 (9.3)	38.8 (7.5)	37.0 (6.3)	35.0 (6.1)	34.9 (4.5)

Abbreviations: RTG, risperidone treatment group; TATG, typical antipsychotic treatment group; PANSS, Positive and Negative Syndrome Scale.

Comparisons of IPT-15 scores between RTG, TATG, and NCG

Comparisons of IPT-15 scores at baseline

One-way ANOVAs revealed a significant main effect of groups (RTG, TATG, and NCG) in kinship, intimacy, deception, competition, status, or total scores (dependent variables) in the IPT-15 (F=30.7, 28.4, 31.5, 31.6, 29.3, and 348, respectively; all df=2; all P=0.000; η^2=0.27, 0.26, 0.20, 0.18, 0.13, and 0.16, respectively). All scores were significantly lower in RTG and TATG than in NCG (P=0.000, 0.001, 0.009, 0.002, 0.010, and 0.000, respectively). There were no differences between RTG and TATG in any measure (P=0.710, 0.645, 0.541, 0.760, 0.0675, and 0.801, respectively) (Table 3).

Comparisons of IPT-15 scores before and after antipsychotic treatment in RTG and TATG

A repeated measures ANOVA was used to analyze IPT-15 scores, with time period (baseline, 4 weeks, and 12 weeks) as the within-subject factor and time period × group (RTG and TATG) as the between-subject factor. A significant main effect of time period was revealed for all IPT-15 performances (kinship: F=24.6, df=2, P=0.000, η^2=0.14; intimacy: F=25.5, df=2, P=0.000, η^2=0.21; deception: F=23.1, df=2, P=0.000, η^2=0.22; competition: F=22.9, df=2, P=0.000, η^2=0.23; status: F=31.7, df=2, P=0.000, η^2=0.18; total scores: F=214.8, df=2, P=0.000, η^2=0.15) and significant time period × group interactions (F=6.8, 7.3, 5.7, 5.9, 4.6, 5.8; all df=2; all P=0.000; η^2=0.25, 0.28, 0.30, 0.27, 0.32, 0.19).

A multivariate ANOVA revealed no significant differences between RTG and TATG on IPT-15 scores after 4 weeks of treatment (F=0.85, 0.65, 0.76, 0.88, 0.73, 1.02; all df=1; P=0.357, 0.226, 0.131, 0.190, 0.215, 0.396; η^2=0.03, 0.07, 0.06, 0.05, 0.06, 0.208); however, there were significant differences between RTG and TATG in all areas of the IPT-15 scores after 12 weeks of treatment (F=15.0, 13.2, 15.4, 19.9, 23.6, 20.3; all df=1; all P=0.000; η^2=0.12, 0.25, 0.19, 0.16, 0.10, 0.09) (Table 3).

Comparisons of WCST performance in RTG, TATG, and NCG

Baseline performance

Dependent variables were total response errors, conceptual level responses, perseverative errors, number of categories completed, and failure to maintain set. One-way ANOVA revealed a significant main effect of group (RTG, TATG, and NCG) (F=114.3, 184.5, 82.6, 56.8, and 11.7, respectively; all df=2; all P=0.000, η^2=0.23, 0.27, 0.21, 0.28, and 0.22). Total response errors, perseverative errors, and failure to maintain set in RTG and TATG were significantly higher than in NCG, and the number of categories completed and

Table 3 IPT-15 scores (presented as mean [SD]) in RTG (n=28), TATG (n=28), and NCG (n=28)

	Baseline			After 4 weeks of treatment		After 12 weeks of treatment	
	RTG	TATG	NCG	RTG	TATG	RTG	TATG
Kinship	1.8 (0.7)	1.7 (0.7)	2.8 (0.4)	1.8 (0.9)	1.7 (0.9)	2.4 (0.6)	1.8 (0.8)
Intimacy	1.6 (0.8)	1.7 (0.8)	2.1 (0.3)	1.7 (0.7)	1.7 (0.8)	2.0 (0.8)	1.8 (0.7)
Deception	1.7 (0.6)	1.7 (0.6)	2.7 (0.5)	1.7 (0.5)	1.7 (0.5)	2.1 (0.5)	1.7 (0.7)
Competition	1.7 (0.7)	1.7 (0.3)	2.2 (0.2)	1.7 (0.6)	1.7 (0.6)	2.3 (0.6)	1.8 (0.9)
Status	1.6 (0.4)	1.6 (0.5)	2.4 (0.3)	1.7 (0.7)	1.6 (0.7)	2.2 (0.8)	1.7 (0.5)
Total scores	8.4 (1.0)	8.4 (1.0)	13.2 (2.9)	8.6 (0.9)	8.4 (1.1)	11.2 (1.3)	8.8 (1.0)

Abbreviations: RTG, risperidone treatment group; TATG, typical antipsychotic treatment group; NCG, normal control group; IPT-15, Interpersonal Perception Task-15.

Table 4 WCST performances (presented as mean [SD]) in RTG (n=28), TATG (n=28), and NCG (n=28)

	Baseline			After 4 weeks of treatment		After 12 weeks of treatment	
	RTG	TATG	NCG	RTG	TATG	RTG	TATG
Total response errors (%)	35.8 (3.5)	37.5 (3.9)	22.6 (4.7)	30.6 (3.9)	33.1 (3.9)	27.7 (3.6)	31.7 (3.6)
Conceptual level responses (%)	49.8 (7.9)	52.9 (6.8)	64.6 (7.3)	55.2 (8.1)	53.6 (8.8)	58.2 (6.70)	54.6 (7.7)
Perseverative errors (%)	23.0 (6.1)	21.6 (6.6)	12.8 (7.5)	20.5 (7.3)	20.1 (8.5)	16.8 (7.4)	19.9 (9.7)
Number of categories completed	5.7 (3.1)	5.9 (4.3)	6.9 (3.2)	6.1 (2.5)	6.0 (2.3)	6.4 (3.1)	6.1 (3.3)
Failure to maintain set	0.8 (0.4)	0.7 (0.4)	0.4 (0.3)	0.6 (0.3)	0.6 (0.3)	0.5 (0.3)	0.6 (0.2)

Abbreviations: RTG, risperidone treatment group; TATG, typical antipsychotic treatment group; NCG, normal control group; WCST, Wisconsin Card Sorting Test.

percentage of conceptual level responses in RTG and TATG were significantly lower than in NCG (total response errors, P=0.009 and 0.002; perseverative errors, P=0.004 and 0.031; failure to maintain set, P=0.018 and 0.018; number of categories completed, P=0.032 and 0.021; percentage of conceptual level responses, P=0.011 and 0.008). There were no differences between RTG and TATG on any of the five factors of the WCST (P=0.123, 0.126, 0.231, 0.109, and 0.139) (Table 4).

Performances RTG and TATG before and after antipsychotic treatment

WCST performances were analyzed using a repeated measure ANOVA, with time period (baseline, 4 weeks, and 12 weeks) as the within-subject factor and time period × group (RTG and TATG) as between-subject factors. There was a significant main effect of time period for WCST performances (total response errors: F=444, df=2, P=0.000, η^2=0.27; conceptual level responses: F=365, df=2, P=0.000, η^2=0.18; perseverative errors: F=497, df=2, P=0.000, η^2=0.16; number of categories completed: F=598, df=2, P=0.000, η^2=0.13; percentage of conceptual level responses: F=912, df=2, P=0.000, η^2=0.21), and significant time period × group interactions (F=17.9, 23.5, 18.5, 20.3, and 18.9; all df=2; P=0.039, 0.012, 0.024, 0.134, and 0.010; η^2=0.04, 0.07, 0.06, 0.11, and 0.10).

Multivariate ANOVA revealed significant differences between RTG and TATG in all areas of the WCST after 4 and 12 weeks of treatment (at 4 weeks: F=5.9, 3.4, 5.6, 5.7, and 3.2; all df=1, P=0.018, 0.026, 0.013, 0.019, and 0.021; η^2=0.13, 0.18, 0.12, 0.19, and 0.09; at 12 weeks: F=25.6, 23.9, 15.6, 21.9, and 33.1; all df=1; all P=0.000; η^2=0.29, 0.20, 0.19, 0.22, and 0.18) (Table 4).

Discussion

In this study, we used the IPT-15 and WCST to assess cognitive improvement in patients with schizophrenia treated with the atypical antipsychotic risperidone or with a typical antipsychotic. Our results replicate the findings of numerous studies that have demonstrated neurocognitive impairment in people with schizophrenia, specifically deficits in interpersonal perception, social cognition, and executive function. Furthermore, both types of treatment led to improvements in executive function. However, the degree of improvement in patients treated with risperidone was better than in those treated with typical antipsychotics. Importantly, social cognitive function in patients with schizophrenia was improved only by risperidone.

Before this study, it had become established that both typical and atypical antipsychotics can improve executive function in schizophrenia. However, whether the atypical neuroleptic risperidone could improve social impairments remained a subject of debate. Risperidone contains benzisoxazole and piperidine in its structure, and previous studies have indicated that it is an antagonist of the D1 (D1, D5) and D2 (D2, D3, D4) receptor families and that it blocks the mesolimbic, prefrontal corticolimbic, and tuberoinfundibular pathways in the central nervous system. In addition, risperidone acts at 5-HT2A/2C receptors, which may be responsible for its fewer extrapyramidal side effects and better improvement of negative symptoms compared to typical antipsychotics.[26–28] In addition, risperidone acts at α2 adrenergic receptors, which may account for its effects on positive, negative, affective, and cognitive symptoms.[29]

Several studies reported that risperidone did not improve social cognitive impairments. For example, patients with schizophrenia receiving different antipsychotics would perform differently in theory of mind (ToM) tasks.[19] Patients receiving typical antipsychotics or atypical antipsychotics (clozapine, olanzapine, or risperidone), and a NCG were matched for age, sex, handedness, and education, and ToM functioning was assessed with picture sequence, second-order belief, and faux pas tests. Performance of the patient group was found to differ between olanzapine or clozapine, but not between typical antipsychotics or risperidone, which both improved or protected ToM ability.[19] A study used WCST

and the Maryland Assessment of Social Competence to evaluate the effects of clozapine and risperidone on social skill and problem solving in patients with schizophrenia, and showed that both clozapine and risperidone did not improve the social role functioning or social problem-solving capacity of people with schizophrenia in the community.[23] Another study evaluated emotion perception in patients with first-episode schizophrenia, and how it was affected by risperidone,[24] and showed that impairments in emotion perception did not improve after treatment with risperidone. In addition, results from several preliminary studies indicating that risperidone and other atypical antipsychotics reduced cognitive deficits were not robustly confirmed in larger trials, and the procognitive effects of atypical antipsychotics are currently considered small at best.[30–32] Moreover, an 8-week double-blind study in 100 patients with schizophrenia or schizoaffective disorder found no evidence of between- or within-group effects of antipsychotic medication (risperidone, olanzapine, and haloperidol) on social cognition.[33] Finally, controversial findings have been found concerning the association of social cognition with functional outcome in schizophrenia. For instance, the IPT-15 failed to show associations with community functioning in participants with schizophrenia.[34]

There are some differences in sample characteristics between the studies described earlier and the present study; for example, many subjects in previous studies were patients with first-episode schizophrenia. Although it has been argued that most cognitive improvement takes place in the first 2 months of antipsychotic treatment, the short treatment duration may be a weakness of the previous studies as medication-influenced changes in cognition may require more time. It is also likely that possible effects of risperidone on social cognitive impairment were masked by individual differences in dose and treatment period.

In the present study, all schizophrenic patients presented with executive dysfunction and social cognitive impairment, and 12 weeks of treatment with risperidone improved executive function and social cognition. Our results indicate that the treatment effect of risperidone for schizophrenia is superior to that of typical neuroleptics. Furthermore, risperidone improved social cognitive impairment after 12 weeks but not 4 weeks, suggesting that this effect depends on a sufficient duration of treatment.

The main limitation of this study is the small sample size. Our results should be considered preliminary and should be validated using similar parameters and experimental paradigms in future studies with more participants.

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Author contributions

Zhenhe Zhou conceived and designed the experiments and wrote the paper. All authors performed the experiments, analyzed the data, contributed reagents/materials/analysis tools, read and approved the final version of the manuscript, contributed toward data analysis, drafting and critically revising the paper, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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