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Familial covariation of facial emotion recognition and IQ in schizophrenia

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ABSTRACT

Alterations in general intellectual ability and social cognition in schizophrenia are core features of the disorder, evident at the illness' onset and persistent throughout its course. However, previous studies examining cognitive alterations in siblings discordant for schizophrenia yielded inconsistent results. Present study aimed to investigate the nature of the association between facial emotion recognition and general IQ by applying genetically sensitive cross-trait cross-sibling design. Participants (total $n=158$; patients, unaffected siblings, controls) were assessed using the Benton Facial Recognition Test, the Degraded Facial Affect Recognition Task (DFAR) and the Wechsler Adult Intelligence Scale-III. Patients had lower IQ and altered facial emotion recognition in comparison to other groups. Healthy siblings and controls did not significantly differ in IQ and DFAR performance, but siblings exhibited intermediate angry facial expression recognition. Cross-trait within-subject analyses showed significant associations between overall DFAR performance and IQ in all participants. Within-trait cross-sibling analyses found significant associations between patients' and siblings' IQ and overall DFAR performance, suggesting their familial clustering. Finally, cross-trait cross-sibling analyses revealed familial covariation of facial emotion recognition and IQ in siblings discordant for schizophrenia, further indicating their familial etiology. Both traits are important phenotypes for genetic studies and potential early clinical markers of schizophrenia-spectrum disorders.

1. Introduction

Cognitive alterations (i.e. alterations in general intellectual ability and social cognition) seen in patients with schizophrenia are now recognized as a core feature of the disorder (Billeke and Aboitiz, 2013; Cannon et al., 2000; Elvevag and Goldberg, 2000). Not specific to the illness' subtypes, they are evident at the onset of the illness (in unmedicated patients), largely state-independent and persistent in a trait-like fashion, thus potentially reflecting a genetic liability to schizophrenia-spectrum disorders.

The neurodevelopmental hypothesis proposes that cognitive alterations, which may represent altered brain development resulting from gene-environment interactions, are likely to emerge during childhood/adolescence and to precede full-blown psychosis (Marenco and Weinberger, 2000). It is well known that most pre-schizophrenia subjects fail to reach their expected level of general cognitive ability during childhood (Jones et al., 1994) and that general IQ alterations characterize a majority of schizophrenia patients throughout the lifespan (Bilder et al., 2006; Kremen et al., 2001). Likewise, facial emotion recognition impairment has been reported early in the course of schizophrenia, and it is believed to generalize across emotional valences with the illness progression (Addington et al., 2006; Kohler et al., 2010).

Although social cognition requires general cognitive capacities and there may be some functional overlap of brain areas underlying social cognition and other more general cognitive processes, previous evidence have shown that aforementioned cognitive domains are distinct from one another and that social cognitive impairments in schizophrenia are separable from the general cognitive ability (Allen et al., 2007; Sergi et al., 2007). Neuroimaging and lesion studies have shown that social tasks activate specific brain areas that can be distinguished from those activated by non-social tasks, for example superior temporal sulcus, medial prefrontal cortex (Adolphs, 2001; Harris et al., 2005; Mitchell et al., 2004), amygdala, fusiform gyrus and insular regions (Bar-On et al., 2003). Consecutively, the MATRICS-NIMH consensus cognitive

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battery for schizophrenia categorized social cognition as one of the seven major separate cognitive domains that are altered in schizophrenia, alongside with: Speed of Processing, Attention/vigilance, Working Memory, Verbal Learning and Memory, Visual learning and Memory and Reasoning and Problem Solving (Green et al., 2004).

Since it has been shown that some of the healthy siblings of patients with schizophrenia also exhibit certain cognitive alterations (i.e. alterations in general IQ and facial emotion recognition), it has been proposed that aforementioned cognitive changes might represent indicators of vulnerability to schizophrenia-spectrum disorders, deriving from primarily genetic (and/or shared environmental) etiologic influences (Cannon et al., 2000; Lavoie et al., 2013). However, previous studies examining cognitive alterations in siblings discordant for schizophrenia yielded inconsistent results, and the degree to which these alterations co-segregate in schizophrenia-spectrum families have yet to be further investigated.

Many first degree relatives of schizophrenia patients are predisposing genotype carriers without manifesting the disorder phenotypically. Sibling status represents an indirect measure of genetic risk since the risk for schizophrenia in those individuals is increased 5- to 10-fold, and twin studies have shown that familial clustering is mainly due to genetic factors (Sullivan et al., 2003). Research in those individuals, deemed to be at different level of genetic risk for psychosis, could provide better insight to the pathogenesis of the illness and to indicate potential targets for preventive treatments. Thus, it might be worthy investigating familial covariation of alterations in general IQ and emotion recognition performance. Both phenotypes have been shown to cluster within families, but the nature of the aforementioned relationships is still insufficiently evaluated and clarified. It might reflect a shared familiar etiology with a possible genetic basis. Alternatively, both IQ and emotion recognition performance might be on a common causal pathway or secondary to another factor.

The present study aimed to investigate whether a shared familial liability may underlie the association between facial emotion recognition alteration and general IQ alteration by applying genetically sensitive cross-trait cross-sibling design (previously described by GROUP investigators Fett et al. (2013) and Lataster et al. (2012)) in a sample comprised of three groups of participants with decreasing levels of familial schizophrenia liability (patients, their unaffected siblings, healthy controls). Cross-trait cross-sibling analyses allow investigation of an etiological association between (subclinical level of expression of) two phenotypes, while removing the effects of illness-related factors, such as residual symptoms and medications.

At the first step, we explored facial emotion recognition performance and general IQ in schizophrenia probands and their unaffected siblings compared to controls. Next step was the analysis of the association between facial emotion recognition and general IQ within patient and sibling group (cross-trait within subject analysis), to confirm the assumption of the overlap between aforementioned domains. Furthermore, we explored familial clustering of general IQ and facial emotion recognition performance (within-trait cross-sibling analysis). Finally, we explored the associations between patients' facial emotion recognition performance and siblings' general IQ, and between patients' IQ and their siblings' facial emotion recognition ability (cross-trait cross-sibling analyses). The presence of such associations would be indicative of a shared familial etiology of both traits, while finding of associations within patients only would suggest that the overlap between lower IQ and impaired facial emotion recognition was rather due to the individual factors (i.e. secondary to illness related effects).

2. Methods

2.1. Sample and procedure

Present sample comprised 158 participants originating from Belgrade and surroundings catchment area: 52 patients with schizophrenia-spectrum disorders, 55 of their unaffected siblings and 51 healthy controls. Patients were recruited from regional mental health institutions, unaffected siblings were recruited through participating patients, while control group was randomly recruited from the catchment area via local marketing agency. Inclusion criteria for all participants were: age $\geq$ 18 years, IQ $\geq$ 70, normal vision (or corrected to normal), no recent history of alcohol or drug abuse, being able and willing to give informed consent. Patients had to meet DSM-IV criteria for psychotic disorder as assessed by Mini International Neuropsychiatric Interview (Sheehan et al., 1998), not caused by neurological disorder, currently remitted (GAF score $>$ 40), whereby the illness duration did not exceed 10 years. Additional inclusion criteria for unaffected siblings of schizophrenia patients and controls were the absence of personal history of psychiatric disorders, and the absence of family history of psychiatric disorders for control group only. The study was conducted in accordance with the Declaration of Helsinki and its design was approved by the Medical Ethics Committees of the School of Medicine University of Belgrade, the Clinical Center of Serbia and Special Hospital for Psychiatric Disorders Kovin. All participants gave their written informed consent, and control subjects received compensation (vouchers) for their study participation.

2.2. Measures

The Benton Facial Recognition Test (BFRT) (Benton et al., 1983), an accurate measure of the ability to match non-emotional unfamiliar faces, was used for the assessment of participants' general facial recognition ability. Participants were simultaneously presented with one target and six other black and white photos of unfamiliar male or female faces with their hair and clothing shaded out. Afterwards, they were asked to: (1) match a frontal view of the target with an identical photo, (2) match a frontal view of the target face with 3 photos taken from different angles, and (3) match a frontal view of the target face with three photos of that person taken under different lighting conditions. Total number of correct answers served as main outcome parameter.

The Degraded Facial Affect Recognition Task (DFAR) (Van 't Wout et al., 2004) was used for the assessment of participants' ability to recognize four basic emotional facial expressions: neutral, happy, fearful and angry. This experimental task consists of 64 face presentations (16 in each emotion category) of two male and two female actors depicting aforementioned emotions. Visual contrast was reduced by 30% in order to enhance the contribution of interpretation. Main outcome parameters were the percentages of correct answers per each facial expression and the overall percentage of correct answers.

Wechsler Adult Intelligence Scale- III (WAIS-R) (Velthorst et al., 2013). A brief, 15-min, version of the WAIS scale, comprised of subtests Arithmetic, Digit Symbol Coding, Information and Block Design, was used to assess participants' general intellectual ability. It has been previously shown that this scale gives reliable estimates of the Full Scale IQ in all three groups of participants (patients with schizophrenia-spectrum disorders, their unaffected siblings and unrelated healthy controls), thus it was proposed as a useful screening device for general intellectual ability in research settings.

Global Assessment of Functioning scale (GAF) (Hall, 1995). Numeric scale (ranging from 0 to 100), designed for the