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# Decoding emotion of the other differs among schizophrenia patients and schizoaffective patients: A pilot study

Hagar Tadmor [a,b,1], Maya Levin [b,1], Tzameret Dadon [a,1], Meital E. Meiman [a,2], Alaa Ajameeh [a], Hosam Mazzawi [a], Amihai Rigbi [c,d], Ilana Kremer [a,e], Idit Golani [f], Alon Shamir [a,e,*]

[a] Psychobiology Research Laboratory, Mazor Mental Health Center, Akko, Israel
[b] Faculty of Medicine in the Galilee, Bar-Ilan University, Zefat, Israel
[c] Department of Behavioral Science, Kinneret Academic Collage on the Sea of Galilee, Israel
[d] Research Authority Unit, Beit Berl Academic College, Kfar Sava, Israel
[e] The Ruth and Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel
[f] Department of Biotechnology, Ort Braude College, Karmiel, Israel

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ABSTRACT

The deficit in ability to attribute mental states such as thoughts, beliefs, and intentions of another person is a key component in the functional impairment of social cognition in schizophrenia. In the current study, we compared the ability of persons with first episode schizophrenia (FE-SZ) and individuals with schizophrenia displaying symptomatic remission (SZ-CR) to decode the mental state of others with healthy individuals and schizoaffective patients. In addition, we analyzed the effect of dopamine-related genes polymorphism on the ability to decode the mental state of another, and searched for different genetic signatures. Our results show that overall, individuals with schizophrenia performed worse in the "Reading the Mind in the Eyes" (eyes) test, a simple well-defined task to infer the mental state of others than healthy individuals. Within the schizophrenia group, schizoaffective scored significantly higher than FE-SZ, SZ-CR, and healthy individuals. No difference was observed in performance between FE-SZ and SZ-CR subjects. Interestingly, FE-SZ and SZ-CR, but not schizoaffective individuals, performed worse in decoding negative and neutral emotional valance than the healthy control group. At the genetic level, we observed a significant effect of the DAT genotype, but not D4R genotype, on the eyes test performance. Our data suggest that understanding the mental state of another person is a trait marker of the illness, and might serve as an intermediate phenotype in the diagnostic process of schizophrenia disorders, and raise the possibility that DA-related DAT gene might have a role in decoding the mental state of another person.
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## 1. Introduction

"Theory of mind" (ToM or "mentalizing") refers to the cognitive ability to attribute mental states such as thoughts, beliefs, and intentions to people, allowing an individual to explain, manipulate, and predict behavior. Originally this term was defined in 1978 by Premack and Woodruff following their work on social cognition in non-human primates, and was described as the ability to explain the observed behaviors of others by referring to their mental states. It is widely accepted that ToM can be divided into cognitive and affective aspects (Shamay-Tsoory et al., 2007; Shur et al., 2008). Cognitive ToM is the ability to make inferences about beliefs and motivations, while affective ToM refers to the ability to infer what a person is feeling. In other words, cognitive ToM corresponds to knowledge about others' beliefs or intentions, whereas affective ToM corresponds to the appreciation of the others' emotional states. The cognitive ToM network primarily engages the dorsomedial prefrontal cortex, the dorsal anterior cingulate cortex, and the dorsal striatum, while the affective ToM network primarily engages the ventromedial and

* Corresponding author at: The Psychobiology Research Laboratory, Mazor Mental, Health Center and the Ruth and Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, D.N. Oshrat, Akko, 25201, Israel. Tel.: +972 4 995 4708; fax: +972 4 955 9523.
*E-mail address:* alons@mazor.health.gov.il (A. Shamir).
[1] Contributed equally to the work.
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orbitofrontal cortices, the ventral anterior cingulate cortex, the amygdala, and the ventral striatum (Abu-Akel and Shamay-Tsoory, 2011).

ToM can be measured by a variety of means, including the classical Sally-Anne false belief test, the verbal and eye-gaze cues task, reading the mind in the eyes test (referred to as the eyes test), and through stories and jokes. For all, the subject's ability to evaluate and judge the mental state of another is assessed. For example, the ability to understand that another person has beliefs different from one's own is measured by the false belief test, while decoding another's complex mental state is measured by the eyes test (Aboulafia-Brakha et al., 2011; Baron-Cohen et al., 2001; Brüne, 2005).

A relationship between ToM and schizophrenia was first proposed by Frith in 1992. He claimed that several symptoms of schizophrenia could be explained by mentalizing impairment. This led to a substantial body of research which suggested that ToM is impaired in individuals with schizophrenia. Two meta-analyses reported a large magnitude of deficits in a number of ToM tasks in schizophrenic patients, including the false belief sequencing, false belief stories, the Hinting, and the "Reading the Mind in the Eyes" (eyes) test (Bora et al., 2009; Sprong et al., 2007). However, it is unclear whether deficit in the interpretation of others' emotions, intention, and beliefs is dependent on the state of the illness or a trait. It has been argued that delusions could be explained as misinterpretation of others' intentions, and that the absence of a mental representation of a patient's own intended action would affect the patient's capacity to assign mental states to other persons' actions. Thus, ToM deficits are expected to occur in non-remitted patients with prominent thought and delusions, whereas remitted patients are predicted to have preserved ToM abilities, suggesting that mentalizing deficits depend on the state of the illness (Pousa et al., 2008). On the other hand, several studies suggested that ToM is altered in first degree relatives (Ho et al., 2015; Irani et al., 2006), in high risk individuals (Bora and Pantelis, 2013; Stanford et al., 2011), and in individuals with schizophrenia in remission (Herold et al., 2002). Thus, ToM dysfunction could be trait dependent and might serve as a trait marker of the disorder.

To extend the understanding of whether the impairment in the ability to attribute mental states of another person in schizophrenia is trait or state dependent, we study the ability of persons with first episode schizophrenia and individuals with schizophrenia in remission to decode the mental state of the other with healthy individuals and schizoaffective patients using the "Reading the Mind in the Eyes" (eyes) test (Baron-Cohen et al., 2001). This task measures the capacity to discriminate the mental state of others from expressions in the eye region of the face. It is considered an advanced ToM test, since participants have to put themselves into the mind of the person shown in the photograph, and attribute a relevant mental state.

The dopaminergic system is thought to play a major role in mediating our ability to mentalize (Abu-Akel and Shamay-Tsoory, 2011). However, only a few studies investigated the molecular genetics of the dopamine (DA)-related gene in the pathogenesis of ToM. D4 receptor (D4R) genetic variation predicts preschoolers' developing theory of mind (Lackner et al., 2012), and it was recently linked to variations in gamma power, a network that increases during cognitive and social–cognitive tasks (Williams and Boksa, 2010). Interestingly, activation of the receptor was shown to enhance gamma oscillations (Kocsis et al., 2013), suggesting that the D4R might have a role in regulating cognitive processes (Furth et al., 2013). It is important to note that the D4 receptor was identified as a risk factor gene for schizophrenia (Lung et al., 2009; Shi et al., 2008), and that the DA acts as a key neurotransmitter in the etiology of schizophrenia (Seeman, 2009; Stone et al., 2007; Winton-Brown et al., 2014), and in cognitive dysfunction (Simpson et al., 2010) and emotional processing deficit (Salgado-Pineda et al., 2005). Therefore, we addressed the possible relations between the D4R exon III polymorphisms and the ability to decode the other's feeling, and searched for a different genetic signature. In addition, we studied the effect of a second major polymorphic DA-related gene — the 3′ VNTR dopamine transporter (DAT), a key regulator of synaptic dopamine uptake, on the performance of the eyes test.

## 2. Methods

### 2.1. Subjects

The study was approved by the Mazor Mental Health Center and the Israel Ministry of Health ethics committees, and all participants gave informed consent to take part in the study.

Forty-one clinically stable individuals with schizophrenia (SZ-CR), 20 first episode-persons with schizophrenia (FE-SCZ), and 9 individuals with schizoaffective (SZ-AF) meeting the DSM-IV criteria were recruited from the open and closed wards of Mazor Mental Health Center, Akko, Israel. The exclusion criteria were: 1) drug or alcohol abuse, 2) mental retardation, and 3) organic brain pathology. Patients underwent a clinical differential diagnosis using the Structure Clinical Interview for DSM disorders (SCID) and their positive and negative symptoms were evaluated using the Positive and Negative Symptom Rating Scale (PANSS). Clinical and sociodemographic data were collected from the electronic medical records of the recruited patients and included the following variables: age, sex, education, military service, ethnicity, age of onset, number of hospitalizations, duration of the illness, and family history.

Two hundred healthy individuals without psychiatric history were recruited from Ort Brauda College of Engineering, Karmiel, Israel. The inclusion criteria were physically healthy without drug or alcohol abuse. Sociodemographic information from self-reported data was collected, and included age, sex, education, military service, and ethnicity.

### 2.2. Reading the mind in the eyes test

"Reading the Mind in the Eyes" (eyes test) test was developed by Baron-Cohen et al. (2001) as a tool to evaluate the ability to infer the mental state of another person. In this task, participants are presented with 36 still pictures of the eye region of faces illustrating emotionally charged or neutral mental states. They were then asked to choose which of four words best described what the person in the picture was thinking or feeling. This task is considered an advanced ToM test since the participants need to imagine themselves in the mind of the person shown in the picture. One limitation of the test is that the participants only decode the relevant mental state without predicting or explaining the action of the other person. The score on the eyes test is calculated as the total number of correctly identified mental states. In addition, we adopted the three-factor model that was described by Vellante et al. (2012). In brief, the model is based on classification of the 36 pictures to positive, negative, or neutral valence. Positive valence included 8 items (playful, fantasizing, thoughtful, friendly, interested, flirtatious, confident), negative valence included 12 items (upset, worried, regretful, accusing, doubtful, preoccupied, defiant, hostile, cautious, distrustful, nervous, suspicious), and 16 items were included in the neutral valence (desire, insisting, uneasy, despondent, cautious, skeptical, anticipating, contemplative, decisive, tentative, pensive, interested, reflective, serious, concerned). Percentage of correct answers was calculated for each valence.

### 2.3. 3′ VNTR dopamine transporter and dopamine D4 receptor exon III polymorphism genotyping assays

DNA was extracted from blood samples of individuals with schizophrenia or from saliva of healthy individuals following the manufacturer's instructions (Fermentas, Life Science, Waltham, MA,

USA; and DNA, Genotek, Ontario, Canada, respectively). The GoTaq Master Mix (Promega, Madison, WI, USA) and set of primers previously described by Vandenbergh et al. (1992) and Mayseless et al. (2013) were used to determine the 3′ VNTR DAT and D4R polymorphisms, respectively. PCR conditions were as follows: an initial denaturation step at 94 °C for 2 min, followed by 35 cycles of denaturation at 94 °C for 10 s, annealing at 63 °C for 30 s and extension at 72 °C for 30 s. The reaction proceeded to hold at 72 °C for 6 min. The PCR products were electrophoresed on 1.5% agarose gel and visualized by ethidium bromide.

The genotypes of the 3′ VNTR DAT and D4R alleles were determined based on the number of the tandem repeats. In order to maximize the genetic analysis the D4R gene variation was divided into short (≤4) and long (≥5) repeats as previously done by others (Das et al., 2011; Lackner et al., 2012).

### 2.4. Statistical analysis

For baseline comparison between the groups (as presented in Table 1), continuous variables were compared using two-sided t-test, while categorical variables were compared using Pearson's Chi-square test or Fisher's exact test. Association between groups, genetic polymorphism and eyes test scores were tested using multivariate linear regression models. These models included the main independent variables of interest (i.e. group or group and polymorphism) together with relevant background variables that significantly were different between the groups, and significantly associated with the performance in the eyes test (specific descriptions of each model construction appear in the following Results section). Specific post-hoc comparisons between groups of interest were performed on the predicted eyes test scores yielded by the regression analyses, and followed by Bonferroni correction for multiple testing. Effect sizes for specific comparisons were calculated by converting the t statistic to Pearson's r statistic (Field, 2007) then to Cohen's d measure of effect size (Borenstein et al., 2009), and were interpreted as small (d = 0.1), medium (d = 0.5), or large (d = 0.8) (Cohen, 1992). All analyses were performed using IBM-SPSS 20.

## 3. Results

### 3.1. Between group demographic data

As described above, 270 subjects participated in the study — 70 individuals with schizophrenia (referred to as SZ) and 200 healthy controls (referred to as CT). Among the SZ, 41 were diagnosed as

**Table 1**
Demographic, clinical and genetics data.

| Variable category | Variable | SZ-CR (41) | SZ-AF (9) | FE-SZ (20) | Controls (200) | *p*-value |
|---|---|---|---|---|---|---|
| Demographic | | | | | | |
| | Age, yrs.: mean (SD) | 35.6 (10.0) | 41.6 (8.3) | 26.4 (4.9) | 26.5 (7.5) | <**0.001**[a] |
| | Education, yrs.: mean (SD) | 11.8 (2.2) | 11.3 (2.2) | 12.0 (1.6) | 13.8 (2.6) | <**0.001**[b] |
| | Gender: n (%) | | | | | <**0.001** |
| | Men | 34 (83%) | 7 (78%) | 16 (80%) | 106 (54%) | |
| | Women | 7 (17%) | 2 (22%) | 4 (20%) | 92 (46%) | |
| | Nationality: n (%) | | | | | 0.1 |
| | Jewish | 33 (81%) | 9 (100%) | 12 (60%) | 146 (73%) | |
| | Arab | 8 (19%) | 0 (0%) | 8 (40%) | 53 (27%) | |
| | Ethnicity: n (%)[c] | | | | | **0.02** |
| | Ashkenazi | 17 (55%) | 5 (56%) | 11 (92%) | 67 (46%) | |
| | Non-Ashkenazi | 14 (45%) | 4 (44%) | 1 (8%) | 79 (54%) | |
| **Clinical** | | | | | | |
| | Onset, yrs.: mean (SD) | 25.1 (7.3) | 26.1 (8.3) | 25.5 (4.7) | NA | 0.91 |
| | Years of illness: mean (SD) | 11.0 (7.2) | 15.4 (7.9) | 1.1 (0.6) | NA | <**0.001**[d] |
| | No. of hospitalizations: mean (SD) | 6.2 (5.0) | 8.5 (6.9) | 1.0 (0.0) | NA | <**0.001**[e] |
| | PANSS scales score: mean (SD) | | | | | |
| | Positive items | 21.9 (6.4) | 17.3 (4.0) | 41.7 (4.6) | NA | <**0.001**[f] |
| | Negative items | 26.2 (5.8) | 17.8 (5.2) | 22.8 (5.8) | NA | **0.001**[g] |
| | General items | 48.3 (7.4) | 45.9 (5.4) | 58.5 (6.2) | NA | <**0.001**[h] |
| | Total | 96.1 (14.7) | 77.2 (12.6) | 122.9 (10.4) | NA | <**0.001**[i] |
| | Smoking status: n (%) | | | | | <**0.001** |
| | Yes | 24 (60%) | 7 (78%) | 14 (70%) | 46 (23%) | |
| | No | 16 (40%) | 2 (22%) | 6 (30%) | 153 (77%) | |
| **Genetic** | | | | | | |
| | DAT polymorphism: n (%) | | | | | 0.71 |
| | Homozygote 9/9 | 6 (17%) | 0 (0%) | 4 (20%) | 22 (16%) | |
| | Homozygote 10/10 | 17 (49%) | 5 (63%) | 7 (35%) | 55 (39%) | |
| | Heterozygote 9/10 | 12 (34%) | 3 (37%) | 9 (45%) | 64 (45%) | |
| | D4R polymorphism: n (%) | | | | | 0.18 |
| | Short allele | 21 (62%) | 2 (25%) | 14 (70%) | 78 (61%) | |
| | Long allele | 13 (38%) | 6 (75%) | 6 (30%) | 50 (39%) | |

Abbreviations: DAT, dopamine active transporter; D4R, dopamine D4 receptor; PANSS, positive and negative syndrome scale; SZ, chronic schizophrenia; SZ-AF, schizoaffective; FE-SZ, first episode schizophrenia; CT, control group SD, standard deviation.

[a] Post hoc comparisons revealed that the SZ and SZ-AF groups were significantly older than the other groups ($p < 0.001$ for all comparisons).

[b] Post hoc comparisons revealed that the control group had significantly more years of education than the schizophrenic groups ($p < 0.001$, $p = 0.02$, $p = 0.02$, respectively).

[c] This variable is relevant only for Jewish participants.

[d] Post hoc comparisons revealed that the FE-SZ group length of illness was significantly shorter than the other schizophrenic groups ($p < 0.001$ for all comparisons).

[e] Post hoc comparisons revealed that the FE-SZ group number of hospitalizations was significantly smaller than the other schizophrenic groups ($p < 0.001$ for SCZ, $p = 0.001$ for schizoaffective comparisons).

[f] Post hoc comparisons revealed that the FE-SZ group PANSS-positive score was significantly higher than the other schizophrenic groups ($p < 0.001$ for all comparisons).

[g] Post hoc comparisons revealed that SZ-AF PANSS-negative score was significantly lower than the other schizophrenic groups ($p = 0.001$).

[h] Post hoc comparisons revealed that FE-SZ group PANSS-general score was significantly higher than the other schizophrenic groups ($p < 0.001$ for all comparisons).

[i] Post hoc comparisons revealed that the first episode group PANSS-total score was significantly higher than the other schizophrenic groups ($p < 0.001$ for all comparisons); the total score of SZ-CR group was significantly higher that the SZ-AF group ($p = 0.001$).

chronic (referred to as SZ-CR), nine were diagnosed as schizoaffective (referred to as SZ-AF) and 20 were diagnosed as first-episode (referred to as FE-SZ). Table 1 presents demographic, clinical, and genetic characteristics of the study sample. Overall, individuals with schizophrenia (SZ) were significantly older ($F_{2,263} = 24.4$; $p < 0.001$) and had fewer years of education ($F_{3,257} = 11.1$; $p < 0.001$). Compared with the control group, they also contained a greater proportion of men (Fisher exact = 17.3; $p < 0.001$), and more Ashkenazi Jews (Fisher exact = 10.1; $p < 0.02$). In addition, smoking was significantly more frequent among the SZ groups (Fisher exact = 40.1; $p < 0.001$), compared with CT group.

### 3.2. Reading the mind in the eyes is impaired in individuals with schizophrenia

First, we evaluated the ability of the overall SZ group and CT group to decode the mental state of another using the eyes test. Fig. 1A and B summarizes the distribution of the test scores of the healthy and the SZ, respectively. In order to test the association between groups (SZ/CT) and the eyes test scores, four multivariate linear regression models were constructed. One for each eyes test parameter (eyes test total score and positive, negative, and neutral valences), that served as the dependent variables. The independent variables in each model were combined with variables found to be significantly different between the groups (Table 1), and associated with the eyes test parameters. These variables included smoking status, gender, years of education and age (See Supplementary Table 1 for univariate associations between these variables and eyes test parameters). Analysis revealed that the SZ group performed significantly worse in all eyes test parameters, except positive valence (Eyes test total score: $\beta = -0.34$, $t = -4.4$, $p < 0.001$; Negative valence: $\beta = -0.33$, $t = -4.3$, $p < 0.001$; Neutral valence: $\beta = -0.29$, $t = -3.6$, $p < 0.001$; See Supplementary Table 2 for the full models' details). As expected, on average SZ individuals yielded lower predicted eyes test total score than healthy individuals (20.3 [SE = 0.1] and 23.8 [SE = 0.04], respectively; $p < 0.001$, d = 3.95, Fig. 1C). In addition, SZ decoded fewer negative (48.5% [SE = 0.4] and 62.2% [SE = 0.1], respectively; $p < 0.001$, d = 4.74, Fig. 2A), and neutral (60.4% [SE = 0.3] and 70.5% [SE = 0.1], respectively; $p < 0.001$, d = 4.45, Fig. 2B) valences than the control group, with large effect sizes for all comparisons. Interestingly, no difference in decoding positive valence between the comparison groups was found (Fig. 2C).

Next, we compared the ability of individuals with chronic schizophrenia (SZ-CR), schizoaffective (SZ-AF) and first episode (FE-SZ) with the CT group to decode the mental state of another. Multivariate regression model's construction was similar to that described above, with the CT group serving as the reference group. Analysis revealed that SZ-CR and FE-SZ individuals performed significantly worse than the CT group in all eyes test parameters (Fig. 3A–D). However, the SZ-AF group performed better than the CT group in decoding positive, neutral, but not negative valence (Eyes test Total score: $\beta = 0.17$, $t = 2.5$, $p = 0.01$; Positive valence: $\beta = 0.23$, $t = 3.1$, $p < 0.001$; Neutral valence: $\beta = 0.14$, $t = 2.0$, $p = 0.04$; See Supplementary Table 3 for the full models' details). On average, the SZ-AF group yielded higher predicted eyes test total score than the CT group (26.8 [SE = 0.2] and 23.8 [SE = 0.0] respectively; $p < 0.001$, d = 1.26, Fig. 3A). In addition, SZ-AF participants performed better in decoding positive (80.6% [SE = 0.9] and 63.1 [SE = 0.1], respectively; $p < 0.001$, d = 2.28, Fig. 3B) and neutral (80.6% [SE = 0.6] and 70.5 [SE = 0.1], respectively; $p < 0.001$, d = 1.78, Fig. 3C) valences than healthy individuals, with large effect sizes for all comparisons. However, no difference was found between SZ-AF individuals and CT in decoding negative valence (Fig. 3D). Moreover, their performance, in all eyes test parameters, was also significantly better than SZ-CR and FE-SZ participants (Fig. 3A–D). Taken together, these data support the notion that SZ-CR and FE-SZ, but not SZ-AF, patients are impaired in decoding the other's complex mental state, and suggest that this impairment is associated with the reduction in the performance in decoding negative and neutral valences.

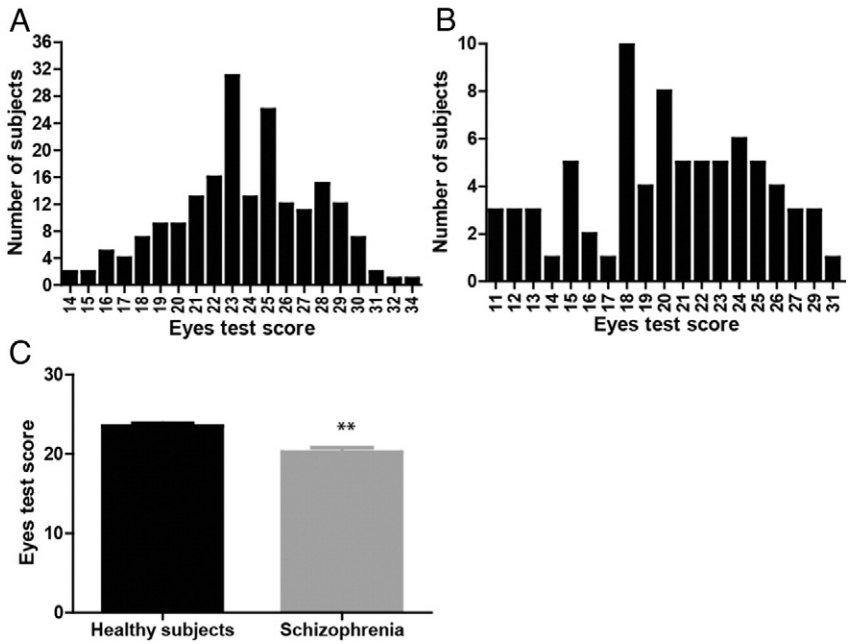


**Fig. 1.** Individuals with schizophrenia are impaired in decoding the emotional state of others. Healthy volunteers (A) and schizophrenic patients (B) total eyes test score distribution. C) Estimated mean differences in total eyes test score ± SEM between overall schizophrenia groups and control group. $^{**}p < 0.001$.

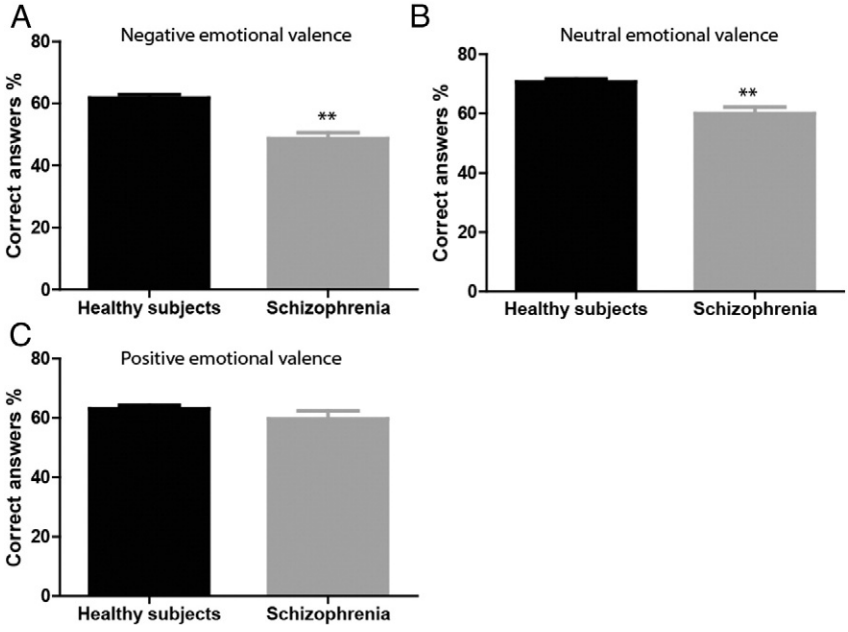


**Fig. 2.** Decoding negative and neural valences is altered in the schizophrenia patients group. Estimated mean differences of presented correct choices ± SEM (A) negative emotional valence, (B) neutral emotional valence, and (C) positive emotional valence. $^{**}p < 0.001$.

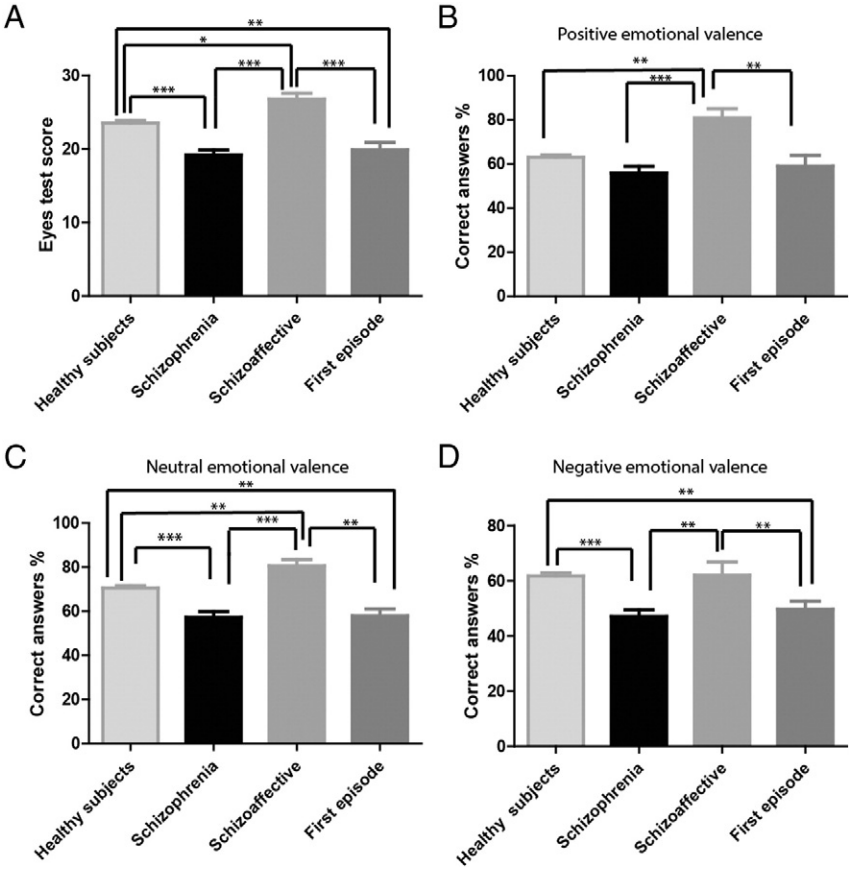


**Fig. 3.** Schizoaffective individuals performed better in the eyes test. (A) Estimated mean differences in total eyes test score ± SEM between individuals with schizophrenia first episode, schizoaffective, and healthy subjects. Estimated mean differences of presented of correct choices ± SEM (B) negative emotional valence, (C) neutral emotional valence, and (D) positive emotional valence. $^{*}p < 0.5$, $^{**}p < 0.001$, $^{***}p < 0.0001$.

### 3.3. Correlation of PANSS scores with the eyes test

Patients' positive and negative symptoms were recorded using the positive and negative score scale (PANSS, Table 1). PANSS scales scores of FE-SZ were significantly higher (Positive: $F_{2,61} = 96.6$; $p < 0.001$; Negative: $F_{2,61} = 8.2$; $p = 0.001$; General: $F_{2,61} = 19.7$; $p < 0.001$; Total: $F_{2,59} = 44.3$; $p < 0.001$) compared with SZ-CR and SZ-AF groups. In addition, SZ-AF patients' PANSS-negative score was significantly lower than that of the SZ-CR group ($p = 0.001$). In addition and as expected, FE-SCZ patients had significantly fewer years of illness ($F_{2,65} = 23.4$; $p < 0.001$) and fewer hospitalizations ($F_{2,61} = 11.7$; $p < 0.001$, Table 1). Overall, a significant inverse correlation was found between the eyes test score (Pearson's $r = -0.38$ $p = 0.002$), positive valence (Pearson's $r = -0.28$, $p = 0.003$), neutral valence (Pearson's $r = -0.38$ $p = 0.002$), and negative symptoms. Since the PANSS measures were correlated with both the clinical sub-groups and the eyes test scores, secondary regression analyses were performed within the SZ participant only, with SZ-CR serving as the reference group, together with PANSS scores. This analysis revealed the same pattern of results described under Section 3.2: the SC-AF group manifested higher eyes total score ($\beta = 0.40$, $t = 3.2$, $p < 0.001$), positive valence ($\beta = 0.30$, $t = 2.2$, $p = 0.03$) and neutral valence ($\beta = 0.30$ $t = 2.5$, $p = 0.04$), compared to the SZ-CR and the FE-SZ groups (full models have not been presented since this analysis is considered secondary).

### 3.4. Association between groups, genetic profile, and performance in the eyes test

Analysis of common allelic variant of the 3′ VNTR DAT polymorphism (9 and 10 times 48 bp repeat; 9R and 10R, respectively) revealed that there is no difference in allelic frequency between CT and the SZ groups (Table 1, DAT: Fisher exact = 3.8; $p = 0.71$; D4R: Fisher exact = 4.7; $p = 0.18$). Association analysis between groups (SZ and CT), DAT polymorphism (homozygotes 10R/10R [referred to as 10R/10R], heterozygotes 9R/10R [referred to as 9R/10R] and homozygotes 9R/9R [referred to as 9R/9R]) and the eyes test scores was performed using a 3-block multivariate linear regression. The first block included the group main effects and DAT polymorphism. The second block added the effects of background variables (see Section 3.2 above), while the third block added the effect of the interaction terms (see Supplementary Table 4 for entire models' details). The analyses revealed significant effects for main effects models only (Models 1 and 2 in Supplementary Table 3), but not for the model included the interaction terms (Model 3 in Supplementary Table 3). A main effect for group was found in the eyes test total score ($\beta = -0.30$, $t = -3.3$, $p < 0.001$) and for the negative ($\beta = -0.30$, $t = -3.3$, $p < 0.001$) and neutral ($\beta = -0.27$, $t = -2.9$, $p = 0.004$) valences. These results replicated the results of 2-group analysis described above (see Section 3.2), and indicate that SZ patients scored below the CT group in these eyes test parameters irrespectively of their 3′ VNTR DAT genotype. In addition, a significant main effect for polymorphism was found in the eyes test total score ($\beta = -0.15$, $t = -2.1$, $p = 0.04$), and neutral valence score ($\beta = -0.16$, $t = -2.1$, $p = 0.04$), indicating that 9R/9R genotype carrier, irrespective of their clinical state (either SZ or CT), performed significantly worse in the eyes test compared to the other polymorphism groups.

Similar multivariate linear regression analyses were performed in order to examine the associations between groups, D4R polymorphism and eyes test parameters. The main effect for group has been replicated, suggesting that individuals with SZ performed worse than the CT group in the eyes test irrespective of their DR4 genotype (see Supplementary Table 5 for full models' details). However, no main effect for polymorphism was detected. Interestingly, a significant interaction effect was found in the ability to decode positive valance ($\beta = 0.32$, $t = 2.9$, $p = 0.004$). Results indicated that individuals with SZ carrying the D4R long allele decoded more positive emotion valances than CT individuals who carry the same allele. In addition, SZ individuals carrying the D4R short allele decoded less positive valances compared with healthy individuals carrying the same genotype.

## 4. Discussion

Impaired affective and non-affective face perception in schizophrenia has been widely reported (Li et al., 2010; Velakoulis et al., 2006). In the current study we report that individuals diagnosed with schizophrenia performed worse in the eyes test and scored on average significantly lower than healthy individuals in decoding negative and neutral emotional valances. These findings are consistent with the notion that poor mentalizing or poor processing of facial emotion information is impaired in overall individuals with schizophrenia (Brüne, 2005). However, within the schizophrenia diagnosed groups, no significant difference in the performance of the eyes test was found between first episode persons (FE-SZ) and individuals with chronic schizophrenia (SZ-CR). On the other hand, schizoaffective persons (SZ-AF) performed better in decoding the mental state of another, and scored significantly higher than FE-SZ, SZ-CR, and healthy individuals. In addition, our study pinpoints the difference in the ability to process positive, negative, and neutral emotional valence between the different diagnosis groups and healthy individuals. SZ-CR and FE-SZ individuals, but not SZ-AF participant, performed worse in decoding negative and neutral emotional valance than the healthy control group. SZ-AF patients performed better in decoding positive valence than healthy individuals and SZ-CR, while recognition of positive facial valence was similar between SZ-CR, FE-SZ, and healthy individuals. Our results suggest that the presence of mood symptoms in SZ-AF individuals is related to better processing of facial information, and might indicate that mood abnormality increases the sensitivity to social cues. This finding is consistent with previous results. Chen et al. (2012) reported that SZ, but not SZ-AF individuals, exhibited deficient performance in both fear and happiness discrimination. Moreover, enhanced accuracy in decoding the mental state of others was reported in dysphoric college students (Harkness et al., 2005), while individuals with elevated levels of depression recognized facial expression more accurately and faster than individuals with mild depression symptoms (Wu et al., 2012). Future studies are needed to assess the relationship between emotional recognition and mood disorders symptoms and state in comparison with other diagnostic groups. It is important to note that the small size of the study groups, especially the SZ-AF group, is a major limitation of the study; therefore, future studies are necessary to validate the initial finding in larger diagnostic groups.

Schizophrenia is a heterogeneous disorder and various subgrouping methods have been used based on different theories regarding the relationship between mentalizing and symptomatology. Clinical findings strongly suggest that the impairment of individuals with schizophrenia in social interaction is related to their reduced capacity to effectively engage in communication. Furthermore, Frith (1992) suggested that mentalizing in schizophrenia patients is compromised because of their failure to monitor their own and other persons' mental states and behavior, which may account for many positive and negative symptoms in schizophrenic disorders. However, Herold et al. (2002) reported contradictory findings of ToM deficits in schizophrenia patients whose positive and negative symptoms were not significant. On the other hand, individuals with schizophrenia at remission and their healthy relatives were observed to have impaired ToM abilities (Anselmetti et al., 2009; Modinos et al., 2010). Others found that the siblings of individuals with

schizophrenia performed significantly worse than healthy participants on theory of mind tests (Bora and Pantelis, 2013; Ho et al., 2015; Janssen et al., 2003). In the current study we report that there is no significant difference in the performance of the eyes test between FE-SZ individuals and SZ. Nor have we found any correlation between characteristics of the state of the illness such as the age of onset, duration of the disease, and number of hospitalizations. Thus, our study supports the idea that alterations in decoding the mental state of others in people with psychosis are a trait marker of the illness, and suggests that the associated neural systems can be investigated as a candidate intermediate phenotype for schizophrenia.

Numerous studies indicated the dopaminergic system as a major contributor to emotional and facial expression recognition. For example, emotional perception is dependent on several brain structures such as the limbic system and frontal cortex that are subject to dopamine innervation (Salgado-Pineda et al., 2005). At the genetic levels, the catechol-O-methyltransferase (COMT) gene rs2020917 and rs737865 SNPs were associated with cognitive ToM performance, while the COMT gene rs5993883 SNP was related to affective ToM in healthy individuals (Xia et al., 2012). In addition, in healthy subjects the response to negative facial expression was influenced by the genetic variation in dopamine (DA) neurotransmission associated with the COMT genotype (Smolka et al., 2005). To further investigate the molecular genetics role of the dopaminergic system in mental state decoding, we investigated, in a small group of patients, whether 3′ VNTR DAT or the D4R polymorphism repeats affect the ability to decode the mental state of the other. We found that overall individuals (both schizophrenia persons and healthy individuals) carrying the 9R/9R allelic repeats performed worse in the eyes test compared with 9R/10R heterozygote or 10R homozygote genotypes. In addition, we report that individuals with schizophrenia carrying the D4R long allele decoded more positive emotional valances, whereas patients with the short allele decoded less positive valances. Studies suggest that the DAT polymorphism has effect on its transcription and protein availability. The DAT 9R carriers have higher striatal DAT availability than do 10R homozygotes, suggesting lower dopamine concentration in the striatum (van de Giessen et al., 2009). Since striatal dopaminergic activity is associated with motivational processes and emotional processing (Badgaiyan, 2010), our data suggest reduced sensitivity to decode the mental state of another in DAT 9R/9R carriers. However, contradictory results have been observed for the relative gene expression of the each allele (Costa et al., 2011); therefore, further studies are needed before definitive conclusions can be reached. Taken together, our and others' findings suggest an association of the dopaminergic risk genes on emotional perception and ToM in individuals with schizophrenia, and raise the possibility that DA-related DAT and COMT risk genes might have a role in the process of understanding the mental state of the other. However, we cannot rule out an indirect effect of the DA-related risk genes on the ability to decode the mental state of others. This association can be driven by other systems such as learning, reward and motivation that were reported to be in interaction with ToM, and under the dopamine circuit's regulation. In addition to the complex interactions between the dopaminergic systems and mentalizing, Bosia et al. (2011) reported that individuals with schizophrenia carrying the C allele of the serotonin 1A receptor, a well characterized functional polymorphism, performed better in ToM compared to the G allele carriers. Moreover, the activation of ToM networks during mentalizing of emotions is altered in healthy individuals carrying the psychosis risk allele in the gene ZNF804A, a gene that has been found to be associated with schizophrenia (Walter et al., 2011). Thus, other schizophrenia risk genes might also contribute to the mental state decoding impairment, and further genetics studies need be considered.

To conclude, our goal was to investigate the possibility that the ability to attribute mental states of another person in schizophrenia is trait rather than state dependent. We show that individuals with FE-SZ do not differ from individuals with SZ in their ability to decode the mental state of others. Thus, understanding the mental state of others might not be influenced by the state of the patient's psychosis. We also provide some preliminary evidence on the role of the DA-related DAT gene in emotional recognition deficit in schizophrenia. In addition, we provide preliminary evidence that SZ-AF individuals might differ in their ability to decode the mental state of other people from SZ and FE-SZ patients, indicating that mentalizing might be an intermediate phenotype in the diagnostic process of schizophrenia disorders. One should note that the small size of the study groups seriously limits the significance of the results, and in order to reach a conclusion, future studies are necessary with larger sample sizes. Furthermore, an extensive body of research has linked neurocognition and ToM (Cook et al., 2013; Shur et al., 2008), suggesting a relationship between cognitive performance and the ability to decode the emotional state of another. Further studies are needed to study this relationship in and between the different diagnostic groups.

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## Contributors

A.S designed this project. M.M, T.D, H.T and I.G recruited subjects for the research. H.T, M.M and M.L preformed the eyes task, whereas A.A and H.M preformed the genetic experiment. A.R undertook the statistical analysis and A.S wrote the paper. All the authors contributed to the discussion and have approved the final manuscript.

## Conflict of interest

The authors declare no conflict of interest

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