Neurobiology of Learning and Memory 125 (2015) 176–188

Contents lists available at ScienceDirect

Neurobiology of Learning and Memory

journal homepage: www.elsevier.com/locate/ynlme

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

ARTICLE INFO

Article history:
Received 25 June 2015
Revised 15 September 2015
Accepted 18 September 2015
Available online 28 September 2015

Keywords:
Sequence learning
Dopamine receptor
COMT
Computational modelling
Prediction error

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 time

* 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).

http://dx.doi.org/10.1016/j.nlm.2015.09.009
1074-7427/

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

eight participants (one male and seven females) were removed from the dataset because they did not meet a performance criterion (see below). The final sample consisted of $N = 161$ participants (61 males and 100 females) with an age range of 18–54 years (mean = 24.8, SD = 8.01 years). Participants were recruited from a mailing list maintained by the School of Psychology, University of Adelaide, and via ads placed around the city and on a local classified advertisement and community website. Participants were eligible for the study if they were Caucasian, aged 18–60, did not suffer from major medical or psychiatric conditions, or from visual disorders, were not taking medications that have sedative or stimulant actions, had not used medication that affects neurological function (e.g., antidepressants, sedatives, antipsychotics) over the past six months, were not suffering from drug or alcohol dependence and did not smoke more than five cigarettes per day. All participants provided informed, written consent and were paid a small honorarium to reimburse their time. Ethical approval was obtained from the University of Adelaide Human Research Ethics committee and all protocols were performed according to the Declaration of Helsinki (2008 version).

2.2. Experimental procedure

Participants completed the sequence learning task described below and a series of computerized psychometric tests to assess reasoning ability, processing speed, and visuo-spatial ability. Furthermore, to investigate whether the effect of the COMT polymorphism is mediated by working memory, we included a test of working memory. Reasoning ability was measured using an abbreviated version of Raven's Advanced Progressive Matrices (Bors & Stokes, 1998). Raven's Advanced Progressive Matrices (Raven, Court, & Raven, 1988) are typically used to assess fluid intelligence, and the 12-item version that we administered to our participants is strongly correlated with the full version ($r = .88$; Bors & Stokes, 1998). Two tasks were used to assess processing speed: Inspection Time (Nettelbeck, 2001) and a computerized version of Symbol-Digit Coding (McPherson & Burns, 2005). Visuo-spatial ability was measured using the Mental Rotation test (Vandenberg & Kuse, 1978). Finally, working memory was measured using the Dot Matrix, also known as the Spatial Verification Span (Law, Morrin, & Pellegrino, 1995).

2.3. Sequence learning task

2.3.1. Task procedure

In order to assess sequence learning, we used a novel task that we developed for this purpose (Urry et al., 2015). The task bears some resemblance to previously used sequence learning tasks in which participants are required to learn to generate a sequence of movements by trial and error (e.g., Robertson & Flowers, 1990; Sakai et al., 1998). Participants were presented with 25 blue squares arranged in a 5×5 grid on the computer screen. Target squares would illuminate by turning yellow one at a time. Participants were required to predict which square would illuminate next by using the mouse to click on the square of their choice (see Fig. 1). If their prediction was correct, the square illuminated and a green tick appeared inside the square; if their prediction was incorrect, the correct square illuminated and a red cross appeared inside the selected square. This feedback was presented for 300 ms, after which time it ceased as all squares turned blue and participants were free to make their next selection. Rosner's extreme Studentized deviate test for multiple outliers was used to detect instances where a participant's performance indicated that they had not understood, or failed to follow, instructions (Rosner, 1983), as a small minority of participants showed a tendency to click on the previously illuminated square instead of attempting to predict which square would turn yellow next.

In most blocks, stimuli followed one of two deterministic sequences, in which the position of an illuminated target square was perfectly predicted by the position of the previously illuminated square. Participants, however, were not instructed about the sequences and had to discover them by trial and error. Sequences were four elements long and each block comprised 12 iterations of a sequence, or 48 stimuli in total. Blocks 1–6, 8–10, and 12 alternated between Sequences 1 and 2. That is, Blocks 1, 3, 5, 8, and 10 comprised 12 iterations of Sequence 1, and Blocks 2, 4, 6, 9, and 12 comprised 12 iterations of Sequence 2. The two alternating sequences used the same four grid locations to maximize the amount of interference when they were switched between blocks. The order in which the two sequences were introduced was counterbalanced across participants. Blocks 7 and 11 were random blocks in which the same four squares were illuminated as in the sequence blocks but the stimulus locations were randomly generated and not predictable.

2.3.2. Performance measures

We measured both reaction time (the latency to select a square) and prediction accuracy. Because we found no genetic effects on reaction time, we only present analyses of prediction accuracy. For each block, accuracy was measured in two ways: (1) as the average distance (in pixels) between the predicted and actual locations of target stimuli, where a distance of zero indicates a correct prediction; and (2) as the number of trials before participants were able to generate the correct sequence at least twice, consecutively, with lower scores indicating better performance as participants made fewer incorrect predictions before generating the correct sequence. The multiplicative inverse of each measure was calculated because both measures had skewed distributions, and z-scores computed for each of the two inverted measures. Because the two sets of z-scores were highly correlated ($r = .92$), they were averaged. These averaged z-scores provided one performance measure for each block, with higher scores indicating better performance.

2.3.3. Performance aspects measured by the task

This task allowed investigation of several aspects of learning performance: the ability to acquire a new sequence, to switch between two learnt sequences, and to recover performance of a previously learnt sequence following interference caused by performing the individual movements in random order. Participants learned Sequence 1 in Block 1 and Sequence 2 in Block 2. Performance in Block 1 in particular reflects the ability to learn a new sequence (performance in Block 2, however, is confounded with the ability to overcome the interference caused by learning Sequence 1 in Block 1, and hence does not purely reflect sequence acquisition). Following acquisition of the two sequences, participants were required to switch between the two sequences in Blocks 3–6. Thus, performance in Blocks 3–6 reflects their ability to switch between the two learnt sequences. Blocks 7 and 11 were random blocks included in the experimental design to determine the extent to which performing movements in random order interferes with the ability to subsequently perform the two previously learnt sequences. We determined the extent to which the random blocks interfered with performance by comparing participant performance immediately after a random block to that preceding it. That is, a ratio was computed for each participant that reflected the change in performance after a random block. For example, the interference caused by the random Block 7 was computed as follows:

$$\text{Block 7 interference} = (\text{Block 8 performance} - \text{Block 6 performance})/\text{Block 6 performance}$$

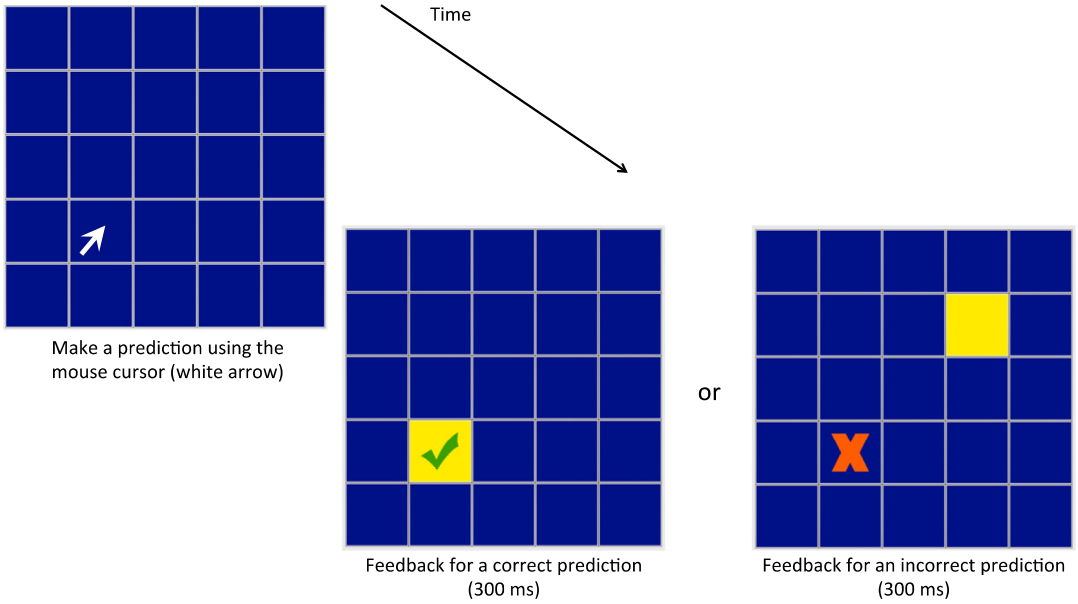

Fig. 1. Training procedure in the sequence learning task. On every trial, participants first predicted which grid location would turn yellow next by clicking on the square of their choice (represented by the white arrow), and this was followed by immediate positive or negative feedback concerning the accuracy of their prediction. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

A similar computation was performed to calculate the change in performance following the random Block 11. The averaged change in performance following Blocks 7 and 11 reflects the extent to which random blocks interfere with performance, with negative values indicating a decrease in performance after random blocks, and values closer to zero indicating quick recovery from random blocks; in other words, less interference.

2.4. Computational modelling

2.4.1. Model details

To simulate learning in our task, we designed an associative model that could learn sequences of movements by using the feedback concerning the location of the yellow square as a teaching signal (full details of the model are provided in Supplementary Material). The model uses a type of prediction error to alter its connections, where prediction error is defined as the discrepancy between internally generated expectations and sensory feedback. Two learning rate parameters, αPos and αNeg, govern the speed with which connections are strengthened or weakened, respectively. A high αPos entails large trial-by-trial increases in connection weights that generate correct choices, whereas a large αNeg entails large decreases in connection weights that generate incorrect choices.

2.4.2. Procedure for estimating parameters for individual participants

We estimated the combination of the two learning rate parameters (αPos and αNeg) that yielded model performance that was closest to each participant's performance. These parameters reflect the capacity to strengthen or weaken connections during sequence learning, respectively. Individual differences in these two learning parameter estimates could explain differences in behavioral performance. We were thus interested in determining whether there is a relationship between dopaminergic genotypes and the estimated αPos and αNeg.

Each simulation began with a random set of weak connections that varied between 0 and 0.2. This ensured that the network would select a grid location even when it had no previous experience with this task. As the first selection was determined on the basis of random connection weights, its prediction was highly likely to be wrong. The prediction error generated by the incorrect prediction was used to strengthen the correct connection and weaken the incorrect connections. For each individual participant, we simulated learning with our model using the exact sequence of square illuminations experienced by that participant.

In order to estimate the best learning rate parameters we performed a grid search whereby the simulation was repeated with different parameter combinations and the best fitting combination was chosen. We chose this procedure because it involves searching the entire parameter space for the best combination, which avoids the local minima problems associated with some optimisation methods. In our simulations αPos and αNeg varied between 0.01 and 1, with a step size of .045. For each simulation, the number of trials until the model was able to generate the sequence correctly in each block was calculated. The squared difference between the model's number of trials until it generated the sequence and the participant's number of trials until he or she generated the sequence was summed across blocks. This sum of squared deviations between the model's performance and the participant's performance was used to select the best fitting combination of parameters. Twenty simulations were run for each combination of αPos and αNeg, and the combination that yielded the smallest average sum of squared deviations was chosen.

The remaining two model parameters described in Supplemental Material, β and ϕ, were fixed for all participants. These two parameters do not influence the model's choices; instead, they can only influence the latency with which the model selects a response (and can thus be used to model reaction times rather than accuracy). Because we estimated the model's fit to participant data in terms of accuracy instead of reaction time, these two parameters cannot influence the outcome of the simulations. That is, the simulation results in identical choices regardless of the values of β and ϕ.

2.4.3. Additional simulations to determine whether two learning rate parameters are necessary

We chose to simulate our participants' data using a model that uses two separate learning rate parameters, one for strengthening

and one for weakening connections. This was motivated by previous research suggesting that dopamine D1 and D2 receptors might have different effects on the hypothesized parameters. It is possible, however, that two learning rate parameters are unnecessary and that a single learning rate parameter that governs the speed of both connection strengthening and weakening might be sufficient. Demonstrating that a model with two learning rate parameters performs better than a model with a single learning rate parameter would further justify our use of such a model to simulate genetic individual differences in learning. Therefore, we compared the model described previously with another that uses a single rate parameter instead of two. For the latter model, the same learning rate was used to update connections, regardless of whether the connections were strengthened or weakened. We used the same procedure described previously to estimate the learning rate parameter that yielded the best model fit for each participant.

We used Akaike's Information Criterion (AIC; Burnham & Anderson, 1998) and the Bayesian Information Criterion (BIC; Kass & Raftery, 1995) to compare the fit of the two models based on least squares. Both criteria penalize models with more parameters. Models with a smaller AIC or BIC are preferred.

2.5. Choice of polymorphisms and genotyping procedure

We investigated the relationship between sequence learning and four commonly-occurring polymorphisms in dopaminergic genes: a DRD1 polymorphism (rs686), the DRD2/ANKK1 TaqIA polymorphism (rs1800497), the COMT Val^{158}Met polymorphism (rs4680), and a DAT1 (SLC6A3) polymorphism (rs28363170). We chose these polymorphisms because their minor allele is relatively frequent (thus allowing us to detect genetic effects within our sample) and previous research has shown that they are associated with individual differences in dopaminergic function.

2.5.1. DRD1

The DRD1 gene codes for the dopamine D1 receptor. The G allele of the DRD1 single nucleotide polymorphism (SNP), rs686, has been associated with lower DRD1 expression compared to the A allele in an in vitro study (Huang et al., 2008). Huang and Li (2009) reported that the G allele decreases DRD1 expression, by inhibiting the binding of microRNA miR-504 to the 3′ untranslated region of the DRD1 gene, thus providing a potential causal mechanism through which this SNP affects gene expression. These results suggest that the G allele might be associated with reduced dopamine D1 receptor density compared to the A allele. Although studies linking the rs686 polymorphism to learning are lacking, there are several reports of associations between the G allele SNP and a number of clinical outcomes including schizophrenia (Zhu et al., 2011), and alcohol (Batel et al., 2008), opioid (Zhu et al., 2013) and nicotine dependence (Huang et al., 2008).

2.5.2. DRD2

Although most probably not a causal polymorphism, the DRD2/ANKK1 TaqIA SNP (rs1800497) seems to be associated with the expression of the gene coding for the dopamine D2 receptor, DRD2, even though the SNP is located on the adjacent gene, ANKK1 (Neville, Johnstone, & Walton, 2004). The TaqIA A1 allele has been shown to be associated with reduced dopamine D2 receptor availability in a series of PET studies (Jonsson et al., 1999; Pohjalainen et al., 1998; Ritchie & Noble, 2003; Thompson et al., 1997) although this finding was not replicated by Laruelle, Gelernter, and Innis (1998). More recently, Zhang and colleagues reported that this SNP is in strong linkage disequilibrium with two other polymorphisms that seem to affect the relative splicing of dopamine D2 short (presynaptic) and long (postsynaptic) receptor variants (Zhang et al., 2007), thus providing a potential explanation for the observed association between TaqIA and various behavioral and clinical outcomes. Indeed, several studies reported associations between TaqIA and alcoholism (Comings & Blum, 2000), smoking (Li, Ma, & Beuten, 2004; Munafo, Clark, Johnstone, Murphy, & Walton, 2004; Verde et al., 2011), obesity (Noble et al., 1994), striatal responses to food intake (Stice, Spoor, Bohon, & Small, 2008), and ADHD (Nyman et al., 2012). Of more relevance here, the A1 allele of the TaqIA SNP is associated with poorer motor learning (Pearson-Fuhrhop, Minton, Acevedo, Shahbaba, & Cramer, 2013), and with reduced learning by trial and error (ability to avoid incorrect choices) in reinforcement learning tasks, in which participants are required to learn a few simple stimulus–response contingencies (Frank & Hutchinson, 2009; Klein et al., 2007). Furthermore, the A1 allele is associated with a reduced ability to choose correct responses and to sustain a newly-rewarded response after a contingency reversal (Jocham et al., 2009). As these behavioral results were accompanied by weaker blood oxygen level-dependent (BOLD) brain responses following negative feedback (Jocham et al., 2009; Klein et al., 2007), it may be that the reduced dopamine D2 receptor density associated with the A1 allele results in a deficit in processing or learning from prediction errors. This hypothesis, however, is not supported by two electrophysiological studies showing enhanced, rather than reduced, responses to prediction errors in adult carriers of the A1 allele (Smillie, Cooper, & Pickering, 2011) and enhanced responses to negative feedback in children carrying at least one A1 allele (Althaus et al., 2009).

2.5.3. COMT

The COMT enzyme is encoded by the COMT gene, which contains a polymorphism (Val^{158}Met, rs4680) that has been associated with differential enzyme activity. The Met allele is associated with markedly reduced COMT activity (Chen et al., 2004), presumably leading to increased prefrontal dopamine levels. Indeed, a recent PET study on patients with Parkinson's disease found higher presynaptic dopamine levels in frontal areas in Met homozygotes compared with Val homozygotes (Wu et al., 2012). Consistent with the notion that performance on working memory tasks benefits from higher prefrontal dopamine levels, higher working memory capacity has been reported in carriers of the COMT Met allele (e.g., Dumontheil et al., 2011; Goldberg et al., 2003), although failures to find this effect have also been reported (e.g., Ho et al., 2005; Tsai et al., 2003; see Savitz et al., 2006, for a review). Several studies have also investigated the relationship between the Val^{158}Met polymorphism and performance on learning tasks, but once again, the findings are inconsistent. Noohi et al. (2014) found poorer sequence learning in individuals with the Val/Val genotype, but this disadvantage was only evident when reaction times were analyzed. In contrast, Witte et al. (2012) reported no effect of COMT genotype on sequence learning. A performance advantage for reinforcement learning in individuals carrying the Met allele has been reported (Collins & Frank, 2012; Frank et al., 2007) although others report an advantage for the Val allele in learning reversals in stimulus–response contingencies (Krugel et al., 2009). Furthermore, Lonsdorf et al. (2009) found that Val carriers extinguished their conditioned fear responses more quickly when the conditioned stimulus was no longer followed by an aversive unconditioned stimulus, thus demonstrating faster adaptation to a change in environmental contingencies.

2.5.4. DAT1

The DAT1 gene (also known as SLC6A3) codes for the dopamine transporter (DAT). A variable number of tandem repeats polymorphism (rs28363170) occurs in the 3′ untranslated region of the DAT1 gene, with the two most common alleles being a 9-repeat

(9R) and a 10-repeat (10R) of a 40-base-pair sequence. Studies investigating the relationship between this polymorphism and gene expression have reported inconsistent results. Three in vitro studies found the 9R allele to be associated with reduced expression of DAT1 relative to the 10R allele (Fuke et al., 2001; Mill, Asherson, Browes, D'Souza, & Craig, 2002; VanNess, Owens, & Kilts, 2005), while Miller and Madras (2002) reported the opposite. In vivo single photon emission computed topography (SPECT) studies have also reported inconsistent results. Two studies found no effect of the rs28363170 polymorphism on DAT availability (Lynch et al., 2003; Martinez et al., 2001). Heinz et al. (2000) reported lower DAT availability in the 9R/10R genotype compared to the 10R/10R genotype, whereas Jacobsen et al. (2000), van Dyck et al. (2005) and van de Giessen et al. (2009) found the opposite result, with carriers of the 9R allele showing an increase in striatal DAT availability relative to 10R/10R homozygotes. It is worth noting that these two latter studies are, to date, the largest of this kind on healthy Caucasians ($N = 96$ and 81, respectively). The other studies either used modest sample sizes (Heinz et al., 2000, $N = 25$; Jacobsen et al., 2000, $N = 27$) or studied samples composed of healthy controls as well as patients (Heinz et al., 2000; Lynch et al., 2003; Martinez et al., 2001).

Despite these inconsistencies, it has been typically hypothesized that carriers of the 9R allele are characterised by reduced DAT expression, and hence enhanced dopamine availability compared to the 10R/10R genotype (e.g., Bertolino et al., 2009; Epstein et al., 2007; Althaus et al., 2010; Eisenegger et al., 2013; Pearson-Fuhrhop et al., 2013; Schuck et al., 2013; Simon et al., 2011; but see Biehl et al., 2011). Consistent with this hypothesis, Simon et al. (2011) found a reliable effect of this polymorphism on performance on a sequence learning task. Conversely, Schuck et al. (2013), found no main effect of this polymorphism on sequence learning, but reported a modest interaction involving another polymorphism and age. Others have investigated different types of learning. Raczka et al. (2011) showed that the 9R allele is associated with faster extinction of fear responses after fear conditioning. When participants were exposed to a conditioned stimulus that was no longer followed by electric shock, 9R carriers showed a more pronounced reduction in fear responses, as well as stronger BOLD signals in the ventral striatum in response to surprising shock omissions. As these shock omissions should have, in principle, generated negative prediction errors (as the omission of the shock is unexpected on the first extinction trials), these results suggest that the 9R allele is associated with enhanced learning from prediction errors. Consistent with this, a study on children with ADHD also showed enhanced event-related potentials in 9R carriers during a feedback-based learning task (Althaus et al., 2010) although others have reported reduced event-related potentials in 9R carriers during a simple motor task designed to generate high error rates (Biehl et al., 2011).

2.5.5. DNA extraction and quantification

DNA extraction and genotyping were performed by the Australian Genome Research Facility, Ltd (AGRF). DNA for each participant was recovered from stabilized saliva samples using the manual prepIT system according to manufacturer's instructions (Oragene DNA (OG-500); DNA Genotek Inc, Ontario, Canada). DNA precipitates were allowed to resuspend for a minimum of 48 h. before quantification by fluorimetry (QuantiFluor™ dsDNA System; Promega Corporation, Madison, Wisconsin, USA) in conjunction with a Gemini™ Spectramax XPS fluorescence microplate reader (Molecular Devices, LLC; Sunnyvale, CA, USA). DNA stocks were adjusted to a working concentration of between 10 and 50 ng μl^{-1} for subsequent genotyping.

The DAT locus was amplified using the PCR primers T3-5Long and T7-3aLong (Barr et al., 2001). Cycling parameters were as published in Demiralp et al. (2007), with the exception that the polymerase used was Immolase (0.3 units per reaction; Bioline (Australia) Pty Ltd). The forward primer for DAT1 was modified by the addition of a 5′ 6-FAM label during synthesis (Geneworks Pty Ltd, Adelaide, Australia). Genotypes were determined by capillary electrophoresis using an AB3730 Genetic Analyser fitted with a 36 cm array, with sizing determined against a Genescan LIZ500 molecular weight marker. Analysis was performed in Genemapper V3.7 software (Life Technologies Australia Pty Ltd., Victoria, Australia).

DRD1, DRD2 and COMT were genotyped using the Sequenom iPLEX MassARRAY® platform according to the methods described by Gabriel, Ziaugra, and Tabbaa (2009). PCR and extension primers were designed using Sequenom Assay Designer v3.1. The following sequences of primers were used: rs686 (PCR-1: ACGTTGGATGGCT CATCCCAAAAGCTAGAG, PCR-2: ACGTTGGATGAGAGTCTCACCG TACCTTAG, extension primer: GAGATTGCTCTGGGG), rs1800497 (PCR-1: ACGTTGGATGTGTGCAGCTCACTCCATCCT, PCR-2: ACGTTG GATGTCAAGGGCAACACAGCCATC, extension primer: GCTGGGCGC CTGCCT), and rs4680 (PCR-1: ACGTTGGATGTTTTCCAGGTCTGA CAACGG, PCR-2: ACGTTGGATGACCCAGCGGATGGTGGATTT, extension primer: GCACACCTTGTCCTTCA).

2.6. Statistical analyses

Genetic effects were analyzed via multiple linear regression models that included all four polymorphisms as predictors. Genotypes were defined as continuous variables with three levels to represent the number of minor alleles (0, 1, or 2) possessed by each participant. Because our data revealed some non-linear genetic effects, the linear regression models were extended to include a quadratic term for a polymorphism only if the addition of the quadratic term improved the amount of explained variance and had a significant effect on the dependent variable at least at the uncorrected alpha level. So all regression models included all four polymorphisms as linear predictors, and in a few cases the model included an additional predictor that estimated the quadratic term for a given polymorphism. All regression models also included age and gender to control for their potential confounding effects.

We performed five regression analyses, one for each of the five dependent variables. Of the five dependent variables, three were behavioral measures (sequence acquisition in Block 1, sequence switching in Blocks 3–6, and recovery of performance following random blocks). The remaining two dependent variables were the two learning rates estimated by our learning algorithm. Given that we analyzed five dependent variables, we present two-sided p values that were adjusted for multiple comparisons via the Dubey (1985) and Armitage and Parmar (1986) method. We chose this method because the Bonferroni adjustment procedure is too conservative when the dependent variables are correlated (Sankoh, Huque, & Dubey, 1997). In contrast to the Bonferroni method, the Dubey and Armitage-Parmar procedure takes into account the degree of correlation between the dependent variables, resulting in less conservative p-value adjustments when the dependent variables are correlated. In extreme cases, when the mean correlation between dependent variables is zero this procedure results in a correction equivalent to a Bonferroni adjustment, and when the mean correlation is one no adjustment to the p-values is made.

3. Results

3.1. Behavioral data

Of 169 participants, data from eight participants was omitted from all analyses, on the basis of Rosner's extreme Studentized

deviate test for multiple outliers, which indicated where participants had not understood or failed to follow the sequence learning task instructions. Instead of attempting to predict which square would turn yellow next on every trial, these participants frequently clicked on the square that had just turned yellow (they did so between 95 and 473 times out of a total of 576 responses). The remaining participants clicked on the square that had just turned yellow to a much lesser extent (mean number of clicks = 23.04, SD = 17.20).

3.1.1. Overall performance

Fig. 2 (full line) shows the average number of trials until participants were able to generate the sequence correctly in each training block, which was one of the two accuracy measures. The number of trials until participants were able to generate the correct sequence was relatively high in Blocks 1 and 2, in which they were exposed to the two sequences for the first time. Performance gradually improved with more practice (i.e., participants gradually made fewer incorrect predictions before generating the correct sequence). Participants required more trials to learn Sequence 1 in Block 1 than to learn Sequence 2 in Block 2 ($t(160) = 6.28$, $p < .001$), probably because Sequence 2 used the same grid locations as Sequence 1 and participants had the opportunity to learn these locations in the previous block. The better performance in Blocks 3–6 than in the first two blocks ($t(160) = 11.57$, $p < .001$) suggests that participants were able to retain and retrieve their memory of the two sequences when they were required to switch between them (i.e., performing one sequence did not cause complete forgetting of the previous sequence). As expected, random blocks interfered with performance. This is evidenced by an increase in the number of trials required to generate the sequence on Blocks 8 and 12 that immediately followed a random block compared to Blocks 6 and 10 that preceded a random block ($t(160) = 9.28$, $p < .001$). A similar pattern of results was obtained for the other accuracy measure, the average distance between the participants' prediction and the correct yellow square location (all of the comparisons described above were also significant for this measure, minimum $t(160) = 6.07$, $p < .001$).

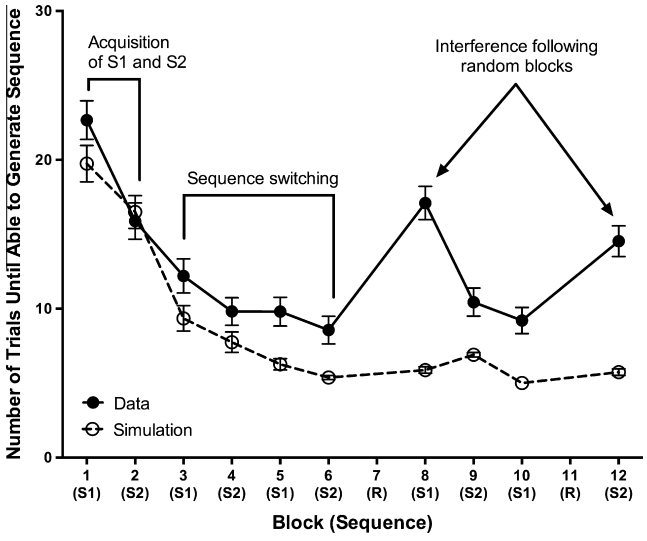

Fig. 2. Mean number of trials until participants were able to correctly generate the sequence in each training block (full line; see Section 3.1.1) and mean number of trials until the model was able to generate the sequence when it was trained with the best fitting parameters for each participant (dotted line; see Section 3.2.1). There is no data for the random blocks 7 and 11 because the square illuminations did not follow a sequence in these blocks. Error bars represent the standard error of the mean. S1 = Sequence 1, S2 = Sequence 2, R = Random block.

3.1.2. Genotyping

DRD1 genotyping failed for one participant, DRD2 genotyping failed for another participant, and COMT genotyping failed for a third participant. Six participants possessed a rare DAT1 genotype (one 6R/10R, one 7R/10R, two 9R/11R, and two 10R/11R) and their data were excluded from analyses involving the DAT1 genotype. The analyzed genotype distributions were as follows: DRD1 A/A ($N = 57$), A/G ($N = 78$), G/G ($N = 25$); DRD2 A2/A2 ($N = 102$), A1/A2 ($N = 52$), A1/A1 ($N = 6$); COMT Val/Val ($N = 38$), Val/Met ($N = 84$), Met/Met ($N = 38$); DAT1 10R/10R ($N = 86$), 9R/10R ($N = 58$), 9R/9R ($N = 11$). The allelic distributions of all four genes were in Hardy–Weinberg equilibrium (maximum $\chi^2 = 2.53$, $p = .281$). For each gene, gender distributions were similar across the three genotype groups and there were no reliable differences in age or psychometric test scores (see Table 1).

3.1.3. Genetic effects on sequence acquisition in Block 1

The regression analysis on Block 1 performance z-scores revealed an effect of the DRD1 polymorphism (Fig. 3, Panel A). A model including a quadratic term for the DRD1 polymorphism revealed modest linear and quadratic effects (linear: $t(145) = 2.26$, uncorrected $p = .025$, corrected $p = .081$; quadratic: $t(145) = 2.14$, uncorrected $p = .034$, corrected $p = .109$). The linear effect suggests that the number of A alleles (associated with higher dopamine D1 receptor density) modestly predicted faster Sequence 1 acquisition. None of the other genetic effects were significant (maximum $t(145) = 0.75$, uncorrected $p = .454$).

3.1.4. Genetic effects on switching performance in Blocks 3–6

Only the COMT polymorphism was associated with switching performance (Fig. 3, Panel B). The COMT Val/Val group, with possibly increased midbrain phasic dopamine release (Bilder et al., 2004), performed better than the Val/Met group. The Met/Met group (with presumably higher prefrontal tonic dopamine levels) also performed marginally better than the heterozygous group. Again, because of evident non-linear effects, the regression model included a quadratic term for the COMT polymorphism in addition to the genotype information for all four polymorphisms. This analysis revealed significant linear and quadratic COMT effects, even after correction for multiple comparisons (linear: $t(145) = 2.54$, uncorrected $p = .012$, corrected $p = .038$; quadratic: $t(145) = 2.68$, uncorrected $p = .008$, corrected $p = .025$). No other polymorphism reached the significance level (maximum $t(145) = 1.47$, uncorrected $p = .143$).

3.1.5. Genetic effects on recovery from interference caused by random blocks

DRD2 was the only polymorphism that was associated with recovery from random blocks (Fig. 3, Panel C). The number of A2 alleles (associated with higher D2 receptor density) predicted less interference following random blocks ($t(146) = 2.44$, uncorrected $p = .016$, corrected $p = .038$). No other genetic effect reached statistical significance (maximum $t(146) = 1.41$, uncorrected $p = .161$).

3.2. Simulation data

3.2.1. Overall fit of the model to participant data

We first determined whether a model with two separate learning rate parameters, αPos and αNeg, would fit the participant data better than a model with a single learning rate parameter.

The model with two learning rate parameters performed considerably better than the one with a single learning rate parameter, resulting in both a smaller AIC (505.12 vs. 510.35) and a smaller BIC (1164.04 vs. 1175.61). According to Burnham and Anderson (1998) an AIC difference of 4–7 is equivalent to 95% confidence that the model with the smaller AIC value provides a better fit.

Table 1
Gender distributions, average age and scores on psychometric tests for the different genotype groups. Standard deviations are reported in parentheses. Significance *p* values are reported for χ^2 tests in the case of gender, and for one-way analyses of variance for all other variables. Note that for Inspection Time, lower values indicate higher processing speed.

	Age	Gender F:M	Abstract reasoning ability	Visuo-spatial working memory	Visuo-spatial ability	Processing speed (inspection time)	Processing speed (symbol-digit coding)
DRD1 A/A	23.28 (5.89)	35:22	6.86 (3.04)	43.02 (7.07)	25.11 (9.16)	104.95 (55.31)	88.27 (16.05)
DRD1 A/G	25.28 (8.60)	47:31	6.47 (3.04)	41.26 (8.21)	21.77 (10.01)	120.87 (59.01)	81.93 (14.28)
DRD1 G/G	26.28 (9.68)	17:8	5.92 (3.08)	40.58 (6.69)	22.96 (9.78)	129.12 (63.99)	86.08 (16.50)
p	.202	.783	.441	.299	.144	.159	.061
DRD2 A2/A2	24.67 (8.11)	64:38	6.74 (2.89)	42.45 (7.45)	23.64 (10.03)	116.65 (61.97)	85.43 (16.92)
DRD2 A1/A2	24.71 (7.83)	31:21	6.37 (3.30)	40.84 (8.02)	22.25 (9.25)	114.22 (54.80)	83.96 (13.31)
DRD2 A1/A1	26.67 (8.96)	4:2	4.67 (2.94)	40.33 (4.72)	23.83 (6.46)	135.96 (43.16)	81.83 (6.79)
p	.839	.903	.241	.420	.694	.697	.769
DAT1 10R/10R	24.30 (7.21)	54:32	6.74 (3.14)	42.19 (7.51)	23.48 (9.54)	114.92 (57.17)	85.95 (15.34)
DAT1 9R/10R	24.91 (8.24)	34:24	6.64 (2.79)	41.39 (7.29)	23.93 (10.15)	114.80 (62.71)	84.04 (15.17)
DAT1 9R/9R	21.63 (3.01)	7:4	5.64 (3.17)	40.91 (9.85)	20.91 (8.36)	137.54 (51.26)	85.27 (18.09)
p	.407	.869	.523	.767	.639	.472	.774
COMT Val/Val	24.32 (7.03)	21:17	7.32 (3.01)	42.81 (6.45)	23.82 (9.67)	102.68 (45.39)	86.46 (15.87)
COMT Val/Met	24.93 (8.51)	56:28	6.24 (3.06)	42.44 (7.96)	23.12 (9.49)	116.84 (59.54)	84.17 (14.22)
COMT Met/Met	24.82 (7.96)	22:16	6.41 (2.95)	39.50 (7.40)	22.74 (10.19)	130.42 (67.60)	84.61 (18.14)
p	.926	.411	.191	.101	.885	.133	.757

The AIC difference between the two models tested here is 5.23. Similarly, according to Kass and Raftery (1995) a BIC difference larger than 10 suggests there is very strong evidence in favour of the model with the smaller BIC value. The BIC difference here was 11.57. Therefore, we report genetic analyses on the parameters estimated by the model with two learning rate parameters given its better fit.

In order to determine whether the model fitted the behavioral data reasonably well, we compared the model's performance to the participants' performance. A simple linear regression analysis was performed on the participants' performance using the model's simulated performance as a regressor. That is, the participants' average number of trials until they were able to generate the sequence correctly in all sequence blocks was regressed on the average number of trials until the model was able to generate the sequence correctly when the simulation was run with the best estimated parameters for each participant. The model's performance was closely similar to the participants' performance as it explained 85% of the variance in participant performance ($t(159) = 29.69$, $p < .001$). Thus, the model generally successfully approximated the behavior of individual participants when only two of its parameters were allowed to vary. However, it did not fully capture all aspects of the behavioral data. Fig. 2 (dotted line) shows the mean number of trials until the model was able to generate the sequence correctly in each training block when it was trained with the best fitting parameters for each participant. The model gradually required fewer trials to generate the two sequences over successive blocks, which is very similar to the trend seen in the

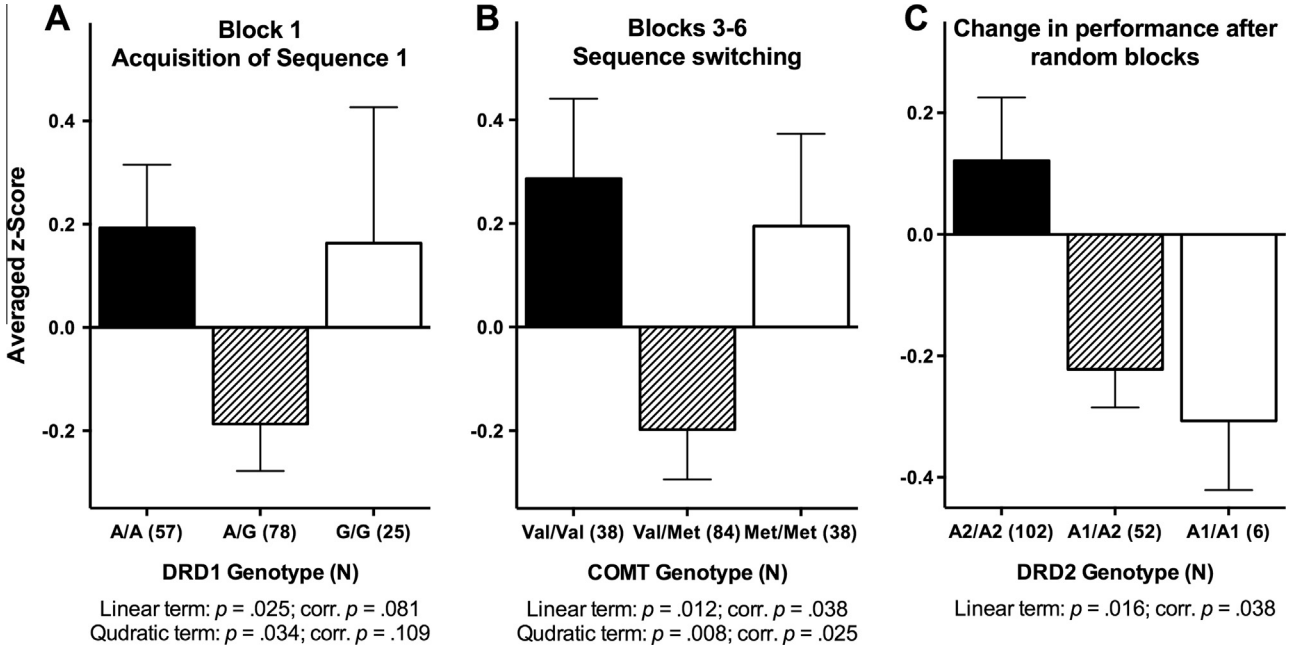

Fig. 3. Genotype effects on Sequence 1 acquisition in Block 1 (A), sequence switching performance in Blocks 3–6 (B), and performance disruption caused by random blocks (C). Error bars represent the standard error of the mean. The number of participants belonging to each genotype group is indicated in parentheses. The displayed significance *p* values are from the regression analyses reported in Sections 3.1.3–3.1.5.

behavioral data. However, although it did predict a modest interference effect following random blocks, it substantially underestimated it.

3.2.2. Genetic effects on estimated parameters

We also investigated if the genetic effects on performance (described above) were also accompanied by effects on the learning rate parameters estimated by our computational model. If so, our computational modelling might help us discover potential learning mechanisms that mediate the relationship between dopaminergic genes and behavioral performance. Regression analyses on the learning rate parameters estimated for each participant revealed an effect of the DRD1 genotype on αPos (Fig. 4, Panel A). The magnitude of the estimated αPos was positively associated with the number of DRD1 A alleles ($t(146) = 2.46$, uncorrected $p = .015$, corrected $p = .049$). In contrast, αNeg was associated with the DRD2 genotype (Fig. 4, Panel B). The number of DRD2 A2 alleles predicted a higher estimated αNeg parameter ($t(146) = 3.12$, uncorrected $p = .002$, corrected $p = .006$). There were no other genetic effects on either learning rate parameter (maximum $t(146) = 1.99$, uncorrected $p = .048$, corrected $p = .127$).

3.2.3. Relationship between the DRD1 and DRD2 genotypes, estimated parameters, and performance

Our computational modelling provides potential learning mechanisms that could explain the DRD1 and DRD2 behavioral effects reported earlier. The DRD1 A allele was not only associated with faster acquisition of Sequence 1 in Block 1 (though it was a modest effect), but also with a higher estimated αPos. Our modelling suggests that acquisition of a new sequence might strongly rely on the capacity to strengthen connections and, to a lesser extent, on the ability to weaken existing connections. Indeed, the correlation between the participants' performance in Block 1 correlated more strongly with their estimated αPos ($r = .84$) than with their estimated αNeg ($r = .35$; see Table 2). The two correlations were different from each other according to Williams' test (Williams, 1959; see also Steiger, 1980) ($t(158) = 8.60$, $p < .001$). Thus, according to this modelling, faster acquisition of a sequence relies on the capacity to strengthen appropriate connections rather than to weaken inappropriate connections.

The DRD2 polymorphism, on the other hand, was associated with performance recovery after random blocks and the estimated αNeg, the learning rate used to weaken incorrect connections. The A2 allele of the DRD2 polymorphism, which has been shown to be predictive of higher dopamine D2 receptor density, was associated with less interference after experiencing random blocks and with a higher estimated αNeg. Our modelling suggests that recovery from random blocks relies more heavily on the capacity to weaken, rather than strengthen, existing connections: The participants' performance after random blocks (i.e., on Blocks 8 and 12) positively correlated with αNeg, but not with αPos (see Table 2). The difference between the two correlations was significant ($t(158) = 2.44$, $p = .016$). Thus, our model predicts that the capacity to weaken existing connections is more important when recovering from the interference caused by random blocks than the capacity for strengthening connections, and there is a simple explanation for this prediction. In our modelling, random blocks caused strengthening of connections that were detrimental to the performance of the two sequences. This is because the four square locations lit up in random order, and some of the successive illuminations were not part of any sequence that had been trained. When a random block was then covertly switched to a sequence block, these irrelevant connections exerted a detrimental influence on the model's choices, and were subsequently weakened as feedback indicated they were incorrect. A high αNeg would allow faster pruning of the irrelevant connections that had formed during a random block, thus reducing the amount of interference they could cause. This might explain why the performance of participants with the A2/A2 DRD2 genotype did not decrease following random blocks. It is possible that their presumably higher D2 receptor densities caused faster weakening of the irrelevant connections that had formed during random blocks, allowing these participants to quickly return to a high performance level on subsequent sequence blocks.

3.2.4. Relationship between COMT genotype, sequence switching, and working memory

The COMT polymorphism was associated with sequence switching performance. Our modelling, however, could not capture the effect of the COMT polymorphism, as there were no reliable relationships between the estimated learning rate parameters and COMT genotype. It is possible that the capacity to flexibly switch between two learnt sequences does not involve learning mechanisms, or that it additionally involves working memory

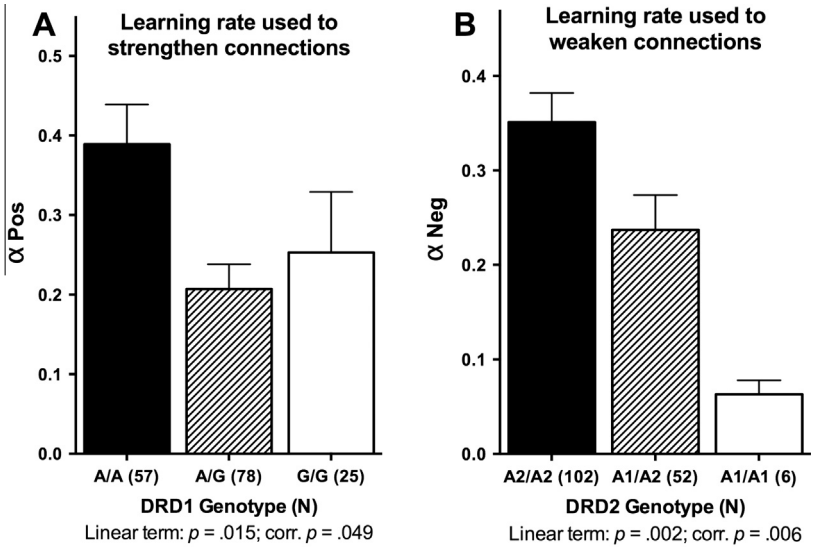

Fig. 4. Genetic effects on estimated learning rates used for strengthening (A) or weakening (B) connections. Error bars represent the standard error of the mean. The number of participants belonging to each genotype group is indicated in parentheses. The displayed significance p values are from the regression analyses reported in Section 3.2.2.

Table 2
Correlations between sequence learning performance *z*-scores and estimated αPos, αNeg, and visuo-spatial working memory. All correlations greater than.16 are significant at the .05 level, and all correlations greater than .26 are significant at the .001 level. * and † indicate that the two correlations are significantly different from each other.

	Acquisition of Sequence 1 Block 1	Sequence switching Blocks 3–6	Performance after random blocks Blocks 8 and 12	All sequence blocks Blocks 1–6, 8–10, 12
αPos	.84*	.43	.14†	.49
αNeg	.35*	.40	.36†	.51
Working memory	.26	.34	.15	.40

processes that retrieve context-appropriate representations from long-term memory and maintain them in a working memory buffer (e.g., Oberauer, Souza, Druey, & Gade, 2013). Indeed, Bo and Seidler (2009) reported a significant association between visuo-spatial working memory and sequence learning, a finding that we replicated in this study (see Table 2). Our simple learning model, however, could not simulate working memory processes, which might explain why it could not account for the COMT effects.

It has been argued that COMT could have an effect on learning performance because it might influence working memory capacity (Collins & Frank, 2012; Frank et al., 2007). Consistent with this hypothesis, Collins and Frank (2012) found that improving their reinforcement learning algorithm by adding a working memory buffer that could maintain the outcome of recent trials in working memory improved the fit of their model and could explain the enhanced performance they observed in participants with the Met/Met genotype. In their simulations, participants with the Met/Met genotype had a higher estimated working memory capacity, but not higher estimated learning rates. However, although Collins and Frank estimated the working memory capacity of their participants from their performance on the learning task, they did not directly measure their participants' working memory capacity using a test designed for this purpose, nor did Frank et al. (2007), but we did. We could thus directly test the hypothesis that the effect of the COMT polymorphism on learning is mediated by working memory. Yet, there was no association between COMT genotype and working memory (Table 1; if anything, the Met allele was associated with a slight decrease in working memory capacity). Even assuming that our Met/Met participants had a higher working memory capacity (that perhaps we did not detect with only one working memory test), it would still not explain the high learning performance of our Val/Val group, who, presumably, should have had the lowest working memory capacity. Hence, differences in working memory capacity are unlikely to explain the effects of the COMT polymorphism on sequence learning.

4. Discussion

We investigated whether polymorphisms that affect different aspects of dopamine function are associated with different aspects of sequence learning. We found that participants carrying the DRD1 A allele, associated with higher gene expression, learned a novel sequence faster. In our simulations, this advantage was afforded by a higher estimated αPos, the learning rate used to strengthen connections. The DRD2 polymorphism, on the other hand, was associated with performance after random blocks, with the A2 allele, associated with higher D2 receptor density, being correlated with better recovery of performance following random blocks. In our simulations, the advantage afforded by the A2 allele was explained by a higher estimated αNeg, which allowed more efficient pruning of the irrelevant connections formed during random blocks.

The DRD1 and DRD2 effects that we report here are consistent with the work described by Frank and colleagues (Frank & Hutchinson, 2009; Frank et al., 2007), despite differences in the learning tasks administered to the participants and the computational models used to simulate their performance. Frank and colleagues used a reinforcement learning task in which participants learned by trial-and-error which of two response choices was more likely to result in positive feedback. They found that individuals with a genotype associated with increased striatal D1 receptor function were more likely to select correct choices. In contrast, individuals with genotypes associated with increased D2 receptor density were more likely to avoid incorrect choices. They further modelled their participants' performance using a reinforcement learning algorithm that uses prediction error to update the value of alternative response choices, and found a relationship between the D1-related polymorphism and the learning rate used to increase the value of correct choices (analogous to αPos in our modelling). The DRD2 polymorphisms, on the other hand, had an effect on the learning rate used to decrease the value of incorrect choices (analogous to αNeg).

Taken together, our results and those of Frank and colleagues suggest that genetically determined differences in dopamine D1 and D2 receptor activity might affect synaptic plasticity along the direct striatonigral and indirect striatopallidal pathways, respectively, which are thought to be differentially involved in learning to select correct actions and to suppress incorrect ones (Apicella, Scarnati, Ljungberg, & Schultz, 1992; Frank, 2005; Kravitz & Kreitzer, 2012). It is hypothesized that D1-mediated long-term potentiation of synapses along the striatonigral pathway facilitates the selection of appropriate motor plans, which might explain why we observed a relationship between the DRD1 polymorphism and sequence acquisition in Block 1. In contrast, the D2-mediated plasticity is thought to strengthen the indirect pathway, which prevents response execution. This might explain why we found that the genotype associated with a higher D2 receptor density suffered less interference following random blocks and also had a higher estimated capacity to weaken irrelevant connections.

Our computational modelling revealed no differences in the estimated learning rate parameters between the COMT genotype groups, thus failing to simulate the behavioral effects of this polymorphism. Interestingly, Frank et al. (2007) also investigated the Val^{158}Met COMT polymorphism and found no relationship between this polymorphism and the estimated learning rates used to slowly adapt the value of choices, a result that mirrors our own. They argue that COMT does not influence midbrain phasic dopamine release, so it should not affect slow reinforcement learning in the basal ganglia. Instead, its influence on prefrontal tonic dopamine levels might affect working memory capacity, which could explain some of the observed effects of the COMT polymorphism on performance in learning tasks. Our results, however, are inconsistent with this hypothesis because we found no significant relationship between visuo-spatial working memory and COMT genotype. Our findings are consistent with previous research showing that this polymorphism is associated with individual differences in sequence learning in the absence of a significant effect on visuo-spatial working memory (Noohi et al., 2014).

The high learning performance level associated with our Val/Val group is not completely inconsistent with previous literature. A small study by Krugel et al. (2009) comparing 12 Val/Val

participants to 14 Met/Met participants found enhanced performance in the Val/Val group on a reversal learning task. Participants learned by trial and error which of four possible responses led to the highest monetary reward. Once they achieved a performance criterion, the contingencies were covertly switched and another response was associated with the largest payoff. The Val/Val genotype group reached the performance criterion more often and earned more than the Met/Met group. The Val/Val group also had larger BOLD responses in the ventral striatum in response to positive prediction errors (for payoffs larger than expected) and negative prediction errors (for payoffs smaller than expected), which were accompanied by larger estimated learning rate parameters when their choices were modelled by a reinforcement learning model.

It is possible that our task (and that used by Krugel et al., 2009) involves more than gradual learning of the appropriate stimulus–response contingencies. Because both tasks employed regular reversals in the stimulus–response mappings, participants could have learned not only the current mappings, but also the more general structure of the task in which these contingencies are regularly switched. There is evidence that the dopamine system is involved not only in learning contingencies by trial and error, but also in learning more general task rules. For example, when stimulus-reward contingencies are repetitively switched (e.g., one stimulus is rewarded and another is not in any given block of trials, and these contingencies are reversed several times over a series of blocks), animals seem to be able to learn the more general task environment. Once they detect a switch in the contingencies (e.g., one of the stimuli is followed by the opposite outcome), they are able to infer that the outcome of the other stimulus has changed as well before actually experiencing it. This ability to infer the outcome of the second stimulus without directly experiencing it seems to involve midbrain dopamine neurons (Bromberg-Martin, Matsumoto, Hong, & Hikosaka, 2010), and the prefrontal cortex (Pan, Sawa, Tsuda, Tsukada, & Sakagami, 2008).

COMT might be involved in this kind of learning of 'reversal sets' that were also present in our task. For example, once participants have learnt the two sequences, they could have performed the correct sequence in a given block until one of the sequence movements was followed by negative feedback. This very first negative feedback at the beginning of a switching block is sufficient to indicate that the sequence was switched, and would be sufficient to immediately retrieve the opposite 'sequence set' before all movements in the old sequence were performed. A pure learning model, on the other hand, requires the performance of all four movements in the old sequence in order to slightly extinguish these connections before it is able to switch to the new sequence. Hence, our model requires a minimum of four trials before switching to a new sequence. In contrast, some of our participants switched to the new sequence in fewer than four trials, which suggests that they were able to retrieve from memory and perform the new sequence before experiencing negative feedback for all the movements in the old sequence. They were thus capable of switching the 'sequence set' before extinguishing all the connections of the old sequence, whereas a pure learning model would not. COMT was the only polymorphism that showed some association with this sequence switching behavior: only 22.6% of participants with the Val/Met genotype could switch between the two sequences in fewer than four trials in Blocks 3–6, whereas this percentage was higher in the Met/Met (36.8%) and Val/Val (39.5%) groups (the Val/Met versus Met/Met comparison was not significant, $\chi^2(122) = 2.68$, $p = .101$; but the comparison between the Val/Met and Val/Val groups was very close to significance, $\chi^2(122) = 3.70$, $p = .054$). Hence, future computational modelling might require a representation of general task rules that can be learned in order to capture the effects of the COMT polymorphism on sequence switching.

Finally, the performance aspects that we assessed map onto different symptoms in disorders of the dopamine system, such as Parkinson's disease. Elucidating the relationship between genetic variations and these different performance aspects might help us understand the underlying mechanisms that generate movement and learning abnormalities in these disorders, as well as the effects of pharmacological manipulations that affect dopamine transmission. For instance, Parkinson's disease may be characterised not only by a deficit in performing movements, but also by a reduced ability to learn to select appropriate motor plans. Consistent with this learning deficit hypothesis, some studies reported that patients with Parkinson's disease have more difficulty acquiring a novel sequence of movements (Doyon, 2008; Nieuwboer, Rochester, Müncks, & Swinnen, 2009). We assessed acquisition of a novel sequence (measured by performance in Block 1) and discovered that those with a genotype associated with increased dopamine D1 receptor density exhibited faster acquisition. This suggests that treatments targeting D1 receptors may improve de novo learning in those suffering from an acquisition deficit. Furthermore, it has been suggested that Parkinson's disease in an unmedicated state might involve aberrant synaptic plasticity that can be detrimental to the performance of a previously learnt sequence, thus causing symptoms such as akinesia (Beeler, Petzinger, & Jakowec, 2013; Zhuang, Mazzoni, & Kang, 2013). This was simulated in our task by the inclusion of a block of random stimulus locations that caused participants to perform random movements, and potentially learn irrelevant stimulus–response connections. We found that individuals with a genotype associated with increased dopamine D2 receptor density exhibited an increased ability to initiate and perform a previously learnt sequence following a random block. Our simulations suggest that D2 receptor availability might contribute to recovering from the interference caused by a random block by increasing the rate with which irrelevant connections are pruned. These results suggest that, upon recovery of normal dopamine levels, treatments targeting dopamine D2 receptors might contribute to the weakening of aberrant connections that may have formed during the unmedicated state of Parkinson's disease, thus potentially improving the speed with which a previously learnt sequence of movements is initiated.

To conclude, our results suggest different roles for dopamine D1 and D2 receptors, and for COMT in sequence learning. Whereas dopamine D1 and D2 receptors seem to be involved in learning new stimulus–response mappings and weakening previously learnt connections, COMT seems to influence sequence switching possibly via non-learning mechanisms. We hope that our findings shed light on the specific contributions of dopamine transmission to sequence learning, and more generally to information processing during learning.

Acknowledgment

This work was supported by an Australian Research Council Discovery Early Career Researcher Award to IB (DE140100750).

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.nlm.2015.09.009.

References

Althaus, M., Groen, Y., Wijers, A. A., Minderaa, R. B., Kema, I. P., Dijck, J. D. A., & Hoekstra, P. J. (2010). Variants of the SLC6A3 (DAT1) polymorphism affect performance monitoring-related cortical evoked potentials that are associated with ADHD. *Biological Psychology, 85*, 19–32.

Althaus, M., Groen, Y., Wijers, A. A., Mulder, L. J., Minderaa, R. B., Kema, I. P., ... Hoekstra, P. J. (2009). Differential effects of 5-HTTLPR and DRD2/ANKK1 polymorphisms on electrocortical measures of error and feedback processing in children. *Clinical Neurophysiology, 120*, 93–107.

Apicella, P., Scarnati, E., Ljungberg, T., & Schultz, W. (1992). Neuronal activity in monkey striatum related to the expectation of predictable environmental events. *Journal of Neurophysiology, 68*, 945–960.

Armitage, P., Parmar, M. (1986). Some approaches to the problem of multiplicity in clinical trials. In *Proceedings of the XIIth international biometrics conference, seattle*.

Badgaiyan, R. D., Fischman, A. J., & Alpert, N. M. (2007). Striatal dopamine release in sequential learning. *Neuroimage, 38*(3), 549–556.

Badgaiyan, R. D., Fischman, A. J., & Alpert, N. M. (2008). Explicit motor memory activates the striatal dopamine system. *NeuroReport, 19*(4), 409–412.

Barr, C. L., Xu, C., Kroft, J., Feng, Y., Wigg, K., Zai, G., ... Kennedy, J. L. (2001). Haplotype study of three polymorphisms at the dopamine transporter locus confirm linkage to attention-deficit/hyperactivity disorder. *Biological Psychiatry, 49*(4), 333–339.

Batel, P., Houchi, H., Daoust, M., Ramoz, N., Naassila, M., & Goodwood, P. A. (2008). A haplotype of the DRD1 gene is associated with alcohol dependence. *Alcoholism, Clinical and Experimental Research, 32*(4), 567–572.

Beeler, J. A., Petzinger, G., & Jakowec, M. W. (2013). The enemy within: Propagation of aberrant corticostriatal learning to cortical function in Parkinson's disease. *Frontiers in Neurology, 4*, 134.

Bertolino, A., Fazio, L., Di Giorgio, A., Blasi, G., Romano, R., Taurisano, P., ... Sadee, W. (2009). Genetically determined interaction between the dopamine transporter and the D2 receptor on prefronto-striatal activity and volume in humans. *Journal of Neuroscience, 29*, 1224–1234.

Biehl, S. C., Dresler, T., Reif, A., Scheuerpflug, P., Deckert, J., & Herrmann, M. J. (2011). Dopamine transporter (DAT1) and dopamine receptor D4 (DRD4) genotypes differentially impact on electrophysiological correlates of error processing. *PLoS ONE, 6*, e28396.

Bilder, R. M., Volavka, J., Lachman, H. M., & Grace, A. A. (2004). The catechol-O-methyltransferase polymorphism: Relations to the tonic-phasic dopamine hypothesis and neuropsychiatric phenotypes. *Neuropsychopharmacology, 29*, 1943–1961.

Bo, J., & Seidler, R. D. (2009). Visuospatial working memory capacity predicts the organization of acquired explicit motor sequences. *Journal of Neurophysiology, 101*, 3116–3125.

Bors, D. A., & Stokes, T. L. (1998). Raven's advanced progressive matrices: Norms for first-year university students and the development of a short form. *Educational and Psychological Measurement, 58*, 382–398.

Bromberg-Martin, E. S., Matsumoto, M., Hong, S., & Hikosaka, O. (2010). A pallidus-habenula-dopamine pathway signals inferred stimulus values. *Journal of Neurophysiology, 104*, 1068–1076.

Burnham, K. P., & Anderson, D. R. (1998). *Model selection and inference*. NY: Springer-Verlag.

Chen, J., Lipska, B. K., Halim, N., Ma, Q. D., Matsumoto, M., Melhem, S., ... Weinberger, D. R. (2004). Functional analysis of genetic variation in catechol-O-methyltransferase COMT: Effects on mRNA, protein, and enzyme activity in postmortem human brain. *American Journal of Human Genetics, 75*, 807–821.

Collins, A. G. E., & Frank, M. J. (2012). How much of reinforcement learning is working memory, not reinforcement learning? A behavioral, computational and neurogenetic analysis. *European Journal of Neuroscience, 35*, 1024–1035.

Comings, D. E., & Blum, K. (2000). Reward deficiency syndrome: Genetic aspects of behavioral disorders. *Progress in Brain Research, 126*, 325–341.

Demiralp, T., Herrmann, C. S., Erdal, M. E., Ergenoglu, T., Keskin, Y. H., Ergen, M., & Beydagi, H. (2007). DRD4 and DAT1 polymorphisms modulate human gamma band responses. *Cerebral Cortex, 17*(5), 1007–1019.

Doyon, J. (2008). Motor sequence learning and movement disorders. *Current Opinion in Neurology, 21*, 478–483.

Dubey. S. D. (1985) Adjustment of *p*-values for multiplicities of intercorrelating symptoms. *Proceedings of the VIth international society for clinical biostatisticians*, Germany.

Dumontheil, I., Roggeman, C., Ziermans, T., Peyrard-Janvid, M., Matsson, H., Kere, J., & Klingberg, T. (2011). Influence of the COMT genotype on working memory and brain activity changes during development. *Biological Psychiatry, 70*, 222–229.

Eisenegger, C., Pedroni, A., Rieskamp, J., Zehnder, C., Ebstein, R., Fehr, E., & Knoch, D. (2013). DAT1 polymorphism determines L-DOPA effects on learning about others' prosociality. *PLoS ONE, 8*, e67820.

Epstein, L. H., Temple, J. L., Neaderhiser, B. J., Salis, R. J., Erbe, R. W., & Leddy, J. J. (2007). Food reinforcement, the dopamine D2 receptor genotype, and energy intake in obese and nonobese humans. *Behavioral Neuroscience, 121*, 877–886.

Frank, M. J. (2005). Dynamic dopamine modulation in the basal ganglia: A neurocomputational account of cognitive deficits in medicated and non-medicated Parkinsonism. *Journal of Cognitive Neuroscience, 17*, 51–72.

Frank, M. J., & Hutchinson, K. (2009). Genetic contributions to avoidance-based decisions: Striatal D2 receptor polymorphisms. *Neuroscience, 164*, 131–140.

Frank, M. J., Moustafa, A. A., Haughey, H. M., Curran, T., & Hutchinson, K. E. (2007). Genetic triple dissociation reveals multiple roles for dopamine in reinforcement learning. *PNAS, 104*, 16311–16316.

Fuke, S., Suo, S., Takahashi, N., Koike, H., Sasagawa, N., & Ishiura, S. (2001). The VNTR polymorphism of the human dopamine transporter DAT1 gene affects gene expression. *Pharmacogenomics Journal, 1*, 152–156.

Gabriel, S., Ziaugra, L., & Tabbaa, D. (2009). SNP genotyping using the sequenom MassARRAY iPLEX platform. *Current Protocols in Human Genetics*, 2.12.1–2.12.18.

Goldberg, T. E., Egan, M. F., Gscheidle, T., Coppola, R., Weickert, T., Kolachana, B. S., ... Weinberger, D. R. (2003). Executive subprocesses in working memory: Relationship to catechol-O-methyltransferase Val158Met genotype and schizophrenia. *Archives of General Psychiatry, 60*, 889–896.

Grace, A. A. (1991). Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: A hypothesis for the etiology of schizophrenia. *Neuroscience, 41*, 1–24.

Heinz, A., Goldman, D., Jones, D. W., Palmour, R., Hommer, D., Gorey, J. G., ... Weinberger, D. R. (2000). Genotype influences in vivo dopamine transporter availability in human striatum. *Neuropsychopharmacology, 22*, 133–139.

Ho, B. C., Wassink, T. H., O'Leary, D. S., Sheffield, V. C., & Andreasen, N. C. (2005). Catechol-O-methyl transferase Val158Met gene polymorphism in schizophrenia: Working memory, frontal lobe MRI morphology and frontal cerebral blood flow. *Molecular Psychiatry, 10*, 229–235.

Huang, W., & Li, M. D. (2009). Differential of dopamine D1 receptor gene (DRD1) is modulated by microRNA miR-504. *Biological Psychiatry, 65*, 702–705.

Huang, W., Ma, J. Z., Payne, T. J., Beuten, J., Dupont, R. T., & Li, M. D. (2008). Significant association of DRD1 with nicotine dependence. *Human Genetics, 123*, 133–140.

Jacobsen, L. K., Staley, J. K., Zoghbi, S. S., Seibyl, J. P., Kosten, T. R., Innis, R. B., & Gelernter, J. (2000). Prediction of dopamine transporter binding availability by genotype: A preliminary report. *American Journal of Psychiatry, 157*, 1700–1703.

Jocham, G., Klein, T. A., Neumann, J., von Cramon, D. Y., Reuter, M., & Ullsperger, M. (2009). Dopamine DRD2 polymorphism alters reversal learning and associated neural activity. *Journal of Neuroscience, 29*, 3695–3704.

Jonsson, E. G., Nothen, M. M., Grunhage, F., Farde, L., Nakashima, Y., Propping, P., & Sedvall, G. C. (1999). Polymorphisms in the dopamine D2 receptor gene and their relationships to striatal dopamine receptor density of healthy volunteers. *Molecular Psychiatry, 4*, 290–296.

Karabanov, A., Cervenka, S., de Manzano, O., Forssberg, H., Farde, L., & Ullen, F. (2010). Dopamine D2 receptor density in the limbic striatum is related to implicit but not explicit movement sequence learning. *Proceedings of the National academy of Sciences of the United States of America, 107*, 7574–7579.

Kass, R., & Raftery, A. (1995). Bayes factors. *Journal of the American Statistical Association, 90*, 773–795.

Kaufman, S. B., DeYoung, C. G., Gray, J. R., Jimenez, L., Brown, J., & Mackintosh, N. (2010). Implicit learning as an ability. *Cognition, 116*, 321–340.

Klein, T. A., Neumann, J., Reuter, M., Hennig, J., von Cramon, D. Y., & Ullsperger, M. (2007). Genetically determined differences in learning from errors. *Science, 318*, 1642–1645.

Kravitz, A. V., & Kreitzer, A. C. (2012). Striatal mechanisms underlying movement, reinforcement, and punishment. *Physiology, 27*, 167–177.

Krugel, L. K., Biele, G., Mohr, P. N. C., Li, S. C., & Heekaeren, H. R. (2009). Genetic variation in dopaminergic neuromodulation influences the ability to rapidly and flexibly adapt decisions. *Proceedings of the National academy of Sciences of the United States of America, 106*, 17951–17956.

Laruelle, M., Gelernter, J., & Innis, R. B. (1998). D2 receptors binding potential is not affected by Taq1 polymorphism at the D2 receptor gene. *Molecular Psychiatry, 3*, 261–265.

Law, D. J., Morrin, K. A., & Pellegrino, J. W. (1995). Training effects and working-memory contributions to skill and skill acquisition in a complex coordination task. *Learning and Individual Differences, 7*, 207–234.

Li, M. D., Ma, J. Z., & Beuten, J. (2004). Progress in searching for susceptibility loci and genes for smoking-related behaviour. *Clinical Genetics, 66*, 382–392.

Lonsdorf, T. B., Weike, A. I., Nikamo, P., Schalling, M., Hamm, A. O., & Ohman, A. (2009). Genetic gating of human fear learning and extinction: Possible implications for gene-environment interaction in anxiety disorder. *Psychological Science, 20*, 198–206.

Lynch, D. R., Mozley, P. D., Sokol, S., Maas, N. M. C., Balcer, L. J., & Siderowf, A. D. (2003). Lack of effect of polymorphisms in dopamine metabolism related genes on imaging of TRODAT-1 in striatum of asymptomatic volunteers and patients with Parkinson's disease. *Movement Disorders, 18*, 804–812.

Martinez, D., Gelernter, J., Abi-Dargham, A., van Dyck, C. H., Kegeles, L., Innis, R. B., & Laruelle, M. (2001). The variable number of tandem repeats polymorphism of the dopamine transporter gene is not associated with significant change in dopamine transporter phenotype in humans. *Neuropsychopharmacology, 24*, 553–560.

McPherson, J., & Burns, N. R. (2005). A speeded coding task using a computer-based mouse response. *Behavior Research Methods, 37*, 538–544.

Mill, J., Asherson, P., Browes, C., D'Souza, U., & Craig, I. (2002). Expression of the dopamine transporter gene is regulated by the 3′ UTR VNTR: Evidence from brain and lymphocytes using quantitative RT-PCR. *American Journal of Medical Genetics, 114*, 975–979.

Miller, G. M., & Madras, B. K. (2002). Polymorphisms in the 3′-untranslated region of human and monkey dopamine transporter genes affect reporter gene expression. *Molecular Psychiatry, 7*, 44–55.

Munafo, M. R., Clark, T. G., Johnstone, E. C., Murphy, M. F. G., & Walton, R. T. (2004). The genetic basis for smoking behavior: A systematic review and meta-analysis. *Nicotine & Tobacco Research, 6*, 583–597.

Nakamura, T., Ghilardi, M. F., Mentis, M., Dhawan, V., Fukuda, M., Hacking, A., ... Eidelberg, D. (2001). Functional networks in motor sequence learning: Abnormal topographies in Parkinson's disease. *Human Brain Mapping, 12*, 42–60.

Nettelbeck, T. J. (2001). Correlation between inspection time and psychometric abilities: A personal interpretation. *Intelligence, 29*, 459–474.
Neville, M. J., Johnstone, E. C., & Walton, R. T. (2004). Identification and characterization of ANKK1: A novel kinase gene closely linked to DRD2 on chromosome band 11q23.1. *Human Mutation, 23*, 540–545.
Nieuwboer, A., Rochester, L., Müncks, L., & Swinnen, S. P. (2009). Motor learning in Parkinson's disease: Limitations and potential for rehabilitation. *Parkinsonism & Related Disorders, 15S3*, S53–S58.
Nissen, M. J., & Bullemer, P. (1987). Attentional requirements of learning: Evidence from learning measures. *Cognitive Psychology, 19*, 1–13.
Noble, E. P., Noble, R. E., Ritchie, T., Syndulko, K., Bohlman, M. C., Noble, L. A., ... Grandy, D. K. (1994). D2 dopamine receptor gene and obesity. *International Journal of Eating Disorders, 15*, 205–217.
Noohi, F., Boyden, N. B., Kwak, Y., Humfleet, J., Burke, D. T., Müller, M. L., ... Seidler, R. D. (2014). Association of COMT val158met and DRD2 G>T genetic polymorphisms with individual differences in motor learning and performance in female young adults. *Journal of Neurophysiology, 111*, 628–640.
Nyman, E. S., Loukola, A., Varilo, T., Taanila, A., Hurtig, T., Moilanen, I., ... Peltonen, L. (2012). Sex-specific influence of DRD2 on ADHD-type temperament in a large population-based birth cohort. *Psychiatric Genetics, 22*, 197–201.
Oberauer, K., Souza, A. S., Druey, M. D., & Gade, M. (2013). Analogous mechanisms of selection and updating in declarative and procedural working memory: Experiments and a computational model. *Cognitive Psychology, 66*, 157–211.
Pan, X., Sawa, K., Tsuda, I., Tsukada, M., & Sakagami, M. (2008). Reward prediction based on stimulus categorization in primate lateral prefrontal cortex. *Nature Neuroscience, 11*, 703–712.
Pearson-Fuhrhop, K. M., Minton, B., Acevedo, D., Shahbaba, B., & Cramer, S. C. (2013). Genetic variation in the human brain dopamine system influences motor learning and its modulation by L-DOPA. *PLoS ONE, 8*, e61197.
Pohjalainen, T., Rinne, J. O., Nagren, K., Lehikoinen, P., Anttila, K., Syvalahti, E. K., & Hietala, J. (1998). The A1 allele of the human D2 dopamine receptor gene predicts low D2 receptor availability in healthy volunteers. *Molecular Psychiatry, 3*, 256–260.
Raczka, K. A., Mechias, M. L., Gartmann, N., Reif, A., Deckert, J., Pessiglione, M., & Kalisch, R. (2011). Empirical support for an involvement of the mesostriatal dopamine system in human fear extinction. *Translational Psychiatry, 1*, e12.
Raven, J. C., Court, J. H., & Raven, J. (1988). *Manual for Raven's progressive matrices and vocabulary scales (Section 4)*. London: H.K. Lewis.
Ritchie, T., & Noble, E. P. (2003). Association of seven polymorphisms of the D2 dopamine receptor gene with brain receptor-binding characteristics. *Neurochemical Research, 28*, 73–82.
Robertson, C., & Flowers, K. A. (1990). Motor set in Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry, 53*, 583–592.
Rosner, B. (1983). Percentage points for a generalized ESD many-outlier procedure. *Technometrics, 25*, 165–172.
Sakai, K., Hikosaka, O., Miyauchi, S., Takino, R., Sasaki, Y., & Pütz, B. (1998). Transition of brain activation from frontal to parietal areas in visuomotor sequence learning. *Journal of Neuroscience, 18*, 1827–1840.
Sankoh, A. J., Huque, M. F., & Dubey, S. D. (1997). Some comments on frequently used multiple endpoint adjustment methods in clinical trials. *Statistics in Medicine, 16*, 2529–2542.
Savitz, J., Solms, M., & Ramesar, R. (2006). The molecular genetics of cognition: Dopamine, COMT and BDNF. *Genes, Brain and Behavior, 5*, 311–328.
Schuck, N. W., Frensch, P. A., Schjeide, B.-M., Bisenack, J., Bertram, L., & Li, S.-C. (2013). Effects of aging and dopamine genotypes on the emergence of explicit memory during sequence learning. *Neuropsychologia, 51*, 2757–2769.
Schultz, W. (2013). Updating dopamine reward signals. *Current Opinion in Neurobiology, 23*, 229–238.
Schultz, W., Dayan, P., & Montague, R. (1997). A neural substrate of prediction and reward. *Science, 275*, 1593–1599.
Shen, W., Flajolet, M., Greengard, P., & Surmeier, D. J. (2008). Dichotomous dopaminergic control of striatal synaptic plasticity. *Science, 321*, 848–851.
Simon, J. R., Stollstorff, M., Westbay, L. C., Vaidya, C. J., Howard, J. H., & Howard, D. V. (2011). Dopamine transporter genotype predicts implicit sequence learning. *Behavioural Brain Research, 216*, 452–457.
Smillie, L. D., Cooper, A. J., & Pickering, A. D. (2011). Individual differences in reward prediction-error: Extraversion and feedback-related negativity. *Social Cognitive and Affective Neuroscience, 6*, 646–652.
Steiger, J. H. (1980). Tests for comparing elements of a correlation matrix. *Psychological Bulletin, 87*, 245–251.
Stice, E., Spoor, S., Bohon, C., & Small, D. M. (2008). Relation between obesity and blunted striatal response to food is moderated by Taq1A A1 allele. *Science, 322*, 449–452.
Thompson, J., Thomas, N., Singleton, A., Piggott, M., Lloyd, S., Perry, E. K., ... Court, J. A. (1997). D2 dopamine receptor gene (DRD2) Taq1 A polymorphism: Reduced dopamine D2 receptor binding in the human striatum associated with the A1 allele. *Pharmacogenetics, 7*, 479–484.
Tobler, P. N., Dickinson, A., & Schultz, W. (2003). Coding of predicted reward omission by dopamine neurons in a conditioned inhibition paradigm. *Journal of Neuroscience, 23*, 10402–10410.
Tsai, S. J., Yu, Y. W. Y., Chen, T. J., Chen, J. Y., Liou, Y. J., Chen, M. C., & Hong, C. J. (2003). Association study of a functional catechol-O-methyltransferase gene polymorphism and cognitive function in healthy females. *Neuroscience Letters, 338*, 123–126.
Urry, K., Burns, N., & Baetu, I. (2015). Accuracy-based measures provide a better measure of sequence learning than reaction time-based measures. *Frontiers in Psychology, 6*.
van de Giessen, E. M., de Win, M. M. L., Tanck, M. W. T., van den Brink, W., Baas, F., & Booij, J. (2009). Striatal dopamine transporter availability associated with polymorphisms in the dopamine transporter gene SLC6A3. *Journal of Nuclear Medicine, 50*, 45–52.
van Dyck, C. H., Malison, R. T., Jacobsen, L. K., Seibyl, J. P., Staley, J. K., Laruelle, M., ... Gelernter, J. (2005). Increased dopamine transporter availability associated with the 9-repeat allele of the SLC6A3 gene. *Journal of Nuclear Medicine, 46*, 745–751.
Vandenberg, S. G., & Kuse, A. R. (1978). Mental rotations, a group test of three dimensional spatial visualisation. *Perceptual and Motor Skills, 60*, 343–350.
VanNess, S. H., Owens, M. J., & Kilts, C. D. (2005). The variable number of tandem repeats element in DAT1 regulates in vitro dopamine transporter density. *BMC Genetics, 6*, 55.
Verde, Z., Santiago, C., Rodriguez Gonzalez-Moro, J. M., de Lucas, Ramos P., Lopez Martin, S., Bandrés, F., ... Gómez-Gallego, F. (2011). 'Smoking genes': A genetic association study. *PLoS ONE, 6*, e26668.
Williams, E. J. (1959). The comparison of regression variables. *Journal of the Royal Statistical Society: Series B, 21*, 396–399.
Witte, V. A., Kürten, J., Jansen, S., Schirmacher, A., Brand, E., Sommer, J., & Flöel, A. (2012). Interaction of BDNF and COMT polymorphisms on paired-associative stimulation-induced cortical plasticity. *Journal of Neuroscience, 32*, 4553–4561.
Wu, K., O'Keeffe, D., Politis, M., O'Keeffe, G. C., Robbins, T. W., Bose, S. K., ... Barker, R. A. (2012). The catechol-O-methyltransferase Val(158)Met polymorphism modulates fronto-cortical dopamine turnover in early Parkinson's disease: A PET study. *Brain, 135*, 2449–2457.
Zhang, Y., Bertolino, A., Fazio, L., Blasi, G., Rampino, A., Romano, R., ... Sadée, W. (2007). Polymorphisms in human dopamine d2 receptor gene affect gene expression, splicing, and neuronal activity during working memory. *Proceedings of the National academy of Sciences of the United States of America, 104*, 20552–20557.
Zhu, F., Yan, C. X., Wang, Q., Zhu, Y. S., Zhao, Y., Huang, J., ... Li, S. B. (2011). An association study between dopamine D1 receptor gene polymorphisms and the risk of schizophrenia. *Brain Research, 1420*, 106–113.
Zhu, F., Yan, C. X., Wen, Y. C., Wang, J., Bi, J., Zhao, Y. L., ... Li, S. B. (2013). Dopamine D1 receptor gene variation modulates opioid dependence risk by affecting transition to addiction. *PLoS ONE, 8*, e70805.
Zhuang, X., Mazzoni, P., & Kang, U. J. (2013). The role of neuroplasticity in dopaminergic therapy for Parkinson disease. *Nature Reviews Neurology, 9*, 248–256.