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Do clinical features relate to theory of mind, empathy and 2D:4D in schizophrenia?

Özge Akgül [a], Onur Küçükçoban[b], Tolga Binbay[c], Emre Bora[c], Köksal Alptekin[c] and Berna Binnur Akdede[c]

[a]Department of Neuroscience, Institute of Health Sciences, Dokuz Eylul University, İzmir, Turkey; [b]Psychiatry, Tepecik Training and Research Hospital, İzmir, Turkey; [c]Department of Psychiatry, Dokuz Eylul University School of Medicine, İzmir, Turkey

ABSTRACT

OBJECTIVE: Digit ratios may be accepted as an indicator of level of prenatal androgen exposure during the fetal developmental period. Female-typical digit ratios have been suggested to be associated with better mentalizing and empathic abilities in general population. Recently, a number of studies have investigated the ratio of hand's second and fourth digit fingers (2D:4D) in schizophrenia. The aim of this study was to investigate the hypothesis that positive symptoms are related to female-biased 2D:4D and relatively less impaired social cognition in schizophrenia, negative dimension is related to male-biased 2D:4D ratio and more pronounced deficits in social cognition.

METHOD: The study was carried out in 48 patients with schizophrenia and 48 healthy controls. Patients were evaluated by Positive and Negative Syndrome Scale (PANSS). A digital caliper was used to measure 2D:4D finger lengths and social cognitive abilities were assessed using the Empathy Quotient (EQ) test and Reading Mind in the Eyes Test (RMET).

RESULTS: Patients with schizophrenia had increased left 2D:4D finger lengths and showed poor theory of mind (ToM) and empathic abilities compared to healthy controls ($p < 0.05$). It was found that negative symptoms but not male-biased 2D:4D ratio were significantly associated with impaired RMET performance ($p < 0.05$).

CONCLUSION: The present study indicates that negative dimension is negatively related to the severity of deficits in social cognition in schizophrenia. There was no evidence for a significant effect of sexual dimorphism as measured by digit ratio on social cognition and symptoms in schizophrenia.

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Introduction

According to the neurodevelopmental perspective of schizophrenia, an early harm to the brain causes a long-lasting change of neural advancement and may prompt psychosis. The fundamental reason for this neurodevelopmental abnormality is not yet fully understood, but rather sex differences in the study of disease transmission, neuropathology, clinical presentation of the disorder and time of onset foresee that schizophrenia might be identified with sexual dimorphism in the brain [1]. Sexual dimorphism might be significant in neurodevelopmental disorders. To illustrate, like schizophrenia, autism is a neurodevelopmental issue and its attributes might be characterized by "Extreme Male Brain (EMB)" hypothesis [2]. As per this hypothesis, autistic people indicate regular male characteristics (lower 2D:4D, empathizing < systemizing) due to a high level of prenatal testosterone.

Taking after Baron-Cohen's idea, Crespi and Badcock portray an expansive arrangement of phenotypic qualities showing diametrically opposite phenotypes in the autistic spectrum versus psychotic spectrum conditions (especially schizophrenia). In this manner, as of late, Crespi and Badcock [3] recommend that "Extreme Female Brain (EFB)" hypothesis is connected with psychosis [3]. Along these lines, it is very conceivable that schizophrenia patients demonstrate generally more female-typical digit ratio (2D:4D) [4–8]. However, results of 2D:4D studies in schizophrenia are conflicting. Supporting EFB hypothesis, while some of these studies reported increased 2D:4D [9,10], others have discovered lower digit ratios [11] or that there was no contrast amongst schizophrenia and control groups [12].

Crespi and Badcock [3] see autism spectrum disorder (ASD) and psychosis as inverse endings of a social mind continuum [3]. Hence social cognition capacities are relied upon to be less compromised in schizophrenia contrasted with autism. Crespi and Badcock's hypothesis [3] also contends that symptoms of positive schizophrenia (e.g. magical ideation, abnormal perceptual experiences and paranoia) and autism (social disability and correspondence issues) are considered as diametrical opposites [3]. Furthermore, they suggest that hyper-empathizing underlies paranoia in comparison with hypo-empathizing in autism.

CONTACT Özge Akgül akgullozge@gmail.com Department of Neuroscience, Institute of Health Sciences, Dokuz Eylul University, İzmir 35340, Turkey

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Assuming that schizophrenia is identified with EFB hypothesis, one should expect their performance on social cognition assignments such as the theory of mind and empathy would be relatively successful. Yet, studies investigating Theory of Mind (ToM) abilities in schizophrenia patients compared to controls found that patients with schizophrenia are severely hindered in comprehensive intentions and empathizing with other individuals [13–17].

However, sexual dimorphism might be relevant for the clinical course of schizophrenia. Crespi and Badcock presume that females are moderately more prone to have positive/paranoid schizophrenia whereas males have negative symptoms, early onset of schizophrenia and they are additionally more impervious to treatment [3]. Dimorphic features of the brain may not be the cause of the disorder but it may modify the course of the disease and change the presentation including the severity of the social cognitive impairment. Some tasks such as Reading Mind in the Eyes Test (RMET) [18] and Empathy Quotient (EQ) [19] might be particularly sensitive for demonstrating the effect of sexual dimorphism on social cognition. In regard to the Austin–Manning hypothesis, 2D:4D should be positively related to women like traits such as ToM and empathic abilities [20]. Concordantly, the aim of this study was (1) to examine whether there were significant differences among 2D:4D ratio, RMET and EQ in patient and control groups and (2) to examine whether there were specific relationships among digit ratio, RMET, EQ and symptoms in schizophrenia patients. The hypotheses of this study were as follows: first, the positive dimension is related to female-biased 2D:4D and relatively less impaired RMET, EQ in schizophrenia. Second, the negative dimension is related to male-biased 2D:4D ratio and more impaired performance on EQ and RMET. Third, ToM abilities and empathic abilities are impaired in patient group in comparison to control group.

Material and methods

Participants

A total of 96 participants (48 patients with schizophrenia and 48 healthy controls; 23 females and 25 males for both groups) were included in the study. The schizophrenia patients were recruited from Outpatient Unit for Schizophrenia and Psychosis-Related Disorders of Dokuz Eylül University (DEÜ) School of Medicine, İzmir, Turkey, with the following inclusion criteria: age between 18 and 55; a diagnosis of schizophrenia by using DSM-IV criteria, having been on the same medication for the last 3 months. Controls were drawn from DEÜ staff and the undergraduate students at the Dokuz Eylül University School of Medicine, İzmir, Turkey, by means of flyers and announcements. Four patients with schizophrenia were reported to be left handed, one patient used both hands and three controls were reported to be left handed. The rest of the sample was stated to be right handed. Patients were evaluated using the Positive and Negative Syndrome Scale (PANSS) [21]. Participants having a neurological disorder or receiving electroconvulsive treatment in the past 6 months were excluded. All patients and controls were screened for history of broken fingers or disorders that could have influenced finger length and/or shape. The study was approved by the local institutional ethics board (Institutional Review Board, Dokuz Eylül University School of Medicine, İzmir), and written informed consent following detailed description of the study and procedures was obtained from all participants prior to inclusion. All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2013.

Instruments

Digit ratio measurement

Prior studies have obtained finger lengths by means of photocopies or scans of the hand. However, because of the fact that those measurements may distort ratios [22], digital vernier caliper was used in order to measure digit ratios. Index and ring finger lengths were measured using a digital vernier caliper measuring to 0.01 mm (BGS Technic KG, Wermelskirchen, Germany; Model Bgs Art. 1930 Electronic Digital Caliper). Participants were instructed to place their hands on the table with their palms facing up and to extend their fingers as much as possible. The method was the commonly used measurement method. Absolute lengths of the digits of the right and left hands were taken from the middle of the basal crease where the fingers join the palm to the tip of the fingers. The digit ratio was computed by dividing the length of the index finger by that of the ring finger [23].

"Reading the Mind in the Eyes" test (RMET)

RMET is an advanced mind-reading test, measuring mentalizing (a female-typed trait) in adults [18]. The revised (36-item) RMET consists of photographs of the eye region of actors and actresses. Each item presents four mental-state descriptions (one target and three foil terms, of the same emotional valence). From the visual information alone, respondents are required to choose the word which best describes what the person in the picture is thinking or feeling. Scores are calculated as the total number of correct answers for all 36 items; higher scores on the RMET are associated with the better capacity to infer the

mental states of others. Turkish validity and reliability were conducted by Yıldırım et al. and 32 photographs were found to be applicable for Turkish population [24].

Empathy quotient (EQ)

The EQ is a 40-item questionnaire (20 filler items interspersed), measuring empathy (a female-typed trait) [19]. It includes 60 items and responses made on 4-point Likert scales (0 = "strongly disagree," 1 = "slightly disagree," 2 = "slightly agree," 3 = "strongly agree"). EQ is a self-report scale, presenting statements regarding preferences and habits, with which to agree or disagree, while not actually asking respondents to judge their behaviour. How to evaluate the test is given with the test instructions. A participant can get 80 points at most (between 0 and 80). 80 points show that the participant is very good at empathizing. Bora and Baysan conducted the Turkish validity and reliability of EQ in 2009 [25].

Statistical analyses

SPSS for Windows version 18.0 was used for statistical analysis. Descriptive analyses are presented as mean and standard deviation values. Normal distribution of data was confirmed by the Kolmogorov–Smirnov test. Chi-Square for categorical variables, and univariate ANOVA for continuous variables were conducted. To assess potential ToM and empathy skills differences between groups, univariate analysis of variances was conducted. For the relation of 2D:4D with ToM and empathy, positive and negative dimensions, partial correlation analysis was employed in order to get measures of positive and negative dimensions by controlling general psychopathology dimension.

Results

Statistical analyses comparing sociodemographic variables between cases and controls

Table 1 shows the demographic characteristics of patient and control groups. There were no significant differences between schizophrenia patients and healthy controls in age ($F = 0.144$, $p > 0.05$), gender ($\chi^2 = 0.001$, df = 1, $p = 1.00$), education level ($\chi^2 = 0.001$, df = 2, $p = 1.00$) and total years of education ($F = 0.58$, $p > 0.05$). The marital status of patients and control groups was significantly different ($\chi^2 = 12.660$, df = 2, $p < 0.05$). Moreover, patients were not able to work compared to controls ($\chi^2 = 54.094$, df = 1, $p < 0.05$). Clinical characteristics of the patient group show that age of onset was 23.17 years, duration of illness was 17.125 years and duration of untreated period was 20.96 months.

Table 2 shows the finger digit measures of the patient and the control groups. Univariate ANOVA for left 2D:4D showed significant effect of group ($p = 0.009$). However, there was no significant effect of gender and gender group interaction on left 2D:4D. Also, univariate ANOVA for the right 2D:4D ratio was not significant for group, gender and gender×group.

The patients had a significant deficit in empathy and ToM based on the assessment by the EQ and RMET. Univariate ANOVA for RMET showed significant effect on group ($p = 0.001$). Yet, there was no significant effect for gender and gender×group on RMET. Group ($p = 0.006$) and gender ($p = 0.001$) effect was significant for EQ. However, EQ did not show a gender group interaction. Gender differences on clinical features are also shown in Table 3.

Relation of 2D:4D with RMET, EQ, positive and negative dimensions in schizophrenia patients

PANSS aims to differentiate between positive and negative symptoms, but items sensitive to general psychopathology can hinder the separation of negative and positive dimensions. Therefore, partial correlation analysis was used in order to get pure measures of positive and negative dimensions by excluding common factor of general psychopathology. Without this analysis, PANSS positive and negative dimensions were positively correlated with each other but after partial correlation analysis, they were negatively correlated.

As Table 4 shows, RMET was negatively correlated with negative dimension ($p < 0.05$) which was seen on only females ($p = 0.019$). However, there was no significant relationship among EQ, symptoms and digit ratio ($p > 0.05$).

Discussion

This study aimed to examine the link among positive dimension, female-biased 2D:4D and relatively less impaired social cognition and the link among negative dimension, male-biased 2D:4D ratio and relatively more impaired performance on social cognition and 2D:4D ratio in patients with schizophrenia. Our findings indicated that negative symptoms were negatively correlated with RMET performance and patients with schizophrenia had increased left 2D:4D in comparison with healthy controls. In our study, there was a significant relationship between the severity of negative symptoms and performance on RMET in patients with schizophrenia. It is known that negative symptoms in schizophrenia are related to ToM deficits both in the chronic and first episode [26,27]. Especially, affective ToM function (the capacity to ascribe affective mental states to others) was selectively impaired in patients with schizophrenia who had a high level of negative symptoms [28] and it is well known that

Table 1. Sociodemographic and clinical characteristics of cases and controls.

Variables (mean ± SD)	Patient group ($N = 48$)	Control group ($N = 48$)	F/χ^2	p
Age (years)	39.85 ± 1.309	39.73 ± 1.351	0.144	0.947
Gender (M/F)	25/23	25/23	0.01	1.000
Education (years)	13.32 ± 0.588	12.67 ± 0.579	0.58	0.428
Marital status				
Married	12 (25%)	28 (58.3%)	12.660	**0.002****
Single	32 (66.7%)	15 (31.3%)		
Divorced	4 (8.3%)	5 (10.4%)		
Working status in the past 6 months				
Working	7 (14.6%)	43 (89.6%)	54.09	**0.001****
Not working	41 (85.4%)	5 (10.4%)		
Age of onset	23.17 ± 7.367			
DOI (duration of illness)	17.125 ± 10.690 years			
PANSS Positive Symptoms Scores	17.06 ± 6.827			
PANSS Negative Symptoms Scores	16.94 ± 5.64			
PANSS Scores	68.42 ± 17.996			

Note. SD: Standard Deviation; PANSS: Positive and Negative Syndrome Scale.
* $p < 0.05$.
** $p < 0.005$.

ToM impairments exist in schizophrenia [29]. Early studies concluded that female schizophrenia patients are better at discriminating emotions [30,31]. Moreover, the study showed that those ToM abilities were not influenced by positive symptom severity while negative symptoms showed statistically significant negative association with RMET results. This finding is consistent with the outcome of previous studies investigating the relationship between symptoms and neurocognition in schizophrenia [32]. However, in our study correlation was only seen in females.

In addition to this, while the relationship of 2D:4D with negative dimension and social cognition was in expected direction, it was not significant. The lack of significant relationship between digit ratio and social cognition and symptoms might indicate that sexual dimorphism has no significant effect on social cognitive deficits in schizophrenia. It could be argued that the relation between impaired social cognition and negative dimension is about general rather than sex-related abnormalities in neurodevelopmental processes. However, although the relationship between social cognitive abilities and 2D:4D ratio was not significant, its relation was in the expected direction. Therefore, it is not possible to exclude the potential small effect of sex-specific neurodevelopmental abnormalities on social cognitive deficits in schizophrenia. Also in our study, despite the fact that empathy was expected to be adversely connected with negative symptoms, we found no correlations between the EQ and symptoms. This is possibly because of the EQ being a self-report instrument, it is well known that people are not always able to judge their own social abilities successfully and poor insight in schizophrenia might further decrease the reliability of self-assessment. Therefore, it could have been better to include informant-rated EQ scores in the assessment of empathic abilities [33]. Yet, we found that schizophrenia patients had increased left 2D:4D compared to healthy controls consistent with other findings [9,10], although some studies reported lower digit ratios [11] or no difference [12] compared to controls. The literature about digit ratios in schizophrenia is inconsistent. Hox genes which regulate testosterone levels are thought as one of the factors determining finger lengths in the prenatal period. However, consistent with several studies and meta-analyses, as hypothesized, it was found that schizophrenia patients showed poor performance on ToM tests [13, 34–37] and empathic abilities [28, 38–39]. A number of limitations of the study should be taken into account. The most important limitation is small sample size which may have reduced the power of detecting diagnostic group, sex differences and social cognition, and showing a statistically significant correlation between variables. Therefore, our results should be considered as preliminary. The lack of neurocognitive testing assessment and cross-sectional nature of the study are other limitations. Moreover, although the RMET is one of the commonly used ToM measure, it does not assess every aspect of the multi-dimensional construct of ToM. Therefore, future studies should include multiple tests measuring different aspects of

Table 2. 2D:4D, RMET and EQ in cases and controls.

Variables (mean ± SD)	Patient group ($N = 48$)	Control group ($N = 48$)	F	p	Group ($N = 48$, $N = 48$) F/p	Gender (M = 50, F = 46) F/p	Group × gender F/p
L2D:4D	1.0119 ± 0.04	0.9904 ± 0.032	3.209	**0.008***	7.050/**0.009***	0.165/0.685	1.383/0.243
R2D:4D	1.0067 ± 0.04	1.0069 ± 0.031	0.896	0.978	0.003/0.954	0.864/0.355	0.537/0.466
RMET	18.33 ± 4.34	21.73 ± 3.79	3.351	**0.001****	16.924/**0.001***	1.518/0.221	0.636/0.427
EQ	44.69 ± 11.51	50.25 ± 8.82	4.24	**0.009***	7.757/**0.006***	11.538/**0.001***	0.002/0.968

Note. M: Male; F: Female; RMET: Reading Mind in the Eyes Test; EQ: Empathy Quotient; L2D:4D, left 2D:4D; R2D:4D, right 2D:4D.
* $p < 0.05$.
** $p < 0.005$.

Table 3. Clinical differences between males and females.

Variables (mean ± SD)	Female patient group ($N = 23$)	Male patient group ($N = 25$)	df	p	F/χ^2
DOI (duration of illness)	18.696 ± 11.56	15.680 ± 9.835	46	0.334	0.399
PANSS Positive Symptoms Scores	17.26 ± 6.897	16.88 ± 6.900	46	0.849	0.037
PANSS Negative Symptoms Scores	17.00 ± 6.551	16.88 ± 4.790	46	0.942	1.215
PANSS Scores	69.13 ± 19.01	67.76 ± 17.379	46	0.795	0.045

Note. SD: Standard Deviation; PANSS: Positive and Negative Syndrome Scale.

ToM. Also, in our study we reported that negative dimension is related to ToM. However, we cannot definitely conclude that the relationship between negative dimension and ToM is casual as other variables such as general cognition can mediate this relationship between these two measures.

The lack of significant correlation between digit ratio and other variables including social cognition and symptoms might be related to the inclusion of patients with better functional outcomes as patient and healthy control groups were matched for duration of education.

In conclusion, this study indicates that negative symptoms are related to impaired performance in social cognition. Schizophrenia patients had increased left 2D:4D, decreased ToM and empathy ability scores compared to healthy controls. A study with a larger size would be beneficial to reveal a potentially small effect of sexually dimorphic characteristics of schizophrenia on social cognition and symptoms. Also, since decreased 2D:4D is related to asymmetry and limbic abnormalities, further studies in schizophrenia are needed to examine 2D:4D with brain structure and function as well as the association of digit ratio with empathy, ToM and symptoms in larger populations.

Table 4. 2D:4D with RMET, EQ, positive and negative dimensions.

	Positive symptoms	Negative symptoms	EQ	RMET
L2D:4D				
Correlation	0.062	−0.182	0.022	−0.022
p	0.680	0.221	0.879	0.881
df	45	45	45	45
R2D:4D				
Correlation	0.037	−0.001	0.115	−0.063
p	0.807	0.995	0.436	0.672
df	45	45	45	45
EQ				
Correlation	0.211	0.008		
p	0.154	0.957		
df	45	45		
RMET				
Correlation	−0.155	−0.288		
p	0.298	**0.049***		
df	45	45		
RMET				
Correlation (females)	−0.039	−0.495		
p	0.864	**0.019***		
df	20	20		

Note. RMET, Reading Mind in the Eyes test; EQ, Empathy Quotient; L2D:4D, left 2D:4D; R2D:4D, right 2D:4D.
* $p < 0.05$.

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No potential conflict of interest was reported by the authors.

ORCID

Özge Akgül http://orcid.org/0000-0001-8321-5485

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