"הקשר בין DAT פולימורפיזם ועיבוד רגשות בסכיזופרניה.

מחקר ראשוני"

"Association between DAT polymorphism and mentalization in schizophrenia; a pilot study"

עבודת גמר למילוי חלקי של הדרישות לקבלת תואר "דוקטור לרפואה"

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תודות

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האחת והיחידה- הגר תדמור.

מעבר לסיוע הטכני בביצוע העבודה ולימוד השיטות, מערך המחקר, הפניה למאמרים רלוונטיים, קיבלתי מכם הרבה עזרה שדרשה לא מעט זמן ומאמצים, דלתכם הייתה תמיד פתוחה בפני ועל כן תודתי.

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ולהורי שנטעו בי את השאיפה ללמוד

"הדממה שבלב בין דפיקה לדפיקה
הדממה הזאת היא שלך"

(נתן אלתרמן)

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תקציר בעברית

הפגם ביכולת לייחס מצב נפשי של אדם אחר כגון מחשבות, אמונות וכוונות המכונה כ "Theory of mind (ToM)" או מנטליזציה הוא מרכיב מרכזי בליקוי הקוגניציה החברתית בסכיזופרניה. הקושי של חולים סכיזופרניים לפרש הבעות רגשיות, הקשרים חברתיים ומצבים נפשי של אחרים יכול להביא לנסיגה חברתית ובידוד חברתי ולהשפיע על תפקוד יומיומי.

מחקר רב על חולים סכיזופרניים באפיזודה ראשונה וחולים כרוניים, קרובי משפחה מדרגה ראשונה של חולים סכיזופרניים ואנשים בעלי סיכון גבוה גורס שפגם בעיבוד רגשי של חולים סכיזופרניים תלוי תכונה וייתכן שיכול לשמש כסמן להפרעה. המחקר הנוכחי מהווה מחקר פיילוט במסגרתו נעריך את היכולת לזהות מצב רגשי של האחר בקרב חולי סכיזופרניה והאוכלוסייה הבריאה ונבדוק קשר (אסוציאציה) בין יכולת זו לבין מופע פולימורפי של הגן המקודד לטרנספורטר של דופמין (DAT).

שיטות: המחקר הוא מחקר אקראי מבוקר הכולל: קבוצת ביקרות (200 סטודנטים ממכללת "אורט בראודה") ו 50 חולים סכיזופרניים או סכיזואפקטיביים. לצורך הערכת העיבוד הרגשי יישמנו את מבחן 'Reading the Mind in the Eyes' (מבחן העיניים) וכל הנבדקים הוערכו בעזרת מדדי PANSS ו- CGI. דגימת דנ"א הופקה מדגימת דם או רוק של הנבדקים והתצורה הפולימורפית של DAT (מספר החזרות של רצף המקודד על ידי 48 בסיסים באקסון 3) נבדקה על ידי הגברה של אזור הרצף החוזר ב- PCR.

תוצאות: בדומה למחקרים קודמים, מצאנו ליקוי משמעותי ב ToM בחולים סכיזופרניים ויחס הפוך בין פגם זה וסימנים שליליים של סכיזופרניה. מעבר לכך, החולים הסכיזופרניים הדגימו ביצוע לקוי במבחן ה RMET בעוד שהחולים הסכיזואפקטיביים לא. ממצא זו עולה בקנה אחד עם הרעיון שעיבוד רגשי דל או עיבוד אינפורמציה מהבעות פנים קלוקל מקושר לסימנים שליליים של סכיזופרניה. אולם, גודל המדגם הקטן מגביל קשות את משמעותיות התוצאות.

כמו כן, היכולת לזהות רגשות אצל האחר נמצאה פגועה אצל חולים סכיזופרנים הנושאים את התצורה הפולימורפית 9/10 או 10/10 בגן המקודד ל- DAT בהשוואה לחולים הנושאים את התצורה 9/9 ולאוכלוסייה הבריאה. לא נמצא קשר (אסוציאציה) בין רמת ביצוע המטלה לבין התצורות הפולימורפיות בקרב האוכלוסייה הבריאה.

מסקנות: ממצאים אלו תומכים בהשערה שהיכולת לזהות רגשות אצל האחר פגועה בחולים סכיזופרנים. בנוסף, ממצאים אלו ניתן להניח שלכאורה יכולת זו נמצאת באסוציאציה עם הגן המקודד ל-DAT בחולים סכיזופרנים ולכן מעלים את האפשרות שהליקוי בעיבוד רגשי יחד עם הגן המקודד ל- DAT יכולים להוות סמן לאיתור קבוצות יותר הומוגניות של חולים.

<u>מילות מפתח:</u> מנטליזציה, סכיזופרניה, סכיזואפקטיביים , נשא דופמין (DAT)

Abstract

Deficit in the ability to attribute mental states of another person such as thoughts, beliefs and intentions, also referred to as 'Theory of mind' (ToM) or "mentalization", is a key component in the functional impairment of social cognition in schizophrenia. The difficulty of patients with schizophrenia to interpret emotional expression, social contexts and mental state of others can result in social withdrawal, social isolation and effect daily functioning. Substantial research in first episode and chronic schizophrenia patients, first degree relatives of schizophrenic patients and in high risk individuals suggests that deficit in mentalizing in patients with schizophrenia is trait dependent and may serve as a marker of the disorder. To further explore the genetic basis of mentalizing of emotion in general and particularly in schizophrenic patients we aimed to investigate whether the most abundant DAT polymorphism repeats affecting the ability to mentalize emotion.

Methods: The study was a randomized control study, which included: a control group (200 healthy students from Orot Brauda) and the 50 schizophrenic or schizoaffective patients. To evaluate the ability to mentalize emotion we applied the reading the mind in the eyes test (eyes test). PANSS questionnaire used to evaluate the patients positive and negative symptoms. DNA was extracted from salvia or blood, and the DAT polymorphic variable number tandem repeat (VNTR) was determined by PCR.

Results: Like previous results, we found a substantial impairment in decoding the mental state of the other in schizophrenic patients, but not in schizoaffective patients. This impairment was in inverse correlation with negative signs of schizophrenia. In addition, we found that schizophrenia patients with the tandem repeat 9R/10R or 10R/10R performed worse in the eye test compare with healthy individuals. **Conclusion**: Our results provide further evidence for the impairment of decoding the mental state of the other in schizophrenia, and suggest that DAT 3' VNTR polymorphism genotype might affect the performance of the eye test only in schizophrenia patients.

Keywords:

Theory of Mind (ToM), mentalization, Schizophrenia, Schizoaffective, Dopamine transporter (DAT)

Introduction

`Theory of mind' (ToM) and '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[1]. It is widely accepted that ToM can be divided into cognitive and affective aspects.[2, 3] .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.

ToM can be measured using a variety of methods including the classical Sally-Anne false belief test, the verbal and eye-gaze cues task, ''Reading the Mind in the Eyes'' (RMET) and through stories and jokes[4]. During these tasks, the subject's ability to evaluate and judge the other mental state is tested. For example the ability to understand that another person has other believes is measured by the false belief test[5], whereas decoding others complex mental state by looking at the eyes region of the face is measured by the–RMET test (henceforth eyes test)[7]. In fact, the eyes test is the simplest emotion recognition test and one of the most widely used. Its validity has been confirmed several times. Actually, a systemic review' published in 2012 provided an evidence that the eyes test can be effectively scored as a single factor[6]. The core of the eyes test involves the matching of the semantic definition of a mental state (e.g., ''worried'', ''annoyed'') to the picture of the eye-region expression displayed in the screen. This test 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. It is assumed to involve an unconscious, automatic and rapid matching of past memories concerning similar expressions with a lexicon of mental state terms[7].

For the past 20 years researchers have shown a growing interest in the role of ToM in human development and psychopathology. Following a study by Baron-Cohen et al. (1985), which reported severe ToM impairment

in autistic disorder, other studies suggested a relationship between ToM impairment and other mental disorders including schizophrenia. Although schizophrenia is a disorder that has been historically characterized by the presence of positive symptomatology, decades of research has shown the importance of cognitive deficits and social impairment in this disorder. Recent meta-analysis reported large effects for deficits in a number of ToM tasks in schizophrenic patient, including the Eyes task[7, 8]. This relationship was first proposed by Frith in 1992, he argued that several symptoms of schizophrenia could be explained by mentalization impairment. According to him, delusions could be explained as misinterpretation of others intentions, whereas Hardy-Bayle´ (1994) has argued that the absence of a mental representation of a patient's own intended action would also compromise a patient's capacity to assign mental states to other persons actions. Thus, ToM deficits are expected to occur exclusively in patients with prominent thought and language disorganization whereas patients without disorganization symptoms are predicted to have preserved ToM abilities, suggesting that mentalization deficits is depended on the state of the illness. However and on the other hand, Herold et al showed that theory of mind impairment was still present in the remission phase of the illness. In addition, it has been suggested that mentalizing is also altered in first degree relatives[9] and high risk individual[12]. For example Wykes found that unaffected siblings of patients with schizophrenia were likewise impaired in ToM task performance. Taken together, these data suggests that mentalizing dysfunction is trait and not state dependent and might serve as a trait marker of the disorder. These contradiction and inconclusive data raise the debate whether mentalization deficit in schizophrenia is a trait marker or state dependent.

Despite the fact that many studies have been conducted, the pathophysiological of ToM in schizophrenia is still unclear. A number of imaging studies of schizophrenic patients have documented abnormal hemodynamic response in several regions involving in ToM, such as medial and lateral portions of the prefrontal cortex, posterior superior temporal sulcus and medial temporal cortex, relative to healthy controls. For example, Benedetti and his colleagues reported that low performance in ToM in schizophrenic patients is correlated with reduced activity of the right temporal lobe[10]. In addition, schizophrenic patients showed lower activity of the

middle frontal gyrus and insula during the performance of eye-gaze, a task that tests the ability to evaluate the mentalizing state of other by looking on the person's gaze direction.

There is substantial body of evidence for neuronal disconnectivity in mentalizing dysfunctioning in schizophrenic patients, meanwhile, little is known about the molecular genetics of mentalization in schizophrenia as well. In fact, only a few studies investigated the genetic variance underlies the pathogenesis of mentalization. To date, most of the studies focus on studying the association between the dopaminergic and the serotoninergic systems, two neuromodulation systems that have been suggested to be involved in mediate our ability to mentalize[11]. Bosia and his colleagues reported that schizophrenic patients carrying the C allele of the serotonin 1A receptor, a well characterized functional polymorphism, performed better in ToM compared to the G allele carriers[16]. 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[12]. In addition, 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[13]. These data suggests that dysfunction of ToM is associated with network disconnectivity and with genetic risk variants for schizophrenia. Since the dopamine transporter gene (DAT) has been implicated in the pathogenesis of numerous psychiatric[14] and neurodevelopmental disorders, including schizophrenia, in this study, we chose to investigate whether the dopamine transporter (DAT) tandem repeats polymorphism affects the ability to decode the emotion of other.

The goal of this pilot study is to further explore the genetic basis of mentalizing of emotion in general and in particular in schizophrenic patients, to investigate the association between DAT polymorphism and mentalization in schizophrenia and whether DAT could serve as novel risk genes underlying this ability. Novel genetic risk factors would be new candidate targets for therapeutics or diagnosis in addition to its role as a predictor of clinical and psychosocial functioning for those individuals diagnosed with schizophrenia. Impaired cognition may also represent an endophenotype or intermediate trait that lies between an underlying genotype and expression of the clinical phenotype that can be used to identify individuals at greatest risk for the illness.

Methods

Subjects

Forty one schizophrenic patients and nine schizoaffective meeting the DSM-IV criteria recruited from the open and closed wards of Mazra Mental Health Center. Inclusion criteria: physically healthy. Exclusion criteria: drug or alcohol abuse and mental retardation. 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). Two hundred healthy individuals without psychiatric history recruited form Ort Brauda College. Inclusion criteria: physically healthy without drug or alcohol abuse. The groups were matched for gender and age. All material to be used for subject recruitment and study advertisement was approved by the local and national Helsinki Committees.

The Eye Test:

Reading the mind in the Eyes Test was developed by Baron-Cohen[7] as a tool to evaluate the ability to infer the mental state of another person. In this task, participants 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 for what the person in the picture was thinking or feeling. This task is considered an advanced mentalization 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.

3' VNTR DAT polymorphism genotyping assay:

DNA was extracted from blood samples of schizophrenic patients or from salvia of healthy individuals. The GoTaq Master Mix (Promega, Medison, WI, USA) and set of primers previously described by Vandenbergh DJ et al were used to determine the 3' VNTR DAT polymorphism. PCR products were electrophoresed on 1.5% agarose gel and visualized by ethidium bromide.

The genotype of the 3' VNTR DAT was determined based on the number of the repeats: 280 bp (5 repeats), 320 bp (6 repeats), 360 bp (7 repeats), 400 bp (8 repeats), 440 bp (9 repeats), 480 bp (10 repeats), 520 bp (11 repeats), and 600 bp (13 repeats).

Statistical analysis

Student's t-test was used to compare the performance in the eye test between the ganders, the case and controls and the patients groups. Analysis of 3' VNTR DAT allelic frequencies was performed with chi square, while Pearson's correlations performed to study associations between RMET scores and variables as age of onset, illness duration, PANSS scores and number of hospitalizations. Two-way ANOVA was used for the genotype–phenotype correlation determinations. Data were analyzed using the SPSS21.0 statistical analysis software package.

Results

Mentalizing of emotion is impaired in individuals with schizophrenia

The participants' demographic and clinical data are summarized in Table 1. Schizophrenia patients and healthy individuals were matched for their age and education, but not for gender. Schizophrenia patients had significantly more males then females. The ability of healthy volunteers and individuals with schizophrenia and schizoaffective (refer as schizophrenia patients) to decode the mental state of the other was evaluated using the eye test. Figure 2 A and B summaries the distribution of the eyes test across the studied groups. As expected schizophrenia patients performed worse in the eye test and scored in average significantly lower than healthy individuals (20±5 and 24±4 correct choice ±S.D, respectively; $p>0.0001$, Student's t-test; Figure 2C). No significant difference between males and females in the ability to identify correctly the metalized state presented in the photograph was found in both healthy individuals and schizophrenia patients (Healthy individuals; Males: 23±4; Female: 25±2; Schizophrenia patients; Males: 20±5; Female: 22±6; Student's t-test, $p>0.05$). Interestingly, schizoaffective patients performed better in the eye test, and score significantly higher than individuals with schizophrenia (27±2 and 19±4 correct choice ±S.D, respectively; $p>0.0001$, Student's t-test; Figure 3). In addition, we found an inverse correlation between negative symptoms and RMET score (Pearson; $r = -0.3328$ $p= 0.0273$; Figure 4A). However, we did not find a correlation between negative symptoms and RMET score when we analyzed the individuals with schizophrenia without the schizoaffective patients (Pearson; $r = -0.1170$ $p= 0.5033$; Figure 4B). In addition, there was no correlation between positive symptom, general symptoms, total score of the PANSS questionnaire, age of onset, illness duration, number of hospitalizations and number of years of education to eye test performance.

Association of the 3' VNTR DAT polymorphism with the ability to mentalized emotion in schizophrenia patients

Analysis of common allelic variant of the 3' VNTR DAT polymorphism (9 and 10 times 48bp repeat; 9R and 10R, respectively) revealed that there is no difference in allelic frequency between healthy individuals and schizophrenia patients (Table 2, chi square=0.902, p=0.637). Two-way ANOVA (diagnosis X genotype) analysis of the eye test performance showed a statistically significant effect of the diagnosis group ($p<0.005$; Table 3A) with no significant effect of the genotype. These results indicate that schizophrenia patients scored below the healthy individual in the eye test irrespectively to their 3' VNTR DAT genotype. However, a significant interaction between diagnosis and genotype ($p<0.05$) was detected. As shown in table 3A, schizophrenia patients with 9R/10R or 10R genotype performed worse in the eye test compare with 9R/10R heterozygote or 10R homozygote healthy individuals. A similar diagnosis by genotype interaction was found when we compared the performance in the eye test between schizophrenia, schizoaffective and healthy individuals ($p<0.005$, Table 3B). These results suggest that DAT 3' VNTR polymorphism genotype affect the performance of the eye test only in schizophrenia patients. It is important to note none of the nine schizoaffective patients was 9R homozygote.

Discussion

Schizophrenia and schizoaffective disorder are two diagnoses within the psychotic disorder spectrum. Impaired affective and non-affective face perception in schizophrenia has been widely reported[8, 9]. Yet, it is not completely understood how this processing is related to clinical dimensions of the illness. Several studies have linked poor performance in perceiving non-affective face images to positive psychotic symptoms such as delusions[9]. Meanwhile, others have found that deficiency in emotions facial perception is related to negative symptoms. In the current pilot study we are reporting that individuals with schizophrenia, but not schizoaffective patients, are impaired in decoding the facial emotions of the other. These findings are consistent with the notion that poor mentalization or poor processing of facial emotion information is impaired in schizophrenia patients [15]. Clinical findings strongly suggest that the impairment of schizophrenic patients in social interaction is related to their reduced capacity to effectively engage in communication (e.g., Trognon 1992; Sperber and Wilson 2002). Furthermore, Frith (1992) has foremost suggested that mentalizing (ToM) 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, our results raise a paradoxical question whether mood problems have any beneficial effect on the processing of facial information. In fact, community outcomes do appear to be better in schizoaffective disorder than in schizophrenia[9]. When viewing face images, patients with affective disorders showed a similar visual scanning pattern as healthy controls, whereas schizophrenia patients showed a restricted scan-path style. This result may suggest that mood problems are not a disturbing factor in the processing of face information. Future studies should directly assess the relationship between the perceptual ability to process facial information and the mood statuses in patients. It is important to note that only nine schizoaffective diagnosed patients were recruited to the current study. Therefore, further research with an enlarged number of patients diagnosed with schizoaffective disorder is needed.

Correlation between negative signs and mentalizing performance

One of the main focuses of previous studies is the association between mentalizing and symptoms of schizophrenia. Theories regarding this association are rooted in the theory of Frith (1992). According to Frith, theories of mind skills are impaired during an acute psychotic episode. Therefore, Frith suggested that mentalizing ability is a state rather than a trait variable. Following Frith, Harde-Bayle suggested another well-known theory to explain ToM dysfunction in schizophrenia. This model posited that thought disorders are the source of ToM deficits in schizophrenia[16, 17]. According to this theory, ToM performance should be intact in non-thought-disordered patients. In other words, Hardy-Bayle has argued that patients with highly disorganized thought, language, and communication skills[18] are predicted to perform most poorly on ToM tasks, because they are unable not only to monitor their own actions but also to adequately represent other persons' mental states and to integrate contextual information[19]. It could be concluded that the absence of a mental representation of a patient's own intended action would also compromise a patient's capacity to assign mental states to other persons' actions. According to this model, ToM deficits are expected to occur exclusively in patients with prominent thought and language disorganization, whereas patients without disorganization symptoms are predicted to have preserved ToM abilities. Taken together, the two mentioned theories reinforces the concept that mentalization is probably state dependent and not a trait. Meaning there should be an inverse correlation between schizophrenia symptoms and mentalizing. In this study, we found an inverse correlation between the ability of schizophrenic patients (both schizophrenic and schizoaffective patients) to mentalizing facial emotion and negative symptoms. This finding is a replication of previous studies[2, 20], however, the contribution of negative symptoms to the ability to mentalizing facial emotion of the other is unclear, and therefore other symptoms as cognitive deficits may play a role in the ToM-symptom correlations[2]. Frith (1992) raised the intriguing question of whether psychotic symptoms in schizophrenia might be explained in terms of an underlying cognitive misrepresentation of one's own and others' intentions that is, impaired ToM. Some patients with schizophrenia, for instance, instead of taking beliefs as subjective representations of reality, equate their representations with reality and may therefore have difficulty distinguishing between subjectivity and

objectivity and maintain false beliefs in the form of delusional convictions. Furthermore, schizophrenia patients who have difficulties in experiencing their behavior as the result of their own intentions may interpret their actions as being under alien control. According to him, patients with prominent negative or disorganized (behavioral) symptoms would accordingly be most impaired in ToM performance, similar to autistic persons, because of their incapacity to represent mental states at all. These relationships between symptoms and other cognitive deficits allow us to suggest theoretical models of how ToM may be involved in schizophrenic symptoms, divergent as they may be, waiting for empirical testing.

Nevertheless, no significant correlation was found with positive and general symptoms, and when we analyzed only the schizophrenic patients group, suggesting that the correlation significance is due to the lower grade of the schizoaffective diagnosed patients in the negative symptoms as reflected by the PANSS questionnaire and their higher performance in the eye test (RMET). The lack of correlation between mentalizing impairment and symptoms in schizophrenic patients in light of the correlation found when both schizoaffective and schizophrenic patients scores were analyzed, implicates that schizophrenia is a group of disorders according to the mentalization abilities, and suggesting that mentalizing deficit in schizophrenia patients is probably part of the course of the disease, and therefore is a trait and not state dependent.

Is mentalization a trait or state?

Schizophrenia is a heterogeneous disorder and various subgrouping methods have been used based on different theories regarding the relationship between mentalizing and symptomatology. Ever since Frith's first proposal[3] the association between mentalizing and the core symptoms of schizophrenia has been an important focus of research interest. Frith and his colleagues supported the notion that ToM impairment is a characteristic of acute psychosis[3]. Probably due to the fact that most studies about ToM and schizophrenia were conducted with symptomatic patients and if remitted patients were to be included, no ToM Impairment was found in these patients. However, Herold et al. (2002) reported contradicts findings of ToM deficits in schizophrenia patients whose positive and negative symptoms were not significant. Nor have we found any correlation between characteristics of the state of the illness such as the duration of the disease, number of hospitalizations and the

number of years of education which is in concordance with previous studies that have not found major effects of education on this test as well[7, 9, 21]

A mile stone breakthrough in these studies was published in 2003 by Jannsen et al. In these studies, both patients that were in remission and their healthy relatives were observed to have impaired ToM abilities. Others found that the siblings of individuals with a diagnosis of schizophrenia performed significantly worse than the control participants on theory of mind tests[5]. Taken tougher, these authors suggested that alterations in theory of mind in people with psychosis represent at least in part a trait rather than a state factor. Bora et al. (2008a) provided additional support regarding the prevalence of ToM deficits in remitted schizophrenia patients. . Although the specifics of ToM deficits in schizophrenia may vary[22, 23], the fact that ToM deficits are even found in remission[5, 24] and in people at risk for schizophrenia supports the idea that impaired ToM is a trait marker of the illness, indicating that the associated neural systems can be investigated as a candidate intermediate phenotype for schizophrenia

3' VNTR DAT polymorphism is associated with poor performance in the eye test

Numerous studies have indicated the dopaminergic system as a major contributor to emotional and facial expression recognition. For example, emotional perception is dependent on several brain structures as the limbic system and frontal cortex that subject to dopamine innervation[25]. In addition, in healthy subjects the response to negative facial expression was influenced by the genetic variation in DA neurotransmission associated with the COMT genotype[26]. Therefore, we investigated whether the 3' VNTR DAT polymorphism repeats, a functional polymorphism which affect the expression of DAT, affecting the ability to decode the mental state of the other**.** The genetic analysis of DAT allelic profile revealed no homozygote 9/9 allelic configuration in the schizoaffective diagnosed group of patients. In addition, we found that schizophrenia patients with 9R/10R or 10R genotype performed worse in the eye test compare with 9R/10R heterozygote or 10R homozygote healthy individuals. These results propose that schizophrenic patients who carry the 10R DAT allele be more vulnerable to social cognition impairment. In addition, this finding supports the hypothesis that mentalization defects should serve as a trait and not a state. Meaning that mentalization may partially be an

endophenthype bridging between the phenotype and the genome. One should note that the small size of the study group seriously limits the significance of the results and in order to come to a conclusion, future studies are warranted with larger sample sizes. Maybe then, the mentioned allelic configuration could improve early diagnoses, perhaps assist the clinician to predict a patient's clinical and psychosocial functioning prognosis, in a relatively early stage of the clinical manifestations for those individuals diagnosed with schizophrenia.

Table 1: Demographical data

		HEALTHY CONTROL	PATIENTS
AGE		26.5±7.5	36.6±9.9
GENDER	MEN	106	41
	FEMALE	94	9
	TOTAL	200	50
EDUCATION (YEARS)		13.7±2.6	11.6±2.1
AVERAGE RMET SCORE		23±5.2	20.26±5.0

Table 2: Common alleles frequencies in healthy control individuals and schizophrenia diagnosed patients.

		DAT		
		9/9 (%)	10/10 (%)	9/10 (%)
Dig	SZ	16	47	37
	Healthy	14	41	45

(Chi-square 0.902; p=0.637)

Table 3: Association of DAT polymorphism common alleles with RMET score

A: schizophrenic patients compare with healthy individuals

	9/9		9/10		10/10	
	RMET	#	RMET	#	RMET	#
HEALTHY	22.09±3.8	22	23.62±3.89	72	23.84±4.3	65
SCHIZOPHRENIC PATIENTS	23.28±3.68	7	18.31±5.73*	16	20.65±4.79*	20

Two- way ANOVA (diagnosis X genotype). Results represent the mean ± SEM, * P<0.05.

B: schizophrenic and schizoaffective patients, compare with healthy individuals.

	9/9		9/10		10/10	
	RMET	#	RMET	#	RMET	#
HEALTHY	22.09±3.8	22	23.62±3.89	72	23.84±4.82	65
SCZ.	23.28±3.68	7	16.46±4.52**	13	18.46±2.89**	15
SCZ-AFF	0	0	26.33±2.3	3	27.2±2.86	5

Two-way ANOVA (diagnosis X genotype). Results represent the mean ± SEM, ** P<0.005.

Figure 1: Two still pictures of eyes expression

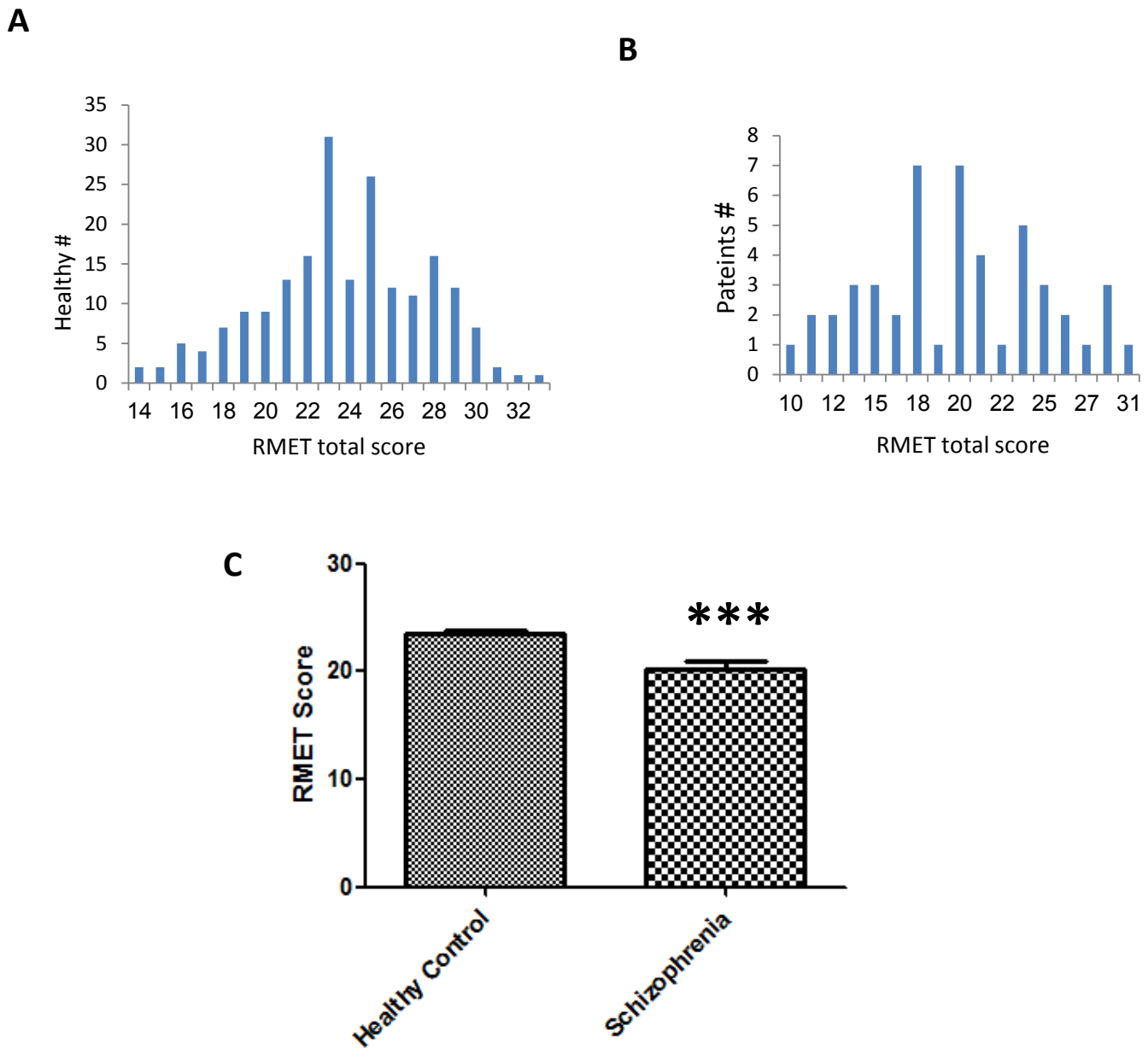

Figure 2: young healthy volunteers (A) and schizophrenic patients (B) RMET score distribution. (C) Schizophrenia patients and Healthy individuals RMET score. Results represent the mean ± SEM, *** P<0.0001.

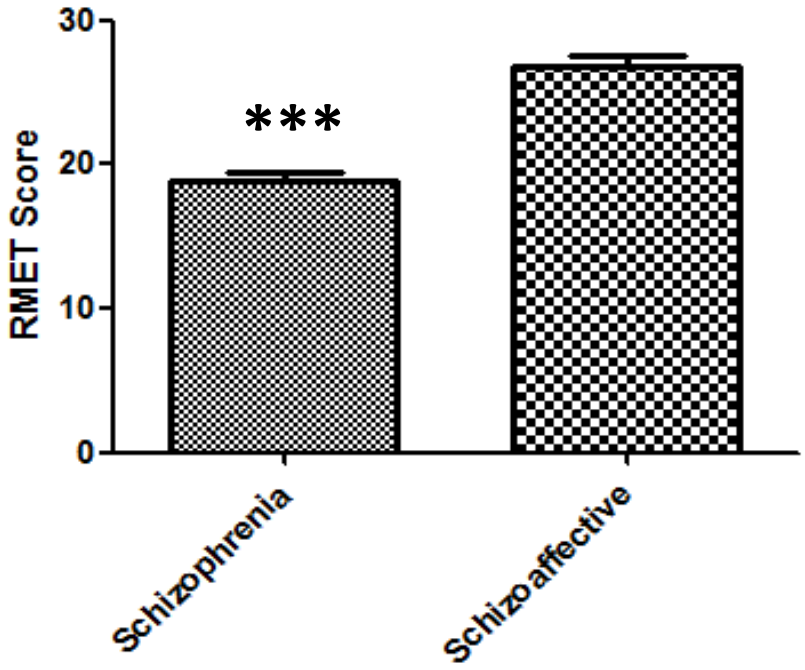

Figure 3: Schizophrenic and schizoaffective patients RMET score (n=41 schizophrenic, n=9 schizoaffective patients). Results represent the mean ± SEM, *** $P<0.0001$.

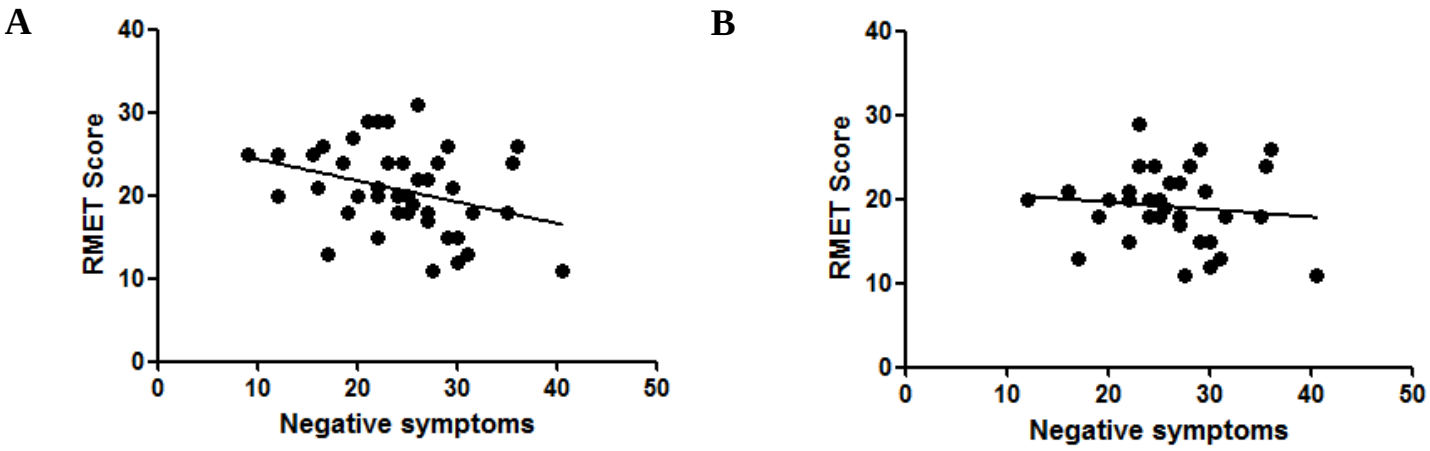

Figure 4: Correlation between RMET score and negative symptoms. (A) Present both schizophrenic and schizoaffective (p=0.0273). (B) Present only Schizophrenia diagnosed patients (p>0.05).

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