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Effects of the DRD4 genotype on neural networks associated with executive functions in children and adolescents

Susanne Gilsbach[a,b,*], Susanne Neufang[c], Susann Scherag[d], Timo D. Vloet[a,b,c], Gereon R. Fink[c,f], Beate Herpertz-Dahlmann[a,b,e], Kerstin Konrad[b,c,e]

[a] Department of Child and Adolescent Psychiatry and Psychotherapy, Medical Faculty, RWTH Aachen University, Germany
[b] Child Neuropsychology Section, Department of Child and Adolescent Psychiatry and Psychotherapy, Medical Faculty, RWTH Aachen University, Germany
[c] Cognitive Neurology, Section Institute of Neuroscience and Medicine (INM-3), Research Centre Juelich, Germany
[d] Department of Child and Adolescent Psychiatry, University of Duisburg-Essen, Essen, Germany
[e] JARA- BRAIN Translational Brain Medicine, Germany
[f] Department of Neurology, University Hospital of Cologne, Cologne, Germany

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ABSTRACT

Genetic variants within the dopamine D4 receptor gene (DRD4) are among the strongest and most consistently replicated molecular genetic findings in attentional functioning as well as attention deficit hyperactivity disorder (ADHD). Functionally, the 7-repeat allele of the DRD4-48 base pair repeat gene leads to a sub-sensitive postsynaptic D4 receptor, which is expressed at a particularly high density in the frontal lobes. We used fMRI to investigate the influence of the 7-repeat allele on BOLD (Blood Oxygen Level Dependency) responses in 26 healthy children and adolescents while they performed a combined stimulus-response Incompatibility Task (IC) and a Time Discrimination Task (TT).

7-repeat non-carriers exhibited increased neural activation of the left middle and inferior frontal gyrus (IFG) in the IC and greater cerebellar activation in the TT. Furthermore, the 7-repeat non-carriers exhibited a stronger coupling in haemodynamic responses between left IFG and the anterior cingulate cortex (ACC) during the IC and between cerebellar activation and brain regions that have high DRD4 density, including the IFG and the ACC during the TT. Our results indicate that the 7-repeat allele influences both regional brain activation patterns as well as connectivity patterns between neural networks of incompatibility and temporal processing.

1. Introduction

Dopamine plays an important role in normal attention and disorders of attention such as in attention deficit/hyperactivity disorder (ADHD) (Thapar et al., 2005; Del Campo et al., 2011). The dopamine receptor genes in particular are of great interest given that they may contribute to diverse aspects of normal and abnormal human behaviour (Thapar et al., 2005). According to human post-mortem and studies with monkeys, the D4 receptor, which is a D2-like receptor (Strange, 1993), is expressed in several brain regions related to planning and reward (Simpson et al., 2010; Meador-Woodruff, 1994; Matsumoto et al.,

Abbreviations: ACC, anterior cingulate cortex; BL, baseline; BOLD, Blood Oxygen Level Dependency; bp, base pair; CER, cerebellum; FWE, family wise error; IC, Incompatibility Task; IFG, inferior frontal gyrus; *k*, cluster size; PPI, psychophysiological interactions; SPG, superior parietal gyrus; TD, typically developing; TT, Time Discrimination Task; VNTR, variable number of tandem repeats.

* Corresponding author at: Neuenhofer Weg 21, D-52074 Aachen, Germany. Tel.: +49 241 8080218; fax: +49 241 8082544.
E-mail address: sgilsbach@ukaachen.de (S. Gilsbach).

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1996; Mrzljak et al., 1996; Ariano et al., 1997; Sanyal and Van Tol, 1997). It plays an important role in the prefrontal cortex and in the anterior cingulate cortex (ACC) (see Oak et al., 2000, for a review). These brain regions are critical for regulating executive functions (Seeman et al., 1993). A frequently studied polymorphism of the *DRD4* gene, which is located on chromosome 11p15.5, is a 48-base pair variable number of tandem repeat (VNTR) in exon III. This region of the *DRD4* gene encodes the third cytoplasmic loop of the D4 receptor, which is responsible for the coupling of a G-protein and activates intracellular responses to dopamine release by changing intracellular cAMP levels (Oak et al., 2000). The 48-bp fragment can be repeated from 2 to 11 times (Van Tol et al., 1992). In functional terms, the *DRD4* 7-repeat allele seems to alter the function of the encoded receptor by making it less sensitive to dopamine compared to other numbers of repeats (Schoots and Van Tol, 2003; Asghari et al., 1995).

Most of the evidence concerning the relevance of differences in the expression of the DRD4 receptor and attentional functioning is based on research within the field of ADHD. The association between ADHD and the 48 bp repeat polymorphism of exon III of the *DRD4* gene is the strongest and most consistently replicated molecular genetic finding in ADHD (Banaschewski et al., 2010). A meta-analysis of more than 30 studies found that the *DRD4* 7-repeat (*DRD4*-7r) allele increases the risk for ADHD, although this increase is only moderate with a pooled odds ratio of 1.34 (Faraone and Doyle, 2001; Li et al., 2006).

Studies investigating cognitive differences associated with the different *DRD4*-48 bp repeat genes in children and adults with ADHD have produced heterogeneous results. Some neuropsychological studies showed that participants carrying the 7-repeat allele indeed performed poorer on tasks of executive functions (Kieling et al., 2006; Langley et al., 2004) than those with other gene variants. In contrast, other studies have reported that children with ADHD who carry the 7-repeat allele have better performance on those tasks (Johnson et al., 2008; Swanson et al., 2000). However, some studies have failed to find any differences in attentional performance between carriers of the 7-repeat allele and those without it (Barkley et al., 2006; Konrad et al., 2010). There is an obvious lack of studies which deal with the effect of *DRD4* gene variants on attentional and executive functions in healthy participants. In addition, to date, only a limited number of studies used neuroimaging to explore the relationship between the *DRD4* 7-repeat allele and differences in brain anatomy or function, although several studies have suggested that neuroimaging methods might be particularly powerful for unravelling gene-brain behavioural relationships (Weinberger et al., 2001). While no other study has yet investigated the impact of *DRD4*-risk alleles on neural networks associated with executive functions, there is first evidence that DRD4 impacts on brain circuits associated with neural responses in brain areas involved in reward processing such as insula and cingulate cortex (Camara et al., 2010; Forbes et al., 2009). Since, genetic variants may have a more direct effect on brain functions than on behavioural phenotypes (e.g., Goldberg and Weinberger, 2004), the aim of the current fMRI study was to explore how genetic variation in the dopamine-regulating gene *DRD4* affects the pattern of neural activation associated with executive functions in typically developing children and adolescents. We decided to investigate children and adolescents since neural networks during development differ from those of adults (see Konrad et al., 2005; Durston and Casey, 2006) and genetically mediated disorders of attention (such as ADHD) typically have their onset during childhood. We analysed behavioural and BOLD responses in typically developing children using two tasks examining executive functions, a combined stimulus-response Incompatibility Task (IC) and a Time Discrimination Task (TT), with the same set of stimuli for both. The rationale for choosing these two tasks were to analyse neural mechanism underlying two different aspects of executive functions (Rubia and Smith, 2004) that are known to be modulated by dopamine (Konrad et al., 2004; Rubia et al., 2009) and which are known to be impaired in many subjects with attentional disorders (Rubia and Smith, 2004; Nigg, 2000; Vloet et al., 2009). We predicted that groups with and without the 7-repeat allele would display differences in neural activation patterns, particularly in brain regions with high dopaminergic receptor density such as the prefrontal cortex. Given the functional consequences of the 7-repeat allele (Asghari et al., 1995) and the association between the risk allele and ADHD (Li et al., 2006), one might hypothesise that 7-repeat-carriers show reduced BOLD responses in brain areas critical for EF task performance, although the unclear and contradicting results of previous neuropsychological studies and the lack of comparable neuroimaging studies hinder a precise prediction of the direction of this effect.

Consecutively, psychophysiological interactions were analysed to further investigate how the *DRD4*-48 bp repeat gene modulates functional connectivity within neural networks related to executive functions.

2. Materials and methods

2.1. Subjects

Twenty-six, typically developing 8–16-year-old Caucasian children and adolescents (17 boys, 9 girls, $M_{age} = 11.4 \pm 2$ years) were recruited by board announcements in local primary and secondary schools. All subjects were carefully screened for childhood psychiatric disorders using a standardised semi-structured interview for the diagnosis of mental disorders in children (Unnewehr, 1995; Kaufman et al., 1997; Delmo et al., 2001) and were free of any past or present mental disorders (i.e., ADHD, pervasive developmental disorders, etc.). Each subject's IQ was also estimated based on a short version of the Wechsler Intelligence Scale for Children III (Tewes et al., 1999). An IQ below 85 resulted in exclusion from the study. All participants were screened for any contraindications against fMRI and were trained prior to scanning in a mock fMRI-scanner to familiarise them with the scanner environment. Please note that some data were included in Neufang et al. (2008). The inclusion in this study was based on the availability of blood samples from the participants as well as on the consent given by participants and parents to participate in genetic studies.