Behavioral/Systems/Cognitive

The Impact of Catechol-O-Methyltransferase and Dopamine D4 Receptor Genotypes on Neurophysiological Markers of Performance Monitoring

Ulrike M. Krämer, Toni Cunillera, Estela Càmara, Josep Marco-Pallarés, David Cucurell, Wido Nager, Peter Bauer, Rebecca Schüle, Ludger Schöls, Antoni Rodriguez-Fornells, and Thomas F. Münte

1Department of Neuropsychology, Otto-von-Guericke-University, 39106 Magdeburg, Germany, 2Department Psicologia Bàsica, University of Barcelona, 08035 Barcelona, Spain, 3Medical University of Hannover, 30163 Hannover, Germany, 5Medical Genetics, University of Tübingen, 72074 Tübingen, Germany, 4Hertie-Institute for Clinical Brain Research, University of Tübingen, 72076 Tübingen, Germany, and 6Institució Catalana de Recerca i Estudis Avançats, 08010 Barcelona, Spain

Dynamic adaptations of one’s behavior by means of performance monitoring are a central function of the human executive system, that underlies considerable interindividual variation. Converging evidence from electrophysiological and neuroimaging studies in both animals and humans hints at the importance of the dopaminergic system for the regulation of performance monitoring. Here, we studied the impact of two polymorphisms affecting dopaminergic functioning in the prefrontal cortex [catechol-O-methyltransferase (COMT) Val108/158Met and dopamine D4 receptor (DRD4) single-nucleotide polymorphism (SNP)-521] on neurophysiological correlates of performance monitoring. We applied a modified version of a standard flanker task with an embedded stop-signal task to tap into the different functions involved, particularly error monitoring, conflict detection and inhibitory processes. Participants homozygous for the DRD4 T allele produced an increased error-related negativity after both choice errors and failed inhibitions compared with C-homozygotes. This was associated with pronounced compensatory behavior reflected in higher post-error slowing. No group differences were seen in the incomparability N2, suggesting distinct effects of the DRD4 polymorphism on error monitoring processes. Additionally, participants homozygous for the COMT Val allele, with a thereby diminished prefrontal dopaminergic level, revealed increased prefrontal processing related to inhibitory functions, reflected in the enhanced stop-signal-related components N2 and P3a. The results extend previous findings from mainly behavioral and neuroimaging data on the relationship between dopaminergic genes and executive functions and present possible underlying mechanisms for the previously suggested association between these dopaminergic polymorphisms and psychiatric disorders as schizophrenia or attention deficit hyperactivity disorder.

Key words: executive functions; COMT; DRD4; error-related negativity; inhibition; dopamine

Introduction

Performance monitoring enables humans to adapt their behavior and comprises error detection and correction, functions that are instigated by the anterior cingulate cortex (ACC), inferior frontal gyrus, dorsolateral prefrontal cortex (PFC), and insular cortex (Carter et al., 1998; Gehring and Knight, 2000; Ullsperger and von Cramon, 2001). Considerable interindividual variability in performance monitoring raises the question for underlying differences in neurotransmitter systems, particularly dopamine functioning (Cohen et al., 2002; Seamans and Yang, 2004). A role of dopamine in performance monitoring is suggested by altered executive functions in diseases such as schizophrenia and Parkinson’s disease (Falkenstein et al., 2001; Laurens et al., 2003) and the rich dopaminergic innervation of aforementioned prefrontal areas (Seamans and Yang, 2004). Moreover, a previous theory posits a central role of the mesencephalic dopaminergic system in the generation of the error-related negativity (ERN), a neurophysiological marker of action monitoring that is generated in the ACC (Holroyd and Coles, 2002).

Previous studies hint at genetic differences that may account for interindividual variation in dopaminergic functioning and thereby in performance monitoring (Fossella et al., 2002; Blasi et al., 2005). One frequently studied single-nucleotide polymorphism (SNP) is located in the catechol-O-methyltransferase (COMT) gene and refers to a G-to-A change at codon 158/108, resulting in a Valine to Methionine substitution. COMT is a major enzyme in dopamine degradation particularly in prefrontal areas because of a lack of the dopamine transporter in this region (Chen et al., 2004). The Methionine allele leads to a threefold to fourfold reduction in COMT activity (Chen et al., 2004). This polymorphism has been related to altered performance in tests for executive functions and differences in both prefrontal brain...


