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

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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.

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

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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,