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Association between COMT genotype and the control of memory guided saccades: Individual differences in healthy adults reveal a detrimental role of dopamine

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ABSTRACT

The neural circuits involved in oculomotor control are well described; however, neuromodulation of eye movements is still hardly understood. Memory guided saccades have been extensively studied and in particular neurophysiological evidence from monkey studies points to a crucial functional role of prefrontal dopamine activity. We exploited individual differences in dopamine regulation due to the well established COMT (catechol-O-methyltransferase) Val[158]Met polymorphism to explore the link between prefrontal dopamine activity and memory guided saccades in healthy subjects. The COMT genotype is thought to modulate dopamine metabolism in prefrontal cortex producing differences in dopamine availability. We investigated memory guided saccades in 111 healthy subjects and determined individual genotypes. Accuracy and precision were reduced in subjects with putatively higher prefrontal dopamine levels. In contrast, we found no modulation of saccade parameters by genotype in a visually guided control task. Our results suggest that increased dopamine activity can have a detrimental effect on saccades that rely on spatial memory representations. Although these findings await replication in larger and more diverse sample sizes, they provide persuasive support that specific oculomotor parameters are sensitive to dopaminergic variation in healthy subjects and add to a better understanding of how dopamine modulates saccadic control.

1. Introduction

Although the neuronal mechanisms of oculomotor control have been explored in great detail (Krauzlis, 2005), knowledge on functional modulation by neurotransmitters lags behind. Indeed, there is a striking discrepancy between the well documented oculomotor deficits in diseases characterized by disturbed neurotransmission, e.g. schizophrenia, and the scarce understanding of which mechanisms drive these deficits. Several lines of evidence from clinical findings in humans and neurophysiological findings in monkeys suggest that the neurotransmitter dopamine plays a significant role in oculomotor control (e.g. Anderson & MacAskill, 2013; Gooding & Basso, 2008; Noudoost & Moore, 2011). Given the ubiquitous relevance of dopamine activity in cognitive and motor processes, many facets of eye movements might be subject to dopaminergic modulation.

The memory guided saccade task represents an extensively studied oculomotor paradigm (see Johnston & Everling, 2008). The task requires saccade planning, inhibiting the saccade, maintaining an accurate spatial representation of the target over the delay period, and finally initiating the saccade to the remembered target position. Key behavioural findings include decreased spatial accuracy, i.e. increased hypometria, increased spatial variability, and increased latencies in comparison to visually guided saccades (e.g. Becker & Fuchs, 1969; Krappmann, 1998; White, Sparks, & Stanford, 1994). Performance in memory guided saccades has been consistently linked to prefrontal cortex where neuronal activity is primarily regulated by dopamine (Fuster, 1973; Goldman-Rakic, 1995; Seamans & Yang, 2004).

Seminal evidence for dopaminergic modulation of memory guided saccadescame from direct pharmacological manipulation in monkeys. When dopaminergic transmission in dlPFC was impaired by antagonist drugs, neuronal activity as well as performance in memory guided saccades were significantly reduced

Abbreviations: COMT, catechol-O-methyltransferase; Val, valine; Met, methionine; DNA, deoxyribonucleic acid; dlPFC, dorsolateral prefrontal cortex; SC, superior colliculus; FEF, frontal eye fields; SEF, supplementary eye fields; LIP, lateral intraparietal area.

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(Sawaguchi, 2000, 2001; Sawaguchi & Goldman-Rakic, 1991, 1994). In humans, a common possibility to explore dopaminergic modulation of specific functions is provided by studies in patients with psychiatric or neurological disorders associated with disturbed dopaminergic transmission, i.e. schizophrenia and Parkinson's disease. Consistently documented deficits include an increased number of premature saccades during the delay period and decreased accuracy (in schizophrenia patients e.g. Everling, Krappmann, Preuss, Brand, & Flohr, 1996; Landgraf, Amado, Bourdel, Leonardi, & Krebs, 2008; in Parkinson's disease patients e.g. Crawford, Henderson, & Kennard, 1989; Hodgson, Dittrich, Henderson, & Kennard, 1999). However, the precise underlying mechanisms have remained controversial for several reasons. Due to the chronic character of the focused disorders, dopaminergic dysregulation in patients is far from localized, but is rather assumed to involve the dopamine network comprehensively. In addition, complications inherent to the clinical setting, e.g. comorbidities, medication effects or chronicity of disease, cannot be controlled sufficiently contributing to ambiguous interpretations of findings.

An alternative non-invasive way to investigate dopaminergic modulation of saccadic control in humans is provided by genetic polymorphisms that are associated with individual differences in neurotransmission. Numerous studies have investigated associations between cognition and dopamine-related genes and findings have been successfully integrated into cognitive theories (Bilder, Volavka, Lachman, & Grace, 2004; Frank & Fossella, 2011; Witte & Flöel, 2012). Though, it has recently come under criticism due to replication failure suggesting a high rate of false positive (Chabris et al., 2012; Payton, 2009). Although this criticism indicates that genetic associations have to be interpreted cautiously, it does not annul the unique value of the approach (see Moonesinghe, Khoury, Liu, & Ioannidis, 2008; van den Oord & Sullivan, 2003).

Probably the best studied and documented dopaminergic polymorphism is the COMT (catechol-O-methyltransferase) Val^{158}Met polymorphism [rs4680]. This polymorphism produces a functional allelic variation in the dopamine degrading enzyme COMT (Lachman et al., 1996). The encoding gene is subject to a common mutation that results in a substitution of methionine (Met) for valine (Val) at codon 158. The Met allele is associated with significantly reduced enzyme activity leading to less efficient dopamine catabolism and thus higher dopamine levels. COMT represents the major dopamine breakdown mechanism specifically in prefrontal cortex and plays only a minor role in other brain areas (Lewis et al., 2001; Slifstein et al., 2008; Tunbridge, Harrison, & Weinberger, 2006; Yavich, Forsberg, Karayiorgou, Gogos, & Männistö, 2007). Fig. 1 summarizes the putative functional mechanism of the COMT Val^{158}Met polymorphism.

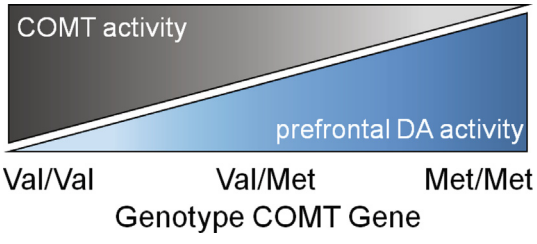

Fig. 1. Putative functional mechanisms of the COMT Val^{158}Met polymorphism: genotype modulates activity of the COMT enzyme that represents the major dopamine breakdown mechanism in prefrontal cortex; Val/Val homozygotes show a three-to-four fold higher activity than Met/Met homozygotes, Val/Met heterozygotes show intermediate activity levels; lower enzyme activity results in higher prefrontal dopamine activity.

Given the seminal evidence from monkey studies that prefrontal dopamine is crucially involved in working memory processes (Sawaguchi & Goldman-Rakic, 1991; Williams & Goldman-Rakic, 1995), it appears quite coherent to expect a link between the COMT Val^{158}Met polymorphism and memory guided saccades in humans. Insights into its role in saccadic control though are sparse. Some findings point to functional effects in the antisaccade task (Ettinger et al., 2008; Haraldsson et al., 2010; Kasparbauer et al., 2015; Kattoulas et al., 2010), but differences were foremost observed in brain activation patterns and not in behavioural measures. The association between COMT genotype and memory guided saccades has not been explored so far. Based on the beneficial role of dopamine in working memory found in monkey studies, it can be hypothesized that Met allele carriers, showing relatively higher prefrontal dopamine activity, outperform Val/Val homozygotes. However, there is also evidence from association studies in humans that COMT genotype might be linked in an inverted U-shaped manner to working memory performance indicating optimal intermediate dopamine levels (Cools & D'Esposito, 2011; Meyer-Lindenberg & Weinberger, 2006; Schacht, 2016). We thus aimed to investigate how the COMT Val^{158}Met polymorphism is linked to memory guided saccades.

2. Methods

2.1. Participants

A total of 111 subjects (18 males) participated in our study. Subjects were undergraduate students enrolled in the psychology program at the Justus Liebig University Giessen. The pronounced bias towards females in the sample was due to the sex distribution in the particular cohort when we ran the study. Given only about 20% of males in this cohort an imbalance in our sample was inevitable. Age ranged from 18 to 45 years with a mean age of 23.7 years (SD = 5.1). All students were naive with respect to the purpose of the study and fulfilled requirements of the study program with their participation. Any history of neurological or psychiatric disorders as well as medications presumed to interfere with oculomotor functioning were screened out. Methods and procedures agreed with the Declaration of Helsinki (World Medical Association, 2013). Informed consent was obtained by all participants and protection of data privacy was provided.

2.2. Genotyping

Genetic analyses were conducted within the Gene Brain Behaviour Project run by the Department of Psychology at the Justus Liebig University Giessen. The project maintains a large subject database characterized by selected polymorphisms functional for neurotransmission and available for behavioural research. All genetic analyses are performed and documented by an experienced technician in the local laboratory. DNA was extracted from buccal cells and was purified by a commercial extraction kit (MagNAPure LC DNA, Roche Diagnostics, Mannheim, Germany).

Genotyping of the COMT Val^{158}Met polymorphism [rs4680] was accomplished by polymerase chain reaction (PCR) and fluorescence melting-curve detection analysis. We used the Light Cycler System (Roche Diagnostics). Amplification and detection were performed using the Light Cycler FastStart DNA Master Hybridization Probes (Roche Diagnostics) with the following contents: reaction buffer, dNTPs mix and Taq DNA polymerase (0.7x) and additionally 1.6 mM magnesium chloride, 0.6 μM of each of the primers, 0.2 μM of each of the hybridization probes and approximately 50 ng of genomic template DNA. All reactions were carried out in a total volume of 21.4 μl. Primers and hybridization probes (TIB

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