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A coding variant of the novel serotonin receptor subunit 5-HT3E influences sustained attention in schizophrenia patients

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Abstract

Sustained attention as measured by the Continuous Performance Test (CPT) has proved a valuable endophenotype for schizophrenia. Recently pharmacological studies suggested a role of the serotonin (5-HT) 3 receptor in schizophrenia. The 5-HT3 receptors are the only ligand-gated ion channels within the 5-HT receptor family. Applying an endophenotype approach, we investigated a potential impact of the genes of the 5-HT3A and 5-HT3B subunits as well as the novel 5-HT3C, 5-HT3D, and 5-HT3E subunits on CPT performance in subjects with schizophrenia. The study included 196 patients with schizophrenia, 113 of their parents, and 205 healthy controls recruited from community registers. Sustained attention was assessed with the Continuous Performance Test-Identical Pairs (CPT-IP). Assessing functional and coding variants of the 5-HT3 receptor subunit genes, we found the GG genotype of the 5-HT3E subunit gene (rs7627615; Thr86Ala) to be associated with better attentional capacities in subjects with schizophrenia and healthy controls. This study provides additional evidence for a role of the serotonergic system and the 5-HT3 receptor in schizophrenia.

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1. Introduction

It is estimated that 1% of the world population suffers from schizophrenia. It has been estimated that up to 80% of variance of schizophrenia symptoms are due to genetic variation (Sullivan et al., 2003). In the last years, our understanding of the genetics of schizophrenia expanded enormously.

However, despite the progress in the field of genetics in schizophrenia there are some limitations and our understanding of the pathogenesis of the disorder is still not satisfying. Although a number of disease-associated candidate genes have been detected, most of these do not explain a substantial amount of variance (Riley and Kendler, 2006; Shi et al., 2009; Stefansson et al., 2009). One explanation for this is the heterogeneity of the schizophrenia phenotype. To overcome this limitation it has been suggested to use intermediate phenotypes, or endophenotypes (Leboyer et al., 1998) for genetic studies. In the literature several highly promising candidates are described which might mediate the relationship between the genotype and the clinical phenotype (Braff et al., 2007; Gur et al., 2007; Turetsky et al., 2007). Although endophenotypes cannot explain the full developed picture of schizophrenia it is assumed that they reflect neuropsychological and neurophysiological factors underlying the disorder (Gottesman and Gould, 2003). All endophenotypes have in common that they are defined to be highly heritable and allow reliable differentiation between affected and non-affected individuals. Moreover, underlining that endophenotypes are under high genetic influence, differences have also been reported in first degree relatives of probands with schizophrenia compared to healthy control probands (Bertolino and Blasi, 2009).

Among others, the cognitive performance has been extensively investigated as an endophenotype in schizophrenia genetics. Patients suffering from schizophrenia show numerous cognitive deficits in the fields of attention, memory, and executive functioning in comparison to non-psychotic control subjects (Heinrichs and Zakzanis, 1998). Numerous studies report deficits in neuropsychological tests in parents, siblings and offspring of schizophrenia subjects emphasising the role of cognitive performance as a potential endophenotype of schizophrenia (Sitskoorn et al., 2004).

Sustained attention measured with the Continuous Performance Test (CPT) has been successfully used as an endophenotype in different studies (Chen and Faraone, 2000; Cornblatt and Malhotra, 2001). Patients with schizophrenia consistently exhibit deficits in the CPT (Heinrichs and Zakzanis, 1998; Mesholam-Gately et al., 2009). This result could be replicated in first-episode neuroleptic-naive patients and in their relatives (Bove, 2008; Wang et al., 2007). Additionally, Chen et al. (1998) demonstrated that performance in the CPT was negatively correlated with schizotypy in a non-affected community sample.

In the search for schizophrenia-related genetic variations a large variety of genes has been investigated (Riley and Kendler, 2006). Among others, markers affecting the serotonergic system have been extensively studied since the pharmacological treatment with atypical neuroleptics acting on 5-HT receptors has become more prevalent. In pharmacological trials it has been demonstrated that ondansetron, a 5-HT3 antagonist, enhances antipsychotic treatment (Akhondzadeh et al., 2009; Zhang et al., 2006). Among symptomatic attenuation of positive and negative symptoms, ondansetron also improved cognitive performance, particularly memory functioning and p50 sensory gating, the latter being linked with attention deficits in schizophrenia (Adler et al., 2005; Akhondzadeh et al., 2009; Levkovitz et al., 2005). Similarly Koike et al. (2005) demonstrated that the administration of tropisetron, another 5-HT3 antagonist, also improved p50 inhibition in patients with schizophrenia.

The 5-HT3 receptor takes a special position among the other 5-HT receptors. According to their structural and functional properties the 5-HT3 receptor subunits are closely related to the nicotinic acetylcholine receptor (Barnes et al., 2009). Both are ligand-gated ion channels without a second messenger system and thus can be directly activated through ligand binding. While other 5-HT receptors are G-protein coupled receptors these structural and functional specifics of the 5-HT3 receptors warrant its unique position (Hoyer et al., 2002). Recently, Niesler et al. (2003, 2007, 2008) described three novel subunits, the 5-HT3C, 5-HT3D, and 5-HT3E receptors. The 5-HT3 receptor is built by a pentameric complex. Only the 5-HT3A can constitute as a functional homopentameric receptor; the 5-HT3B, 5-HT3C, 5-HT3D and 5-HT3E only form a functional heteropentameric receptor, each in combination with the 5-HT3A (Niesler et al., 2007). Exact biophysiological properties of the heteromeric receptors comprising the novel 5-HT3C, 5-HT3D, or 5-HT3E are still unknown but altered cell surface expression has been reported (Niesler et al., 2007). Recently, a coding variant of the 5-HT3E receptor subunit has been associated with improved antipsychotic drug response in subjects with schizophrenia treated with atypical antipsychotics (Schuhmacher et al., 2009).

The aim of this explorative study was to examine a potential association of all known 5-HT3 receptor genes including the novel subunits 5-HT3C, 5-HT3D, and 5-HT3E with CPT performance. Towards this aim, common functional or coding variants of all five 5-HT3 receptor subunit genes were assessed in relation to CPT performance in subjects with schizophrenia, their parents, and healthy control probands, controlling for age, gender, and education.

2. Experimental procedures

2.1. Sample

In a collaborative effort, $n = 197$ schizophrenia patients and $n = 113$ of their parents were recruited in the Departments of Psychiatry of the Universities of Bonn, Cologne, Düsseldorf, Munich, Tübingen, Berlin, Jena, and Mannheim and DNA and neuropsychological data were obtained. Schizophrenia was diagnosed according to the criteria of DSM-IV or ICD-10 (APA, 1994; WHO, 1992). The comparison sample consisted of $n = 205$ healthy subjects randomly drawn from community registers in Bonn, Cologne, and Mannheim, Germany. The healthy control group was screened for psychiatric disorders and subjects were excluded in case of a psychiatric diagnosis. All interviews were conducted by trained psychiatrists and psychologists. Patients with schizophrenia were in most cases treated with antipsychotics but had to be on stable medication for participation in the neuropsychological testing. Subjects with any neurological disturbance were excluded prior to testing. All subjects gave their