Social Cognition and Visual Perception in Schizophrenia Inpatients Treated with First- and Second-Generation Antipsychotic Drugs

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Abstract

Purpose: Social cognition captures affect recognition, social cue perception, "theory of mind," empathy, and attributional style. The aim of our study was to assess social cognition in schizophrenia inpatients being treated with first-generation antipsychotic drugs (FGAs), n=28 (perphenazine and haloperidol, FGAs) or with second-generation antipsychotic drugs (SGAs), n=56 (olanzapine and clozapine, SGAs). **Subjects and Methods:** Eighty-four patients completed the Facial Expression Recognition Test, the Voice Emotion Recognition Test, the Short Recognition Memory Test for Faces, and the Reading the Mind in the Eyes Test. Patients also completed the Visual Object and Space Perception Test (VOSP) as a control task, which would not engage social cognition. The patients were compared with fifty healthy controls matched for age and gender. **Results:** There were no significant differences on social cognitive performance between the FGA- and SGA-treatment groups. Nor was olanzapine superior to clozapine, FGAs or both. However, patients treated with FGAs performed significantly worse on VOSP compared to both groups treated with SGAs, a 10% difference. **Conclusions:** We cannot conclude that SGAs were associated with better social cognition than FGAs. However, there were small but significant advantages for SGAs in non-social visual processing function, as evaluated with the VOSP.

Key Words: Antipsychotic Drugs, Empathy, Schizophrenia, Social Cognition, Visual Perception

Introduction

Adolphs (2001) described social cognition as "the ability to construct representations of the relation between oneself and others and to use those representations flexibly to guide social behavior" (1). Social cognition has been defined as the mental operations underlying social interactions, and is thought to represent a specialized domain of cognition, which captures affect perception, social cue perception, "theory of mind," empathy, and attributional style (2).

Affect perception is the ability to infer emotional information; in other words, what a person is feeling, presented either in visual or auditory form or in some combination (such as video clips). Social cue perception refers to a person's ability to ascertain social cues from behavior provided in a social context, and refers to a person's comprehension of social rules. Attributional style, known as a personalizing bias, refers to an individual's own perception of, and interpretation of, facts and events (3).

The attribution of mental states (such as desires, intentions and beliefs) to other people has been referred to as "theory of mind (ToM)" or "mentalizing" (4).

ToM involves both the ability to understand that others have mental states different from one's own, and the capa-

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Clinical Implications

Our results add to the small body of literature to the effect that first-generation antipsychotics (FGAs) versus second-generation antipsychotics (SGAs) do not impact upon social cognitive functioning, particularly in the form of patients' ability to recognize affect in both visual and auditory modalities and to read "states of mind" in other people. One strength of the study is its relatively homogeneous, large group of right-handed, partially remitted, psychotic patients recruited only from inpatient settings to better control treatment concordance and immediate environment. Moreover, the patients' symptoms including depression were evaluated. Limitations include lack of randomization and cross-sectional design. Unfortunately, our results do not indicate that psychopharmacological choice alone can be utilized as a means to manage poor social cognition and its impact on functional outcome. In this respect, our results are consistent with an increasing body of work, which, sadly, has suggested that the much vaunted advantages of SGAs over FGAs may be more apparent than real.

Alternatively, there has been a growing interest in devising interventions aimed at improving functional outcomes via remediation of social cognitive deficits. In an effort to address these issues, Couture et al. (2006) have developed Social Cognition and Interaction Training (SCIT): a 20-week, manualized, group treatment that targets the three major domains that are impaired in schizophrenia: emotion perception, ToM, and attributional style (3). Roberts and Penn (2009) reported preliminary data from a quasi-experimental study comparing SCIT + treatment as usual (TAU; n=20) to TAU alone (n=11) among outpatients. Results suggested SCIT-related improvements in emotion perception and social skill. A further uncontrolled study of 50 patients suggested that the intervention was feasible in ordinary practice and conferred some improvements. Although numbers are so small that this data can be at best regarded as preliminary, there may be more merit in training and practicing social cognition skills than in expecting any "quick fix" through medication class (41).

bility to make correct inferences about the content of those mental states, primarily others' intentions and beliefs (3). In a meta-analysis based on 29 studies, Sprong et al. (2007) showed a significant and stable mentalizing deficit in schizophrenia. This deficit remained in remitted schizophrenia patients, suggesting a trait-dependent rather than state-dependent nature (5).

A growing body of literature has shown that schizophrenia patients present with social cognitive impairments, in particular in modifying their behavior when interacting with other people and in recognizing emotions and other social information cues (6-8). Social cognitive deficits are believed to be important predictors of functional outcome in schizophrenia, but few studies have estimated the influence of antipsychotic treatment on these deficits.

Littrell et al. (2004) showed that risperidone and olanzapine enhanced social cognition in schizophrenia patients (9), while Mazza et al. (2003) demonstrated an advantage for risperidone combined with donepezil over haloperidol, clozapine, and risperidone alone in ToM ability in schizophrenia after one year of treatment (10). Interestingly, Savina and Beninger (2007) showed that ToM performance of schizophrenia patients was related to maintenance treatment: they suggested that olanzapine and clozapine, but not risperidone or first-generation antipsychotics (FGAs), may improve or protect ToM ability (11). Harvey et al. (2006) reported an improvement in social competence after eight weeks of either quetiapine or risperidone (12). Social competence was evaluated by means of the Social Skills Performance Assessment, which is a validated measure of interactive social skills performed in a role-played manner with an examiner. Furthermore, these changes correlated with concurrent improvement in other aspects of neuropsychological performance such as executive function and memory.

However, Sergi et al. (2007) did not show any evidence of treatment-related differences on social cognition in patients with a diagnosis of schizophrenia in an 8-week, double-blind study of risperidone, olanzapine, and haloperidol (13).

The question is, do second-generation antipsychotics (SGAs) confer any advantages in social cognition compared to FGAs? Despite a number of influential meta-analyses, which seemed to confirm pharma claims that SGAs outperformed FGAs in a range of clinical efficacy parameters, the conclusions of several large, pragmatic, naturalistic clinical effectiveness trials have been at marked variance with this. These include CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness), CUtLASS 1 (Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study), and EUFEST (European First-Episode Schizophrenia Trial), all of which have brought scepticism to any notion of superiority of SGAs over FGAs.

In CATIE, psychosocial functioning in patients treated with FGAs or SGAs was assessed: there were no significant differences between groups in the amount of change in the Quality of Life Scale total score or subscale scores at 6, 12,

or 18 months (14). Furthermore, Penn et al. (2009) assessed emotion perception in 873 patients who completed an emotion perception test immediately prior to randomization and after two months of treatment (15). Non-statistically significant improvement in emotion perception at two months was observed; the treatment groups did not differ from one another.

In CUtLASS 1, a 12-month, open-label trial, 277 patients were randomized to receive an FGA or an SGA. Again, effectiveness was comparable between the two groups, with only limited improvements in psychopathology and quality of life (16).

Similarly, the cognitive effects of FGAs versus SGAs were evaluated in EUFEST: improvement did not differ between the groups (17). Furthermore, other recent studies particularly focusing on the neurocognitive effects of SGAs and FGAs in psychosis seem to show inconsistent results, either including growing evidence of superiority of SGAs over FGAs (18-20), or highlighting no significant differences between treatments regarding neurocognition in schizophrenia (21, 22).

Therefore, a growing body of recent data on effects of SGAs/FGAs on various domains of social cognition in schizophrenia remains inconclusive.

Study

We assessed deficits in social cognitive functioning in a naturalistic, pragmatic sample of partially remitted stable schizophrenia inpatients being treated with FGAs or SGAs. This group of patients was chosen as we assumed that they may manifest greater deficits in social cognition than remitted outpatients and, thus, there should be more probability of demonstrating differences between treatment groups if such exist. All eligible patients (see below) acutely admitted to the hospital were offered participation in the study when clinically judged to be post-acute: neither too psychotic to give valid consent and to participate productively, nor so remitted as to be approaching discharge. Such partial remission was judged clinically without the use of any rating scale evaluation to make sure that patients were not excluded on overly specific criteria. Thus, there was a global clinical judgement of not only positive and negative symptoms, but also affective state and general functioning. Furthermore, after 3–4 weeks of treatment, we assumed that differential therapeutic effects between FGA and SGA treatment would be operative.

We also assessed the contribution of lower level visual tasks to performance on social cognitive measures. Consistent deficits at lower levels of visual processing, including gain control and integration, are observed in schizophrenia (23, 24). There is growing evidence to suggest that impaired retinal processing caused by systemic dopaminergic deficiency can affect visual processing (25). Because of this, we assumed that FGAs and SGAs may act differentially on these low-level visual processes via their disparate effects on dopamine neurotransmission. These differences could be propagated upward into higher levels of visual processing and amplified by the application of separate social cognitive processes adduced to complete visually based social cognition tasks.

Subjects and Methods

Participants

The study was approved by the Ethics Committee of the Lublin University Medical School, and all participants gave informed consent. A total of one hundred and thirty-four people aged between 18 and 60 years were studied.

Participants with schizophrenia (n=84) and healthy controls (n=50) were comparable for age and gender; however, they differed significantly in years of education (see below). Fifty healthy subjects (25 men) (mean age 29.6, SD 11.5 years) with no history of psychiatric illness recruited from the non-professional staff at Lublin University Medical School and Lublin Psychiatric Hospital participated in the study.

All subjects were right-handed (26). Exclusion criteria for all participants included the presence of a neurological disorder (e.g., epilepsy, dementia), and mental and behavioral disorders due to psychoactive substance use (F10–F19, *ICD-10*) (27). Patients who had difficulties with vision, including poor acuity and lack of correction, and severe hearing problems, were also excluded.

Eighty-four patients aged between 18 and 60 years were studied (see Table 1). Eighty-one were diagnosed with schizophrenia and 3 with schizoaffective disorder, according to both *DSM-IV* (28) and *ICD-10* criteria (27). Twenty-eight (13 males) were treated with FGAs (perphenazine, n=14; haloperidol, n=14) and 56 (31 males) were treated with SGAs (olanzapine, n=28; clozapine, n=28). All patients were clinically stable after 3–4 weeks of antipsychotic treatment. The mean daily dose of antipsychotic drugs was converted into chlorpromazine equivalents (CPZE) (29).

Demographic and clinical variables were recorded (see Table 1), grouping the patients according to treatment with FGAs, olanzapine or clozapine: these groups were expected to differ, which they did. Categorical clinical data were recorded (predominant symptom type negative versus positive, duration of schizophrenia less or more than five years). The patients were assessed on the SANS (30) and the SAPS scales (31) by a trained rater, the third author. They also completed the Beck Depression Inventory (BDI) (32).

Table 1 Demographic and Clinical Data for Three Treatment Subgroups

Variable	Perphenazine/Haloperidol n=28		Olanzapine n=28		Clozapine n=28		P(df=2)
	Mean	SD	Mean	SD	Mean	SD	
Age	33.89	15.55	23.00	5.10	36.18	15.66	0.007
Years of education	11.21	2.35	12.86	2.73	11.96	3.02	0.106
Duration of illness	11.11	10.51	2.11	1.44	13.70	11.88	0.000
No. of previous admissions	6.68	5.83	1.50	1.04	6.71	5.36	0.000
CPZE mg/day	422.14	219.40	341.07	118.68	519.64	276.00	0.048
SAPS	42.54	23.81	30.61	16.20	46.71	17.94	0.007
SANS	65.36	24.28	44.25	13.10	67.04	17.47	0.000
BDI	20.79	12.37	14.25	10.46	16.71	12.78	0.157

P-value=the significance level was set at $p<0.05$; CPZE mg/day=chlorpromazine equivalents mg/day; SAPS=Scale for Assessment of Positive Symptoms; SANS=Scale for Assessment of Negative Symptoms; BDI=Beck Depression Inventory

Procedure

Social cognition guides behavior by participating in a variety of processes that modulate behavioral response. Attention, motivation, decision making, emotion, and empathy are all prominently recruited when socially relevant stimuli elicit behavior (1). Tests were chosen to capture major domains of social cognition: emotional perception in both visual and auditory modes, and theory of mind and empathy. By contrast, purely visuospatial processes, including low-level processes, were assessed with the Visual Object and Space Perception Test (VOSP) (33).

Emotional Perception

Facial Expression Recognition Test (FERT)

This comprises thirty-six faces from a standardized series, which portrays prototypical facial expressions of the six basic emotions (fear, disgust, anger, surprise, happiness, sadness, and neutral) (34). Participants view the faces and decide the emotion displayed by each one.

Voice Emotion Recognition Test (VERT)

Participants are presented with a series of five semantically neutral sentences (e.g., "In winter there are short days and long nights"; "They will go first, the others will follow them"). Each sentence is spoken aloud by a professional male actor in such a manner as to convey one of the six basic emotions (see above) in addition to a neutral tone of voice. The neutral tone of voice was used as a "control" auditory task. Thirty-five sentences were recorded, digitized and normalized for average amplitude in a recording studio (Cronbach's 0.614; test-retest reliability was 0.96) (35).

Theory of Mind/Empathy

Reading the Mind in the Eyes Test (revised version)

This is a measure of adult "mentalizing" in terms of how well participants can put themselves into the mind of another person and "tune into" their mental state (36). The participant sees twenty-five photographs of the eye region of unknown faces and is asked to choose which of four words best describes what the person is thinking or feeling.

Facial Processing

Short Recognition Memory Test for Faces (RMTF)

This is a forced-choice recognition memory test, which was used as a control measure for the Facial Expression Recognition Test (FERT). It consists of twenty-five unfamiliar, gray-scale male faces, which are presented at a rate of one every three seconds (timed by stop watch). The subject is required to respond "yes" or "no" to each item, depending on whether the face is judged to be pleasant or not. Recognition memory is assessed immediately after the presentation of the stimuli using a two-choice format, each stimulus item being paired with one distractor item. The total number of correct choices was recorded (37). The RMTF was used in the study as a control task to evaluate whether deficits in emotional perception exist independently, or they are strongly related to impairments in face processing.

Visuospatial Processes

Visual Object and Space Perception Test (VOSP)

This is a standardized, validated battery of eight subtests

(33). Three subtests of object perception (incomplete letters, silhouettes, object decision) and four subtests of space perception (dot counting, position discrimination, number location, cube analysis) were used. These subtests require very simple responses: each one is devised to focus on a single component of low-level visual perception, while minimizing the involvement of other cognitive skills.

Results

All analyses were carried out utilizing SPSS software.

Patients versus Controls

T-tests were used to compare control and patient age and years of education. While age did not differ significantly, years of education did but only by 18 months: controls having been educated for 13.7 years versus 12.2 years for patients. The gender composition did not vary between the groups. The Mann-Whitney test was used to compare test performance of patients versus controls: controls outperformed patients to a highly statistically significant degree ($p<0.01$) in all tests (see Table 2).

Table 2 Patients vs. Controls: Group Statistics, Means of Social Cognition and Visual Perception

Tests / Results	FERT	VOSP	VERT	Eyes Test	RMTF-Short
Patients Mean (SD)	16.33 (4.59)	109.22 (13.32)	87.16 (14.62)	19.13 (5.63)	20.48 (3.36)
Controls Mean (SD)	21.84 (1.83)	124.50 (8.46)	93.66 (8.45)	25.68 (4.52)	22.78 (2.01)

FERT=Facial Expression Recognition Test; VOSP=Visual Object and Space Perception Test; VERT=Voice Emotion Recognition Test; Eyes Test=Reading the Mind in the Eyes Test; RMTF-Short=Short Recognition Memory Test for Faces

FGA versus Olanzapine versus Clozapine

Demographic and clinical differences between the three subgroups (FGAs, and SGAs divided into olanzapine-treated patients and clozapine-treated patients) were examined with the Kruskal-Wallis one-way analysis of variance. Olanzapine-treated patients were much younger and less chronic and symptomatic than the others (see Table 1). Clozapine-treated patients were taking relatively higher doses of antipsychotic medication.

Further Identification of Potential Confounding Variables

In order to identify other potential confounding variables, which may influence the final analysis of FGA- versus SGA-treated patients, scores on the five tests were correlated with the clinical and demographic variables using the Spearman correlation coefficient for non-parametric data. Similarly, Kruskal-Wallis or Mann-Whitney tests were used to determine whether categorical variables significantly influenced test scores.

General Linear Model Analysis of Test Performance Vis-a-Vis FGAs or SGAs

Given multiple sources of variation in the data potentially impacting upon social cognition, general linear model analysis was used to address these. The SPSS GLM Univariate procedure provides regression analysis and analysis of variance for one dependent variable (social cognition test score) by one or more factors (FGAs versus SGAs) and probable covariates whether categorical (e.g., sex), ordinal (e.g., PANSS score) or interval (e.g., age).

A general linear model (GLM) for each of the five tests was then constructed, with the test score as the dependent variable, the type of antipsychotic (FGA or SGA) as a fixed factor alongside the test's categorical confounders as random factors, and its ordinal or interval confounders as covariates.

Results were almost entirely negative. No factor or covariate including FGA vs. SGA produced a significant F ratio ($p<0.05$) for the Short Recognition Memory Test for Faces (RMTF), the Voice Emotion Recognition Test (VERT) or the Reading the Mind in the Eyes Test.

Regarding the Facial Expression Recognition Test (FERT), two random factors—predominant symptom type and early versus chronic duration—produced significant F ratios, $p=0.03$ and 0.04, respectively. Therefore, it was inferred that chronic patients (i.e., those with a duration of more than five years' illness and those with predominant negative symptoms) performed more poorly than the rest, regardless of treatment with FGAs or SGAs.

The single positive result in respect to FGAs versus SGAs arose from the general linear model applied to the VOSP scores: here the fixed factor FGA versus SGA produced an F ratio of 48.6, while the five covariates entered into the model produced F ratios of 0.01–3.10. The F ratio of 48.6, although highly significant ($p<0.001$), translated on further examination to a small difference in mean scores: FGA-treated patients scoring 103.5 (SD 2.7), olanzapine-treated patients scoring 110.5 (SD 2.5) and clozapine-treated patients scoring 111.5 (SD 2.4) on the VOSP.

Discussion

Pragmatism or effectiveness clinical trials such as CATIE, CUtLASS 1, and EUFEST, sponsored by governments as opposed to pharmaceutical companies, have challenged the

view that SGAs are superior to FGAs, and have suggested that FGA treatment has wider clinical applicability than previously thought (38). However, none of these trials studied social cognition in any depth or detail. To turn to our findings, participants with schizophrenia performed highly significantly worse compared to the healthy controls on social cognitive and visual measures, which is in line with previous research (14, 35, 39). The performance of facial expression recognition in chronic patients and those with predominant negative symptoms was, as expected, consistently inferior compared to patients with positive symptoms and in an earlier stage of their illness, regardless of treatment with FGAs or SGAs. This has been previously reported (14, 35, 40).

There were no significant differences on social cognitive performance between the FGA- and SGA-treatment groups. Nor was olanzapine superior to clozapine, FGA or both in any tests. Thus, type of antipsychotic drug seems not to have any substantial effect on social cognitive functioning. Similar reports include: Davidson et al. (2009) (17), Penn et al. (2009) (15), and Sergi et al. (2007) (13).

Our single positive result in respect to FGA versus SGA applied to the VOSP. The patients treated with FGAs performed significantly worse on both object and space perception tasks compared to both groups treated with SGAs, a 10% difference. This could possibly reflect the stronger affinity for dopamine receptors of FGAs, resulting in greater levels of antagonism at the retina impacting adversely on low-level visual processing. Even so, the difference is not reflected in any higher level advantages in visual social cognition for SGA-treated patients.

One explanation for our inability to find differential deficits in social cognition is because social cognition is a "trait," rather than being "state dependent," which is in line again with previous studies (8, 23). Therefore, age, years of education, levels of depressive, positive and negative symptoms, numbers of admissions, and relative drug dosages largely failed to influence social cognition and visual processing ability when controlled for in the analysis. This does not mean that they are all unimportant: common sense dictates that to optimize any cognitive or functional aspect in schizophrenia, symptom control should be optimal, too. Addressing treatable factors in the individual patient is always worthwhile from the general clinical standpoint; however, our results demonstrate that a simple switch to an SGA is unlikely to make much difference. Even so, we do allow that our results may have varied if less sedating SGAs had been utilized, although we had no evidence that SGA patients were sedated compared to the FGA-treated group. Moreover, the single advantage of SGAs in basic processing would not be expected if greater sedative effects were operating.

Our results add to the small body of literature to the effect that FGAs versus SGAs do not impact upon social cognitive functioning, particularly in the form of patients' ability to recognize affect in both visual and auditory modalities and to read "states of mind" in other people. One strength of the study is its relatively homogeneous, large group of right-handed, partially remitted, psychotic patients recruited only from inpatient settings to better control treatment concordance and immediate environment. Moreover, the patients' symptoms including depression were evaluated. Limitations include lack of randomization and cross-sectional design. Unfortunately, our results do not indicate that psychopharmacological choice alone can be utilized as a means to manage poor social cognition and its impact on functional outcome. In this respect, our results are consistent with an increasing body of work, which, sadly, has suggested that the much vaunted advantages of SGAs over FGAs may be more apparent than real.

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Conclusions

We cannot conclude that SGAs were associated with better social cognition than FGAs. However, there were small, but significant, advantages for SGAs in non-social visual processing function as evaluated with the VOSP.

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