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ABSTRACT

Objective: Clozapine and risperidone are used for treatment-resistant schizophrenia and known to improve the positive and negative symptoms. However, there are some conflicts about effects on social cognition, which is measured with facial emotion recognition ability. The impairments in facial emotion recognition ability have frequently been in different stages of the illness and might have negative influences on psychosocial functioning. In the present study, we aimed to examine clozapine and risperidone effects recognizing facial emotions in patient with treatment-resistant schizophrenia.

Methods: Thirty-four patients were screened for the study, and 19 patients were included. All patients were evaluated with Positive and Negative Syndrome Scale (PANSS), Calgary Depression Scale for Schizophrenia, and Functional Remission of General Schizophrenia Scale at baseline and after 16–20 weeks of clozapine ($n = 12$) or risperidone ($n = 7$) treatment. Furthermore, the Facial Emotion Recognition Test was performed before and after treatment. The test included the photos of four male and four female models (totally 56 mixed photos) with happy, surprised, fearful, sad, angry, disgusted, and neutral facial expressions from Ekman and Friesen's catalog.

Results: The mean dose of the index drug in clozapine group was 295.83 ± 103.26 mg/day. The mean positive ($p = .002$), negative ($p = .050$) general psychopathology ($p = .002$), and total score ($p = .002$) according to the PANSS were significantly improved after treatment. The mean dose of the index drug in risperidone group was 6.86 ± 1.57 mg/day. The mean positive symptom ($p = .018$) and total score ($p = .041$) were significantly improved after treatment but negative symptom scale ($p = .396$) and general psychopathology ($p = .149$) scores did not change. There were no significant differences between baseline and after treatment in clozapine and risperidone group according to the accuracy rate of facial emotion recognition expressions ($p > .05$ for each). At baseline phase, the patients were significantly impaired in recognizing disgusted faces in risperidone than those in clozapine group ($p = .032$) and it was significantly poorer after treatment with risperidone than with clozapine ($p = .031$). The patients responded significantly faster after the treatment to all facial emotions except for fearful faces ($p = .355$).

Conclusions: Clozapine and risperidone were not found to have extensive effects on the ability to recognize facial emotions because of ineffectiveness to negative symptoms as in our study. We speculated that the higher dopaminergic receptor occupancy rate of risperidone in insular cortex than that of clozapine might be related with hypo-activation of insula that was associated with particular deficit in ability to recognize expressions of disgust in patients with schizophrenia. Impaired facial emotion recognition ability is present even in first-episode psychosis, which might be a trait marker in schizophrenia.

Introduction

Beyond positive and negative syndrome domains of schizophrenia, there is a growing interest regarding cognition as a third domain particularly social cognition [1]. Impairment in social cognition has been accounted for the underlying pathology of schizophrenia [2], and facial emotion recognition (FER) ability is one of the domains of social cognition [3].

In literature, there is rising interest on the effects of antipsychotic drugs regarding to FER ability. In a recently published review, the authors have reached a negative conclusion on the improvement of social cognition, which included 15 investigations about the influences of antipsychotic drugs [4]. Previously, Hempel et al. [5] revealed that antipsychotic medication did not sufficiently improve the ability of FER. In fact, the effects of antipsychotics on the ability of FER in schizophrenia are also inconclusive.

Clozapine and risperidone are well-prescribed drugs for the treatment-resistant schizophrenia [6]. In this study, we had two hypotheses: as indicated, antipsychotic drug treatments [1] might improve the ability of FER and might improve the response time to each

facial emotion stimuli; clozapine treatment [2] would improve the ability and response time to facial emotions greater than risperidone treatment. Therefore, we aimed to compare the effects of clozapine and risperidone treatment on FER ability in patients with treatment-resistant schizophrenia compared to the baseline and compare the differences of each antipsychotic treatment on FER ability by performing the photo series of Ekman.

Methods

Thirty-four patients were screened for the study who met the diagnostic criteria of schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders, Text Revised (DSM-IV, TR). The inclusion criteria for the study were: indication for hospitalization [1] although being under treatment or nonadherence to treatment, indication for clozapine and risperidone antipsychotic treatment [2], meeting the criteria of treatment-resistant schizophrenia [3,7]. The exclusion criteria were as follows: younger than 18 years or older than 65 years old age [1], comorbid depression or alcohol and/or substance abuse [2], intellectual disability, having neurological disease or head injury history [3], and having visual problems [4]. At the end, 19 patients were included the study.

All patients were evaluated with Positive and Negative Syndrome Scale (PANSS), Calgary Depression Scale for Schizophrenia (CDSS), Functional Remission of General Schizophrenia (FROGS) scale and FER Test at baseline and after within 16–20 weeks clozapine ($n = 12$) or risperidone ($n = 7$) treatment. FER Test included the photos of 4 male and 4 female models (totally 56 mixed photos) with happy, surprised, fearful, sad, angry, disgusted, and neutral facial expressions from Ekman and Friesen's catalog [8]. This study was approved by the Ethical Committee of Istanbul University's Cerrahpasa Medical School.

Statistical analysis

Kolmogorov–Smirnov distribution tests were used to test for normality of continuous variables. The Wilcoxon signed-rank test was used to compare the baseline and post-treatment accuracy rate of FER ability and response time. Mann–Whitney U test was used to compare continuous variables between groups. Chi Square Test was used to compare categorical variables. A p value of <.05 was accepted as significant.

Results

The mean age of the participants' was 34.95 ± 9.76 (median = 34.00) years and mean age was not significant different between clozapine and risperidone group (35.00 ± 11.61 (median = 33.50) vs. 41.43 ± 11.64 (median = 34.00) years, $p = .197$). There were no significant differences between clozapine and risperidone groups according to PANSS, CDSS, and FROGS baseline scores ($p > .05$ for each) (Table 1).

The mean dose of the index drug in clozapine group was 295.83 ± 103.26 (median = 300.00) mg/day. The mean positive (21.50 ± 6.23 (median = 20.00) vs. 10.78 ± 2.86 (median = 10.50), $p = .002$), general psychopathology (38.83 ± 7.50 (median = 36.00) vs. 25.67 ± 5.93 (median = 26.00), $p = .002$) and the mean total score (82.50 ± 18.47 (median = 72.50) vs. 53.67 ± 11.74 (median = 54.00), $p = .002$) according to PANSS were significant improved after clozapine treatment while closer to be significant in negative symptom scale (20.50 ± 6.90 (median = 18.00) vs. 16.25 ± 4.95 (median = 15.50), $p = .050$). The functionality of patients after clozapine was significantly improved (48.00 ± 10.87 (median = 46.00) vs. 67.41 ± 12.51

Table 1. Socio-demographic and clinical features of participants.

	Clozapine $n = 12$	Risperidone $n = 7$	p
[a]Age (years, median (min–max))	33.50 (22.00–60.00)	34.00 (28.00–45.00)	.197
[b]Gender (Male/Female)	5/7	5/2	.210
[b]Education			
Primary	4	4	.27
Middle	1	0	
High	1	2	
University	6	1	
[b]Married/Single	3/9	3/4	.419
[a]Chlorpromazine Equivalent Dose (mg/day) (median (min–max))	600.00 (200.00–900.00)	800.00 (10.00–800.00)	.403
[a]PANSS Score (median (min–max))	72.50 (59.00–107.00)	77.00 (68.00–100.00)	.397
• Positive symptom scale	20.00 (11.00–31.00)	23.00 (15.00–26.00)	.521
• Negative symptom scale	18.00 (10.00–31.00)	18.00 (11.00–26.00)	.610
• General psychopathology scale	36.00 (26.00–50.00)	40.00 (26.00–51.00)	.672
[a]The Calgary Depression Scale (median (min–max))	1.50 (0.00–12.00)	1.00 (0.00–17.00)	.897
[a]FROGS (median (min–max))	46.00 (32.00–69.00)	46.00 (38.00–68.00)	.800

Note: FROGS: Functional Remission of General Schizophrenia Scale.
[a]Mann Whitney U test.
[b]Chi-square test.

Table 2. The comparison of accuracy rate of FER ability and response time between initial and post clozapine treatment.

Facial emotions	Clozapine n = 12	Accuracy rate median (min–max)	p	Response time median (min–max)	p
Happiness	Initial	7.00 (6.00–7.00)	.317	1.50 (0.48–6.03)	.117
	Post treatment	7.00 (5.00–7.00)		1.11 (0.27–5.58)	
Sadness	Initial	6.00 (1.00–7.00)	.675	2.99 (0.80–7.93)	.099
	Post treatment	5.50 (1.00–7.00)		2.88 (0.34–6.74)	
Fearful	Initial	3.00 (0.00–5.00)	.500	2.99 (1.00–9.20)	.875
	Post treatment	3.00 (0.00–7.00)		2.98 (0.46–6.96)	
Disgusted	Initial	5.50 (0.00–7.00)	.095	3.80 (0.58–9.01)	.028*
	Post treatment	2.50 (0.00–7.00)		2.34 (0.30–5.70)	
Angry	Initial	6.00 (1.00–7.00)	.566	3.37 (1.41–5.67)	.308
	Post treatment	6.00 (1.00–7.00)		2.42 (0.38–7.28)	
Surprised	Initial	5.00 (1.00–6.00)	.065	2.59 (0.89–5.63)	.136
	Post treatment	6.00 (2.00–7.00)		1.94 (0.34–7.94)	
Neutral	Initial	6.00 (4.00–7.00)	.112	2.41 (0.58–8.84)	.019*
	Post treatment	7.00 (4.00–7.00)		1.71 (0.36–4.81)	

Note: Wilcoxon signed-rank test was used.
*$p < .05$.

(median = 63.00), $p = .002$). There were no significant differences between baseline and clozapine treatment according to the accuracy rate of FER expressions ($p > .05$ for each) while the response time to disgusted ($p = .028$) and neutral faces ($p = .019$) were significantly faster after clozapine treatment (Table 2).

The mean dose of the index drug in risperidone group was 6.86 ± 1.57 (median = 8.00) mg/day. The mean positive symptom (21.50 ± 6.23 (median = 23.00) vs. 10.78 ± 2.86 (median = 9.00), $p = .018$), and the mean total score (82.50 ± 18.47 (median = 77.00) vs. 53.67 ± 11.74 (median = 51.00), $p = .041$) according to PANSS were significantly improved after risperidone treatment while negative symptom scale (17.86 ± 4.67 (median = 18.00) vs. 16.42 ± 7.25 (median = 18.00), $p = .396$) and general psychopathology (38.83 ± 7.50 (median = 40.00) vs. 25.67 ± 5.93 (median = 23.00), $p = .149$) did not change. The functionality of patients after risperidone was significantly improved (50.71 ± 12.16 (median = 46.00) vs. 67.57 ± 16.43 (median = 51.00), $p = .018$). There were no significantly differences between initial and risperidone treatment according to the accuracy rate of FER expressions ($p > .05$ for each) except the accuracy rate of disgusted faces that became significantly poorer after risperidone treatment (2.73 ± 2.23 (median = 3.00) vs. 0.46 ± 1.13 (median = 0.00), $p = .043$). The response time to happy ($p = .028$), angry ($p = .028$), surprised ($p = .018$), and neutral faces ($p = .018$) were significantly faster after risperidone treatment (Table 3).

There were no significantly differences between clozapine and risperidone groups regarding accuracy rate of facial emotions and response times both at initial and after treatment phases except one. At the baseline phase, the patients were significant impaired in recognizing disgusted faces in risperidone than clozapine group ($p = .032$) and it was significantly poorer after treatment with risperidone than with clozapine ($p = .031$).

Discussion

In this present study, the accuracy rate of FER was not significantly different between healthy controls ($n = 15$) and patients with treatment-resistant schizophrenia whom were under 470 ± 173 mg/day dose of clozapine. The improvement in negative symptoms is suggested to have a positive impact on FER ability [1]. In addition, it is emphasized that there is a significant relationship between negative symptoms and FROGS [9]. Thus, we consider three possible explanations for our results. First, both clozapine and risperidone do not affect FER ability although there was meaningful influence on positive symptoms

Table 3. The comparison of accuracy rate of FER ability and response time between initial and post risperidone treatment.

Facial emotions	Risperidone n = 7	Accuracy rate median (min–max)	p	Response time median (min–max)	p
Happiness	Initial	7.00 (3.00–7.00)	.317	1.30 (0.42–5.18)	.028*
	Post treatment	7.00 (6.00–7.00)		0.71 (0.14–1.18)	
Sadness	Initial	4.00 (1.00–7.00)	.269	2.76 (1.32–8.43)	.099
	Post treatment	6.00 (1.00–7.00)		1.82 (0.95–4.04)	
Fearful	Initial	3.00 (0.00–4.00)	.336	2.89 (1.40–5.00)	.310
	Post treatment	2.00 (0.00–6.00)		1.15 (0.65–65.41)	
Disgusted	Initial	3.00 (0.00–6.00)	.043*	2.64 (1.06–14.42)	.612
	Post treatment	0.00 (0.00–3.00)		1.82 (1.10–13.00)	
Angry	Initial	5.00 (0.00–7.00)	.888	2.59 (1.16–12.26)	.028*
	Post treatment	4.00 (1.00–7.00)		2.35 (0.42–6.95)	
Surprised	Initial	6.00 (4.00–6.00)	.334	2.62 (0.95–6.09)	.018*
	Post treatment	6.00 (2.00–7.00)		0.92 (0.34–2.15)	
Neutral	Initial	5.00 (1.00–7.00)	.705	1.98 (0.48–14.31)	.018*
	Post treatment	6.00 (1.00–7.00)		0.88 (0.18–4.07)	

Note: Wilcoxon signed-rank test was used.
*$p < .05$.

and general functionality. Second, neither clozapine nor risperidone did not improve FER ability because of ineffectiveness to negative symptoms as in our study. Impaired FER ability is present even in first-episode psychosis [10] or in first-degree relatives of patient with schizophrenia [11]. As a third explanation, we thought that affect impaired FER ability might be a trait marker in schizophrenia [12–14].

It is known that second-generation antipsychotics (SGA) have some advantages comparing with first-generation antipsychotics (FGA) on cognitive functions [15]. In a cross-sectional study, Kucharska et al. [16] did not find any superiority of SGAs or FGAs on emotion recognition. In between SGAs, clozapine and risperidone have been studied for social cognition but there are some contradictory results. In a eight-week follow-up study, no differences were found between risperidone, olanzapine, and haloperidol among ability of FER [1]. In another study, emotion perception did not change with quetiapine and risperidone treatment [17]. However, Behere et al. [18] have revealed that the ability of recognizing disgusted and fearful faces was significantly improved after risperidone treatment. According to the literature, our study is the one that monitored participants for a longer time, and we did not find any improvements on facial affect recognition with risperidone or clozapine treatment. At baseline, the ability of recognizing disgusted faces were poorer in risperidone group than in clozapine group and this ability became significantly poorer after risperidone treatment. In a functional MRI study, the impairment in recognizing disgusted facial emotions was related with dysfunction in globus pallidus and insular cortex [18], where the dopaminergic pathway has been involved abundantly. Thus, we considered that higher rate of dopaminergic receptor occupancy in risperidone than clozapine in insular cortex might be related with hypo-activation of insula and hypo-activation of insula, especially anterior part, can be associated with the particular deficit to recognize expressions of disgust in schizophrenia [19].

In the present study, we found that mean response times to several facial emotions significantly became shorter after both clozapine and risperidone treatment. In a study, the patients with treatment-resistant schizophrenia have taken more time while identifying fear and disgusted facial emotions [20]. Nevertheless, the reaction time in identifying facial emotions after treatment with antipsychotics in schizophrenia is missing in literature [18,20], which makes our findings difficult to interpret.

This present study has certain limitations: small sample size [1]; using only static emotions to measure affect recognition [2], which is not possible in real life; lacking of blood concentration of index drugs [3]; lacking of a healthy control group [4], and lacking of knowledge about the duration of illness [5].

In conclusion, the antipsychotic drugs clozapine and risperidone do not seem to have extensive effects on the FER ability. Although both antipsychotic drugs have influential effects on the treatment-resistant patients with schizophrenia, which might be detected with psychometric and functionality scales, these drugs have no similar influential effects on the ability of FER.

Disclosure statement

No potential conflict of interest was reported by the authors.

References

[1] Sergi MJ, Rassovsky Y, Widmark C, et al. Social cognition in schizophrenia: relationships with neurocognition and negative symptoms. Schizophr Res. 2007;90 (1–3):316–324.

[2] Green MJ, Phillips ML. Social threat perception and the evolution of paranoia. Neurosci Biobehav Rev. 2004;28(3):333–342.

[3] Grady CL, Keightley ML. Studies of altered social cognition in neuropsychiatric disorders using functional neuroimaging. Can J Psychiatry. 2002;47(4):327–336.

[4] Kucharska-Pietura K, Mortimer A. Can antipsychotics improve social cognition in patients with schizophrenia? CNS Drugs. 2013;27(5):335–343.

[5] Hempel RJ, Dekker JA, van Beveren NJ, et al. The effect of antipsychotic medication on facial affect recognition in schizophrenia: a review. Psychiatry Res. 2010;178(1):1–9.

[6] Bondolfi G, Dufour H, Patris M, et al. Risperidone versus clozapine in treatment-resistant chronic schizophrenia: a randomized double-blind study. The risperidone study group. Am J Psychiatry. 1998;155(4):499–504.

[7] Fakra E, Salgado-Pineda P, Delaveau P, et al. Neural bases of different cognitive strategies for facial affect processing in schizophrenia. Schizophr Res. 2008;100 (1–3):191–205.

[8] Ekman P, Friesen WV. Pictures of facial affect. Palo Alto: Consulting Psychologists; 1976.

[9] Hunter R, Barry S. Negative symptoms and psychosocial functioning in schizophrenia: neglected but important targets for treatment. Eur Psychiatry. 2012;27(6):432–436.

[10] Mandal MK, Pandey R, Prasad AB. Facial expressions of emotions and schizophrenia: a review. Schizophr Bull. 1998;24(3):399–412.

[11] Kee KS, Horan WP, Mintz J, et al. Do the siblings of schizophrenia patients demonstrate affect perception deficits? Schizophr Res. 2004;67(1):87–94.

[12] Trémeau F. A review of emotion deficits in schizophrenia. Dialogues Clin Neurosci. 2006;8(1):59–70.

[13] Butler PD, Javitt DC. Early-stage visual processing deficits in schizophrenia. Curr Opin Psychiatry. 2005;18(2):151–157.

[14] Addington J, Saeedi H, Addington D. Facial affect recognition: a mediator between cognitive and social functioning in psychosis? Schizophr Res. 2006;85(1–3):142–150.

[15] Woodward ND, Purdon SE, Meltzer HY, et al. A meta-analysis of neuropsychological change to clozapine, olanzapine, quetiapine, and risperidone in

schizophrenia. Int J Neuropsychopharmacol. 2005;8(3):457–472.

[16] Kucharska-Pietura K, Tylec A, Czernikiewicz A, et al. Attentional and emotional functioning in schizophrenia patients treated with conventional and atypical antipsychotic drugs. Med Sci Monit. 2012;18(1):CR44–CR49.

[17] Harvey PD, Patterson TL, Potter LS, et al. Improvement in social competence with short-term atypical antipsychotic treatment: a randomized, double-blind comparison of quetiapine versus risperidone for social competence, social cognition, and neuropsychological functioning. Am J Psychiatry. 2006;163(11):1918–1925.

[18] Behere RV, Venkatasubramanian G, Arasappa R, et al. Effect of risperidone on emotion recognition deficits in antipsychotic-naïve schizophrenia: a short-term follow-up study. Schizophr Res. 2009;113(1):72–76.

[19] Williams LM, Das P, Liddell BJ, et al. Fronto-limbic and autonomic disjunctions to negative emotion distinguish schizophrenia subtypes. Psychiatry Res. 2007;155(1):29–44.

[20] Machado de Sousa JP, Hallak JE. Neurocognitive functioning and facial affect recognition in treatment-resistant schizophrenia treated with clozapine. Schizophr Res. 2008;106(2–3):371–372.