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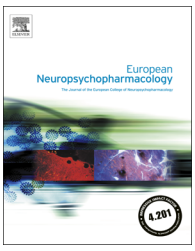

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5-HT3 receptor influences the washing phenotype and visual organization in obsessive-compulsive disorder supporting 5-HT3 receptor antagonists as novel treatment option

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Abstract
A role of the *HTR3A-E* genes in obsessive-compulsive disorder (OCD) can be expected based on promising effects of 5-HT3 receptor antagonists as adjunctive treatment of OCD. We therefore genotyped six common coding or promoter variants within the *HTR3A-E* genes in a case-control-sample consisting of $N=236$ OCD patients and $N=310$ control subjects and in $N=58$ parent-child-trios. Given the heterogeneous OCD phenotype, we also investigated OCD symptom dimensions and cognitive endophenotypes in subsamples. OCD patients scoring high for the washing subtype were significantly more likely to carry the c.256G-allele of the *HTR3E* variant rs7627615 ($p=0.0001$) as compared to OCD patients low for this symptom dimension. Visual organization was impaired in OCD patients and unaffected relatives as compared to healthy control subjects and carriers of the *HTR3E* c.256G/c.256G-genotype performed significantly

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worse ($p=0.007$). The case-control analyses revealed a nominal significant association of the *HTR3D* variant rs1000592 (p.H52R) with OCD ($p=0.029$) which was also evident after combination of the case-control and the trio-results ($p=0.024$). In male subjects, the variant rs6766410 (p.N163K) located in the *HTR3C* was significantly associated with OCD ($p=0.007$). The association findings of the *HTR3C* and the *HTR3E* remained significant after correction for the number of variants investigated. These findings indicate a role of common variants of the *HTR3A-E* genes in OCD and OCD-related phenotypes and further support the use of 5-HT3 receptor antagonists as novel treatment options. The *HTR3E* gene is a novel candidate gene impacting on the individual expression of OC symptoms and OCD-related cognitive dysfunction.

1. Introduction

A central role of serotonin (5-HT) in obsessive-compulsive disorder (OCD) was initially based on the replicable treatment effects of drugs blocking the 5-HT transporter (Zohar et al., 2000). However, other pharmacological agents binding to 5-HT receptors (e.g. the 5-HT2A receptor) were also proven to have some additional effects on OCD symptoms (Dold et al., 2012; Erzegovesi et al., 2005). These findings point to abnormal 5-HT receptor functions which contribute to the development of OCD. In agreement with this assumption, molecular genetic studies reported significant associations of variants located within genes encoding for different 5-HT receptors (e.g. *HTR1B*, *HTR2A*) and OCD (e.g. Denys et al., 2006; Lochner et al., 2004; Taylor, 2012).

Among the different 5-HT receptors, the 5-HT3 receptor subfamily comprising five subunits (5-HT3A-E) takes a unique position based on its structural characteristics (Niesler et al., 2003). While all other 5-HT receptors are G-protein coupled receptors, the 5-HT3 receptors belong to the superfamily of ligand-gated ion channel receptors (Hannon and Hoyer, 2008). The 5-HT3 receptor is built of a pentameric complex surrounding a non-selective cation channel (Barnes et al., 2009). Agonist binding therefore leads to rapid depolarization. In contrast to homomeric 5-HT3A receptors, the other subunits 5-HT3B-E are non-functional when expressed alone (Niesler et al., 2007). However, the coexpression of these subunits with the 5-HT3A receptor forms heteromeric receptors showing different 5-HT efficacies as compared to the homomeric 5-HT3A receptor (Niesler et al., 2007). Expression of the 5-HT3 receptors in the human brain was demonstrated in different studies although conflicting results exist with regard to the exact distribution of the different subunits (Niesler et al., 2003; Walstab et al., 2010). 5-HT3 receptor antagonists show strong antiemetic effects and are administered regularly to treat chemotherapy induced vomiting (Niesler et al., 2008; Thompson and Lummis, 2007). However, there is growing evidence that 5-HT3 receptor antagonists may also be effective in several psychiatric conditions including schizophrenia, anxiety, eating disorders, and cognitive dysfunctions (Niesler, 2011; Walstab et al., 2010). In agreement with this, two recent double-blind placebo-controlled trials demonstrated beneficial effects of 5-HT3 receptor antagonists in treating OCD thus suggesting a novel treatment option (Askari et al., 2012; Soltani et al., 2010).

It has been recognized that OCD constitutes a heterogeneous disorder with a large variability in onset, symptomatic expression, and neurobiological foundations (Miguel et al., 2005; Taylor, 2011). Some researchers have argued that this heterogeneity should be addressed in genetic association studies by investigation of more distinct and homogenous sub-phenotypes (Chamberlain and Menzies, 2009). Among others, sub-dimensions based on the individual expression of symptoms have been suggested as alternative phenotypes (Mataix-Cols, 2006). A second and very common approach in psychiatric genetics is the use of heritable traits assumed to underlie the disorder (Gottesman and Gould, 2003). With regard to OCD, preliminary studies showed that neuropsychological functions including nonverbal memory and executive functions may constitute such endophenotypes (Delorme et al., 2007; Lennertz et al., 2012; Li et al., 2012; Rajender et al., 2011; Segalas et al., 2010).

Based on the encouraging psychopharmacological findings applying 5-HT3 receptor antagonists in OCD, we sought to explore genetic variations within the different *HTR3* genes in OCD patients. In addition to the classic association analyses using the disease phenotype, we also include OCD symptom dimensions and cognitive endophenotypes to address the heterogeneity of the disorder.

2. Experimental procedures

2.1. Case-control-sample, parent-child-trios, and general study design

The study was approved by the appropriate ethics boards of the study centers. All subjects signed the informed consent prior to inclusion. For the genetic association analyses, we genotyped $N=236$ OCD patients, $N=116$ parents of OCD affected patients, and $N=308$ healthy control subjects. A group of $N=220$ OCD patients were recruited in a German family study conducted at the Departments of Psychiatry of Bonn, Cologne, Greifswald, and Homburg (Grabe et al., 2006). In this study, the Schedule for Affective Disorders and Schizophrenia-Lifetime Version, Modified for the Study of Anxiety Disorders (SADS-LA-IV) (Fyer et al., 1995) was used to ensure psychiatric diagnoses. The remaining $N=16$ OCD patients were inpatients of the Department of Psychiatry of the University of Bonn and were assessed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID).

The comparison group included $N=100$ unrelated control subjects recruited within the family study and $N=210$ control subjects randomly selected from the community register of the city of Bonn and assessed at the Department of Psychiatry of the University of Bonn. According to the family study design, the $N=100$ comparison subjects of the OCD family study were allowed to fulfill the lifetime criteria for psychiatric diagnoses other than OCD. The remaining $N=210$ control subjects were free of lifetime psychiatric diagnoses