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# Commonly-occurring polymorphisms in the COMT, DRD1 and DRD2 genes influence different aspects of motor sequence learning in humans

Irina Baetu *, Nicholas R. Burns, Kristi Urry, Girolamo Giovanni Barbante, Julia B. Pitcher

*University of Adelaide, Australia*

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ABSTRACT

Performing sequences of movements is a ubiquitous skill that involves dopamine transmission. However, it is unclear which components of the dopamine system contribute to which aspects of motor sequence learning. Here we used a genetic approach to investigate the relationship between different components of the dopamine system and specific aspects of sequence learning in humans. In particular, we investigated variations in genes that code for the catechol-O-methyltransferase (COMT) enzyme, the dopamine transporter (DAT) and dopamine D1 and D2 receptors (DRD1 and DRD2). COMT and the DAT regulate dopamine availability in the prefrontal cortex and the striatum, respectively, two key regions recruited during learning, whereas dopamine D1 and D2 receptors are thought to be involved in long-term potentiation and depression, respectively. We show that polymorphisms in the COMT, DRD1 and DRD2 genes differentially affect behavioral performance on a sequence learning task in 161 Caucasian participants. The DRD1 polymorphism predicted the ability to learn new sequences, the DRD2 polymorphism predicted the ability to perform a previously learnt sequence after performing interfering random movements, whereas the COMT polymorphism predicted the ability to switch flexibly between two sequences. We used computer simulations to explore potential mechanisms underlying these effects, which revealed that the DRD1 and DRD2 effects are possibly related to neuroplasticity. Our prediction-error algorithm estimated faster rates of connection strengthening in genotype groups with presumably higher D1 receptor densities, and faster rates of connection weakening in genotype groups with presumably higher D2 receptor densities. Consistent with current dopamine theories, these simulations suggest that D1-mediated neuroplasticity contributes to learning to select appropriate actions, whereas D2-mediated neuroplasticity is involved in learning to inhibit incorrect action plans. However, the learning algorithm did not account for the COMT effect, suggesting that prefrontal dopamine availability might affect sequence switching via other, non-learning, mechanisms. These findings provide insight into the function of the dopamine system, which is relevant to the development of treatments for disorders such as Parkinson's disease. Our results suggest that treatments targeting dopamine D1 receptors may improve learning of novel sequences, whereas those targeting dopamine D2 receptors may improve the ability to initiate previously learned sequences of movements.



## 1. Introduction

Learning sequences of movements involves the dopamine system (Badgaiyan, Fischman, & Alpert, 2007, 2008; Karabanov et al., 2010), yet it is unclear whether different components of the dopamine system affect different aspects of sequence learning. The current study investigated this issue by studying whether genetically-determined individual differences in dopamine-related neuronal physiology affect various aspects of sequence learning. In particular, we were interested in the function of dopamine D1 and D2 receptors, which may play different roles in learning (Kravitz & Kreitzer, 2012; Schultz, 2013). As both the prefrontal cortex and the striatum are involved in learning (e.g., Nakamura et al., 2001; Sakai et al., 1998), we were also interested in the role of the catechol-O-methyltransferase enzyme (COMT) and the dopamine transporter (DAT), which regulate dopamine catabolism in the prefrontal cortex and dopamine reuptake in the striatum, respectively.

Several studies have reported a relationship between sequence learning and polymorphisms in genes that code for COMT, DAT and the dopamine D2 receptor (Noohi et al., 2014; Schuck et al., 2013; Simon et al., 2011; but see Witte et al., 2012). These studies used tasks in which sequence learning is inferred from reaction

* Corresponding author at: School of Psychology, University of Adelaide, North Terrace Campus, Hughes Building, Level 4, Adelaide, South Australia 5005, Australia.
*E-mail address:* irina.baetu@adelaide.edu.au (I. Baetu).

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time difference scores (e.g., Nissen & Bullemer, 1987). However, there is emerging evidence that these measures are prone to floor effects (Kaufman et al., 2010; Urry, Burns, & Baetu, 2015) and are, therefore, unreliable when investigating individual differences. Here, we used a novel sequence learning task, in which learning is inferred from predictive accuracy rather than reaction time. Importantly, our task was designed to measure three distinct aspects of sequence learning, namely, the ability to learn new sequences of movements, the ability to switch flexibly between two learnt sequences, and the ability to perform a previously learnt sequence following interference, caused by performing the individual movements in random order. It is possible that these three aspects engage different neurological mechanisms, in which case variations in dopaminergic genes might differentially affect these three measures.

### 1.1. Dopamine D1 and D2 receptors

Past research suggests that dopamine D1 and D2 receptors may be involved in learning to select versus learning to inhibit actions, respectively (Kravitz & Kreitzer, 2012; Schultz, 2013). Such learning may occur as a result of experiencing a prediction error, i.e., a discrepancy between the brain's predicted outcome and the observed outcome. According to this hypothesis, positive prediction errors caused by unexpected outcomes generate striatal phasic dopamine release that is sufficient to activate low-affinity D1 receptors. As these receptors are thought to be involved in synaptic plasticity along the striatonigral 'direct' pathway (Shen, Flajolet, Greengard, & Surmeier, 2008), they may play a direct role in learning to select appropriate actions: D1-mediated long-term potentiation of synapses along the striatonigral pathway would facilitate the execution of motor plans that have been followed by correct feedback. In contrast, as dopamine D2 receptors might be involved in long-term depression in striatopallidal 'indirect pathway' neurons (Shen et al., 2008), it is possible that they play a critical role in learning to inhibit prepared or ongoing action plans. It is hypothesized that dips in dopamine phasic firing in response to negative prediction errors caused by the omission of an expected outcome (Schultz, Dayan, & Montague, 1997; Tobler, Dickinson, & Schultz, 2003) result in striatopallidal neurons being released from the tonic inhibition exerted by D2 receptors. This plasticity mediated by D2 receptors is thought to strengthen the indirect pathway, which could prevent the execution of incorrect motor plans (Frank, 2005).

Consequently, we hypothesized that a polymorphism in the DRD1 gene (rs686) that has been shown to influence receptor density affects the ability to learn by trial-and-error the correct stimulus–response mappings in a sequence learning task. In contrast, we expected a polymorphism in the DRD2 gene (rs1800497) to affect the ability to unlearn, or suppress, the tendency to perform incorrect stimulus–response mappings. As behavioral performance might reflect both processes simultaneously (i.e., a performance improvement might reflect both learning to select correct actions and learning to inhibit incorrect ones), we used computational modelling to separately estimate the speed with which each participant learned to select versus inhibit motor plans. We simulated participant performance using an associative model that learns via a prediction-error algorithm. We expected the DRD1 polymorphism to modulate the estimated speed with which connections are strengthened, and the DRD2 polymorphism to modulate the estimated speed with which connections are weakened.

### 1.2. COMT

COMT is an enzyme that degrades catecholamines such as dopamine, and is found predominantly in the prefrontal cortex. Because it regulates dopamine availability, it is hypothesized to play an important role in cognitive functions that seem to rely on prefrontal dopamine, such as working memory (e.g., Bilder, Volavka, Lachman, & Grace, 2004). The effects of a common polymorphism in the COMT gene (Val$^{158}$Met, rs4680) on cognitive function have been extensively studied. This COMT polymorphism has been linked to working memory, with some studies finding increased working memory capacity in individuals with the Met/Met genotype, associated with increased prefrontal dopamine (e.g., Dumontheil et al., 2011; Goldberg et al., 2003; but see Ho, Wassink, O'Leary, Sheffield, & Andreasen, 2005; Tsai et al., 2003; for a review see Savitz, Solms, & Ramesar, 2006). Given the possible relationship between COMT and working memory, some have argued that carriers of the Met allele should possess enhanced learning abilities owing to a higher working memory capacity. Consistent with this, Frank, Moustafa, Haughey, Curran, and Hutchinson (2007) reported a reinforcement learning advantage for individuals carrying the Met allele, which is especially pronounced in tasks requiring a higher working memory capacity (Collins & Frank, 2012). Consequently, we expected that if the Met allele would afford an advantage on any of the performance aspects measured by our sequence learning task, this would be mediated by a higher working memory capacity.

However, some studies have reported a performance advantage for carriers of the Val allele, especially when the learning task involves one or several reversals of the learned contingencies (Krugel, Biele, Mohr, Li, & Heekaeren, 2009; Lonsdorf et al., 2009). A possible explanation for these results is that changes in prefrontal dopamine levels might affect striatal phasic dopamine release (Grace, 1991). Thus, although the Val allele is associated with lower prefrontal dopamine levels, it may be associated with increased phasic dopamine activity in the striatum (Bilder et al., 2004). Because phasic dopamine activity in the striatum seems to be closely related to processing or learning from prediction errors (Schultz et al., 1997), it is possible that the COMT Val allele affords more flexible adaptation to changes in the environment. These changes in the experienced contingencies presumably trigger large prediction error signals, and heightened phasic dopamine activity would allow more efficient learning from these signals, and hence faster behavioral adaptation. Based on these findings, we expected the Val allele to be associated with an increased ability to switch flexibly between sequences in our task. Furthermore, because enhanced processing of prediction error signals might be the cause of this faster behavioral adaptation in Val carriers, we expected the learning rates estimated by our prediction-error algorithm to be larger in those carrying the Val allele.

### 1.3. The dopamine transporter (DAT)

The DAT is expressed more abundantly in the striatum, where it recaptures extracellular dopamine after release, thus limiting dopamine availability. A polymorphism in the DAT gene (rs28363170) could affect learning by exerting an influence on striatal phasic dopamine release in response to prediction errors. In favour of this hypothesis, a few imaging and electrophysiology studies found a relationship between this polymorphism and brain responses consistent with prediction error (Althaus et al., 2010; Biehl et al., 2011; Raczka et al., 2011). Therefore, we expected this polymorphism to correlate with the learning rates estimated by our prediction-error algorithm.

## 2. Method

### 2.1. Participants

$N = 169$ participants completed a sequence learning task and provided a saliva sample for genetic testing. Data collected from