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Caudate nucleus reactivity predicts perceptual learning rate for visual feature conjunctions

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ABSTRACT

Useful information in the visual environment is often contained in specific conjunctions of visual features (e.g., color and shape). The ability to quickly and accurately process such conjunctions can be learned. However, the neural mechanisms responsible for such learning remain largely unknown. It has been suggested that some forms of visual learning might involve the dopaminergic neuromodulatory system (Roelfsema et al., 2010; Seitz and Watanabe, 2005), but this hypothesis has not yet been directly tested. Here we test the hypothesis that learning visual feature conjunctions involves the dopaminergic system, using functional neuroimaging, genetic assays, and behavioral testing techniques. We use a correlative approach to evaluate potential associations between individual differences in visual feature conjunction learning rate and individual differences in dopaminergic function as indexed by neuroimaging and genetic markers. We find a significant correlation between activity in the caudate nucleus (a component of the dopaminergic system connected to visual areas of the brain) and visual feature conjunction learning rate. Specifically, individuals who showed a larger difference in activity between positive and negative feedback on an unrelated cognitive task, indicative of a more reactive dopaminergic system, learned visual feature conjunctions more quickly than those who showed a smaller activity difference. This finding supports the hypothesis that the dopaminergic system is involved in visual learning, and suggests that visual feature conjunction learning could be closely related to associative learning. However, no significant, reliable correlations were found between feature conjunction learning and genotype or dopaminergic activity in any other regions of interest.

Introduction

Dopamine and learning

Understanding the mechanisms that subserve visual perceptual learning is a matter of substantial current interest (Roelfsema et al., 2010; Seitz and Dinse, 2007; Seitz and Watanabe, 2005). Several lines of evidence point to neuromodulatory systems, particularly the cholinergic and dopaminergic systems, as likely sources of a neural signal that facilitates learning. The activity of both the cholinergic and dopaminergic systems of the brain is known to be correlated with the salience (either physical or motivational) of stimuli in the environment (for recent reviews, see Bromberg-Martin et al., 2010; Noudoost and Moore, 2011a; Schultz, 2010). Moreover, both systems are known to influence synaptic plasticity (Bakin and Weinberger, 1996; Bao et al., 2001; Kilgard and Merzenich, 1998; Seol et al., 2007; Shen et al., 2008). Therefore, the activity of acetylcholine- and dopamine-releasing neurons would serve as a useful guide to the presence of important stimuli in the environment, and could have the capacity to directly enable the synaptic reweighting process thought to underlie learning.

Dopamine is synthesized primarily within the substantia nigra pars compacta (SNpc) and ventral tegmental area (VTA) (Björklund and Dunnett, 2007). Axons from these areas project primarily to the dorsal striatum (caudate/putamen), the ventral striatum (nucleus accumbens), and the frontal cortex (Björklund and Dunnett, 2007). These SNpc and VTA dopaminergic neurons are known to discharge bursts of dopamine into the striatum and frontal cortex in response to behaviorally relevant stimuli, particularly those related to unexpected rewards (Schultz et al., 1997). Dopaminergic signaling has been implicated in mediating visual attention directly and indirectly via frontal visual areas such as the frontal eye fields, although cortical dopaminergic projections do not project posteriorly enough to reach primary sensory areas (Noudoost and Moore, 2011b).

There is some indirect evidence that dopamine plays a role in perceptual learning. Perceptual learning on a tactile discrimination

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task is facilitated by dopamine agonists and inhibited by dopamine antagonists, which also modulate activation strength in sensory cortex during learning (Pleger et al., 2009). In macaques, dopamine antagonists similarly impair visual category learning (Turchi et al., 2008, 2010). Disorders that affect dopamine availability also appear to influence perceptual learning. Patients with schizophrenia (which is linked to elevated dopamine levels) actually perform better than non-patients on some visual learning tasks (Norton et al., 2011). Conversely, patients with Parkinson's disease (which results from a loss of dopamine producing neurons in the substantia nigra) have a reduced capacity to learn efficient detection of targets on visual search tasks, even for highly practiced categories of stimuli (Uc et al., 2006; van Asselen et al., 2009), suggesting that visual learning can be negatively affected by dopamine deficiency.

Together, these lines of evidence suggest that individual differences in dopamine availability might be associated with differences in visual perceptual learning, similar to the strong evidence that the acetylcholine system influences visual perceptual learning (Beer et al., 2013; Rokem and Silver, 2010, 2013). However, to date, no direct human evidence for dopaminergic influences on visual learning has been reported. Here we test the hypothesis that dopamine availability influences visual perceptual learning by investigating the relationship between dopaminergic function and learning rate on a visual feature conjunction search task, in which observers learn to perceive a specific conjunction of visual features (color and position) more efficiently.

Neuroimaging correlates of dopamine release

The dopamine-producing VTA and SN nuclei are small structures in an area of the midbrain highly susceptible to imaging artifacts, so activity within them cannot be reliably measured with standard fMRI (D'Ardenne et al., 2008). However, the striatal regions to which the VTA and SN project are much larger and more amenable to imaging, and activity within them tends to parallel the activity of the dopaminergic nuclei of the midbrain (Schott et al., 2008). Therefore, almost all human neuroimaging studies of dopaminergic signaling focus on these target areas: the dorsal striatum (including the caudate and putamen), the ventral striatum (nucleus accumbens), and, in some cases, the prefrontal cortex, which also receives dopaminergic afferents. The degree to which these dopamine-receiving regions are activated in response to rewarding stimuli varies between individuals (Cohen et al., 2005; Hahn et al., 2011; Koch et al., 2010; Santesso et al., 2008). Clearance of dopamine from prefrontal synapses tends to proceed much more slowly than at striatal synapses (on the order of tens of seconds vs. milliseconds) (Cass and Gerhardt, 1995). Therefore, under the conditions of fMRI involving frequent, repeated reinforcement events, the more transient signal from striatal dopamine targets likely provides a more direct reflection of dopaminergic activity. We therefore selected the three striatal areas (caudate, putamen, and nucleus accumbens) as regions of interest (ROIs) for the present experiment, where activity could be reasonably expected to reflect dopaminergic signaling.

Genetic influences on dopaminergic signaling

There exist common, known variations in the genetic code for several proteins which affect dopaminergic signaling at the synaptic level (Cohen et al., 2005; Dreher et al., 2009; Frank et al., 2007; Hahn et al., 2011). Specifically, variations of genes coding for dopamine receptors and transporters have been associated with differences in behavior and gross-level neural activity evoked by rewarding stimuli (Cohen et al., 2005; Dreher et al., 2009; Frank et al., 2007; Hahn et al., 2011; Krugel et al., 2009). The known characteristics of several of these genes indicate a potential relevance for visual feature conjunction learning processes.

A single nucleotide polymorphism (SNP) in the DARPP-32 gene (rs907094) affects the potency of synaptic plasticity following striatal D1 receptor activation (Frank et al., 2007). Individuals with the homozygous A/A nucleotide polymorphism have been shown to be better at probabilistic reward learning than individuals carrying G nucleotides (Frank et al., 2007). The three genotypes are unevenly distributed across the population; in a Caucasian reference sample (Utah residents with ancestry from northern and western Europe; hereafter abbreviated CEU), reported frequencies are G/G = 5.3%, A/G = 28.3%, and A/A = 66.4% (International HapMap Consortium, 2003; Sherry et al., 2001).

Similar SNPs exist in the COMT gene, which codes for catechol-O-methyltransferase, an enzyme that deactivates dopamine in the synaptic cleft, and influences the efficacy of enzymatic degradation of dopamine (Dreher et al., 2009). One SNP in particular (rs4680) is a G to A substitution that results in a valine to methionine amino acid change at codon 158. The presence of a G allele at this position is associated with more efficacious degradation of dopamine, hence, lower average concentrations of dopamine in synapses (Dreher et al., 2009). Frequencies of the three genotypes in the CEU population are: A/A = 24.8%, A/G = 46.0%, and G/G = 29.2% (International HapMap Consortium, 2003; Sherry et al., 2001).

The DRD2 (Taq1a) SNP (rs1800497) is associated with individual differences in D2 receptors. Carriers of the T allele at the site of the SNP express fewer D2 receptors in the brain (Frank et al., 2007). Thus, the presence of a T allele may be associated with lossier dopaminergic signaling (Frank et al., 2007). Distributions of the different SNP types in the CEU sample are: C/C = 66.4%, C/T = 28.3%, and T/T = 5.3% (International HapMap Consortium, 2003; Sherry et al., 2001).

Another variable gene associated with individual differences in dopamine is the dopamine active transporter (DAT) gene SLC6A3. This gene codes for the dopamine transporter, which pumps dopamine back into presynaptic terminals after it is released, affecting the synaptic dynamics of dopaminergic signaling by modulating the rate of dopamine reuptake (Dreher et al., 2009). The common genetic variation of this gene is associated not with a SNP, but with a variable number tandem repeat (VNTR) at the 40-bp element of the gene. At this location, a particular sequence of nucleotides is repeated a variable number of times (from 3 to 13, but most commonly about 10 times). Population frequencies are not readily available for a Caucasian sample, but reported frequencies from blood donors in Oman are that 33.2% carry 9 repeats and 60.9% carry 10 repeats, with other repetition numbers carried by a few individuals (Simsek et al., 2005). Individuals with fewer repeats express fewer dopamine transporters and therefore have slower dopamine reuptake, making them more sensitive to reward stimuli, both behaviorally and neurally (Dreher et al., 2009; Hahn et al., 2011).

Experimental rationale and design

Individuals show substantial variation in the rate at which they learn to perceive visual feature conjunctions efficiently (Frank et al., 2015). If dopaminergic signaling contributes to a mechanism for learning of visual feature conjunctions, then individuals with high reinforcement-sensitivity in the dopaminergic system and genetic polymorphisms that increase efficacy of dopamine neurotransmission would be expected to learn faster than individuals scoring lower on those measures. The present experiment uses a correlational approach, with a holdout sample (i.e., a second, independent group of participants with whom replicability of positive results observed in the experimental group can be assessed), to test whether individual differences in the dopaminergic system, namely, reward-reactivity of dopamine-target regions (specifically, the striatum, comprising the caudate nucleus, putamen, and nucleus accumbens, where activity most directly parallels dopamine release from the VTA and SN) and genotype for particular dopamine receptor and transporter variants (the four described above), are correlated with the rate at which individuals learn visual feature conjunctions.

Materials and methods

Participants

In total, 36 Dartmouth students were recruited as members of the main experimental group. Three did not attend the post-training session in which demographic information was collected, so their demographic information is unavailable. For the remaining 33 participants, 18 were females, and the average age was 19.7 (SD = 1.3).

A non-overlapping group of 24 different participants were in the holdout sample for the visual search training and genotyping analyses. The holdout sample participants were members of the main experimental sample in several behavioral experiments to be published elsewhere (Reavis, Frank, & Tse, in preparation). Correlation analyses for the holdout sample were performed separately from those for the experimental sample.

All participants gave written informed consent and received course credit or monetary compensation for their participation. The experiment was approved by the Dartmouth Committee for the Protection of Human Subjects Institutional Review Board.

Design and procedure

The overall goal of the experiment was to identify dopamine-related correlates of conjunction learning rate. Learning rate was measured across seven sessions of training, within two weeks, on a visual search for a particular conjunction of features among similar distractors. Learning rate on this visual search task, as described more precisely below, served as the outcome measure in all correlational analyses.

Two different classes of putative dopaminergic variables were measured in the same participants, shortly after the visual search training: (1) neural response magnitudes to positive versus negative feedback on an orthogonal mental math task in brain areas known to be targeted by dopaminergic neurons (measured using fMRI), and (2) genetic polymorphisms that influence dopaminergic signaling (measured via genotyping).

Possible relationships between these three classes of measurements – genes, brain, and behavior – were investigated using subject-wise correlations. Because of the very exploratory nature of the genetic association component of the study, and the need to attempt multiple statistical comparisons in a relatively small experimental sample that might not be representative of the population, we also collected genetic samples from an independent holdout sample: participants who had trained on the same search task (or slight variations upon it) during other behavioral experiments. Use of a holdout sample is an alternative to statistical threshold corrections (e.g., the Bonferroni method) in instances when many exploratory statistical tests are required. We designed our experiment using a holdout sample so we could appropriately conduct various statistical tests on the main experimental sample without α-correction. Instead, we obtained the holdout sample so we could independently confirm or disconfirm any significant correlations obtained in the main experimental sample between learning rate and genotype. Using this method, only positive statistical findings from the experimental sample that are also replicated in the holdout sample are properly construed to be statistically significant.

For the MRI-based investigation of brain-behavior relationships, which was less exploratory, we employed a more conventional approach: we did not collect a holdout sample of MRI data, but instead corrected for multiple comparisons using the Bonferroni method in an ROI-based analysis with three areas of interest (yielding Bonferroni-corrected α levels of 0.0167).

Across all three types of data, and both the experimental and holdout groups, we assessed the presence of outliers and possible need for normalization (either of which might spuriously inflate obtained correlations). All continuous measures (i.e., all measures but individual genotype assays) were plotted on a histogram and visually inspected for normality and outliers. Participants with a score more than three standard deviations from the mean on a particular measure were excluded from group-level analyses utilizing that measure. Such outliers were rare, and are identified in the Results section for each analysis.

Visual search training

Participants completed seven sessions of training on a search task for a conjunction of visual features very similar to one utilized previously (Frank et al., 2014). Participants were asked to complete the seven sessions within two weeks.

Search stimuli were bisected disks that were half red and half green. Participants searched for a target disk (red on the left, green on the right) among distractors with horizontally reversed colors (green on the left, red on the right) while fixating on a central point (see Fig. 1 for an example search array). Fixation was monitored continuously using a head-mounted, video-based Eyelink2 eye-tracking system (SR Research, Ontario). The red and green hues of the search stimuli were made isoluminant for each participant using a standard flicker fusion technique.

Each session consisted of 120 trials (lasting approximately 15 min). Each trial contained between 2 and 32 search stimuli arranged in four concentric rings around a central fixation point. Stimuli in the four rings were scaled by eccentricity according to an estimate of the cortical magnification factor (Duncan and Boynton, 2003). Placeholder rings appeared around all 32 positions continuously, even when only some positions contained search stimuli.

Participants' task was a five-alternative forced-choice: they were instructed to indicate as quickly and accurately as possible which ring the target appeared in using the 1–4 number keys, or to press the spacebar if there was no target (20 catch trials appeared in each session). Stimuli remained on the screen until a response was made, jittering slightly within the placeholder rings every 100 ms to counteract perceptual fading due to retinal ganglion cell adaptation. After each response, when the search stimuli disappeared, the fixation point changed color to provide feedback about the response: a green dot indicated a correct response and a red dot an incorrect response.

Learning rate for each participant was calculated in the following manner. Within each visual search training session, a linear function was fitted to describe the relationship between the number of items in the search array and reaction time. The slope of this function (the search slope), indicating processing time per item, was adjusted according to the participant's accuracy score for that session by dividing the

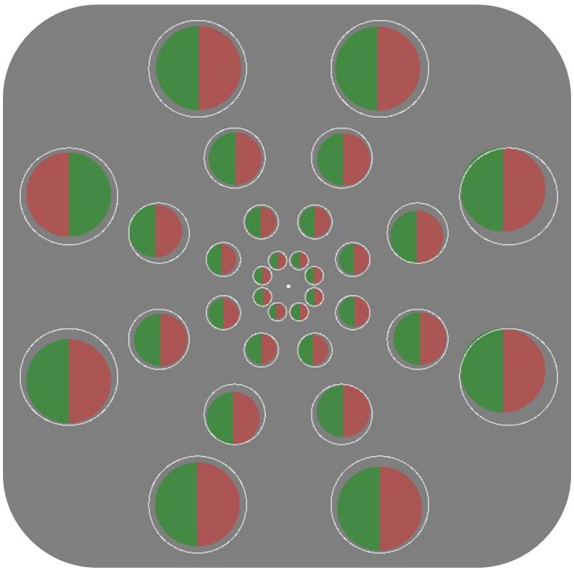

Fig. 1. Example search array with a target in the outermost ring.

search slope by percentage correct (Townsend and Ashby, 1978). In this way, sessions with fast processing times-per-item but low accuracy would have slower processing times-per-item entered into the final analysis. A power function was fitted to these adjusted processing times, over sessions. The slope of this power function was used as the index of learning rate for that participant in all correlational analyses.

Genotyping

Buccal cell samples were collected using Isohelix Buccal Swabs (Cell Projects, Ltd.; Kent, England). DNA was extracted from the samples using a Buccalyse kit, according to standard procedures (Cell Projects, Ltd.; Kent, England). Quant-It PicoGreen dsDNA reagent (Life Technologies; Carlsbad, Cal.) was used to determine the concentration of DNA in each sample. 5 ng of DNA was isolated for each genotyping reaction, except in two participants where concentrations in the extracted sample were less than 1 ng/μl, for whom 3 ng was used.

Each SNP genotyping assay was performed using 12.5 μl of Taqman Universal Master Mix II, no UNG (Life Technologies; Carlsbad, Cal.), 1.25 μl of 20× primer mix, and 11.25 μl of DNA template. PCR reactions were heated to 95 °C for 10 min, followed by 50 cycles of 95 °C for 15 s then 60 °C for 90 s. Analysis was performed using an Applied Biosystems 7500 Fast real-time PCR system (Life Technologies; Carlsbad, Cal.).

The VNTR genotyping assay was performed via a fragment analysis technique. Labeled (with both 5′-FAM blue and 5′-HEX green fluorescence) and unlabeled primers were obtained from Integrated DNA Technologies (Coralville, Iowa), using published sequences (Simsek et al., 2005). Extracted buccal swab samples were normalized to a concentration of 5 ng/μl, and 3 μl of this template was used in each PCR reaction. PCR reactions also contained 1× PCR buffer II, 0.2 mM dNTP mix, 1.5 mM $MgCl_2$, 5% DMSO, 0.2 μM of each primer and 0.02 units of AmpliTaq Gold, in the final concentration (Life Technologies; Carlsbad, Cal.). This mixture was heated to 94 °C for 3 min, then cycled through 35 iterations of 94 °C for 45 s, 67 °C for 60 s, then 72 °C for 30 s. After the final cycle, the temperature was held at 72 °C for an additional 5 min, then chilled to 4 °C. Prior to analysis, 1 μl of PCR product was mixed with 10 μl of Hi-Di Formamide and 0.25 μl 500Rox (Life Technologies; Carlsbad, Cal.), heated to 95 °C for 5 min, then chilled on ice for 5 min. These samples were analyzed on an Applied Biosystems 3500 Genetic Analyzer (Life Technologies; Carlsbad, Cal.). GeneMapper software was utilized to analyzed the results (Life Technologies; Carlsbad, Cal.). Blue (FAM) peaks were used for the primary analysis; green (HEX) peaks were used to verify the results.

The discrete categorical variables of genotype for each marker were converted into a continuous variable to test for potential correlations between dopaminergic genotype and learning rate or brain activity. First, at each SNP we counted the number of alleles coding for the version of the gene associated with enhanced dopaminergic signaling (e.g., expression of more dopamine receptors, or less effective enzymatic degradation of dopamine within the synaptic cleft). Thus, for each SNP, each participant scored 0, 1, or 2. Similarly, the VNTR results were converted into an index form. The modal (and maximal) observed number of repeats of the VNTR on each copy of the gene was 10 (i.e., 20 repeats total). Fewer repeats were associated with higher dopamine availability due to lower expression of the dopamine active transporter (DAT). Therefore, DAT genotype was indexed as the number of repeats less than 20. This resulted in a DAT index with a range of 0 to 3, with smaller numbers being more common. These index values for individual genes were then combined into a single index score for each participant, which corresponded to the sum of scores across the four genetic markers. Thus, individuals with higher index scores would be expected to have more robust dopaminergic signaling in general. The index score was used as the primary measure in each correlational analysis. The general approach of calculating a continuous index score via a linear sum of 'dopaminergic efficacy alleles' has been used successfully in previous investigations of the relationship between dopaminergic genotype and the magnitude of striatal responses to primary and secondary reward stimuli, albeit with a different set of dopaminergic genes (Nikolova et al., 2011; Stice et al., 2012).

MRI

Task and scanning procedure

Participants took part in a scan session after the end of their visual search training. During the scan session, they completed four functional imaging runs of the mental math task described below. Two high resolution anatomical scans were also collected.

Each task run contained 32 trials of a mental math task. On each trial, participants viewed a math problem and four possible responses, one of which was correct. Plausible incorrect responses were generated by replacing a randomly chosen numeral of the correct response with a different random value. There were four types of math problems: addition, subtraction, multiplication, and division. Each run contained an equal number of each trial type, in a random order. The difficulty of each type of problem was constantly adjusted using four staircase procedures to keep participants' performance on each near 50% correct. In the staircase procedure, difficulty was increased or decreased after each trial by adding or deleting a place value to one of the operands presented on the next trial of that type. These difficulty adjustments carried over within a run and across run breaks.

In each trial, the math problem to be solved appeared for up to 4 s near the center of the screen, above a countdown timer, 'REMAINING TIME:', which ticked down from 4 s to 0, in steps of 1 s. The four multiple-choice responses appeared simultaneously at the top, bottom, left, and right of the screen, in the same arrangement as the four buttons on the response box. Participants were asked to respond as quickly as possible to each question, but also accurately. Immediately after each response, the stimuli disappeared and were replaced by a fixation cross in the center of the screen. Feedback appeared after a delay. On half of the trials (counterbalanced), the feedback appeared at the onset of the first TR after the four-second trial period. On the other half, feedback was delayed by an additional 2 s. Thus, feedback onset was temporally jittered relative to responses within a possible range of 0 to 6 s (i.e., up to 4 s of the trial period following the response, plus 0 to 2 s). Feedback was presented textually in the center of the screen: 'CORRECT', 'INCORRECT', or 'TOO SLOW', were the possible feedback types. All feedback presentations lasted 2 s. Each feedback presentation was followed by a variable inter-trial delay of 2, 4, 6, or 8 s, during which time only a fixation cross was displayed. A schematic of the trial structure is shown in Fig. 2.

All scanning took place on a Philips Achieva 3-Tesla MRI scanner with a 32 channel head coil at the Dartmouth Brain Imaging Center. Functional scans were conducted using standard Echo-Planar Imaging (EPI) sequences with a 2-second TR (time to repeat), 35 ms TE (time to echo), and 90° flip-angle. EPI volumes contained 80 × 80 × 35 voxels at 3 mm isotropic resolution and no inter-slice gap. Each run contained 195 TRs (i.e., each run lasted approximately 6.5 min). Anatomical scans used a standard Magnetization-Prepared Rapid Gradient-Echo (MP-RAGE) sequence. The MP-RAGE volumes spanned 256 × 256 × 220 voxels at 1 mm isotropic resolution. They were collected using an 8.176 ms TR, 3.72 ms TE, and 8° flip-angle.

Analysis

Anatomical regions of interest were localized for each participant using automatic subcortical segmentation in FreeSurfer, via the standard processing pipeline (Fischl et al., 2002, 2004). The segmentation was performed on an average of the two high-resolution anatomical scans of each participant. Volumetric ROI masks obtained from FreeSurfer were projected into the analytical space of the first anatomical scan using a transformation matrix computed via FSL FLIRT (Jenkinson et al., 2002).

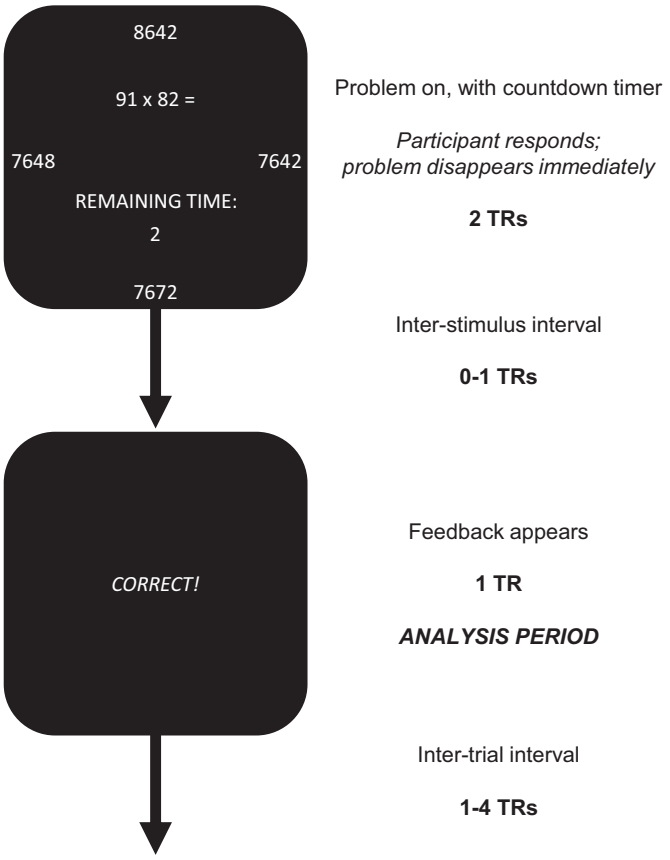

Fig. 2. Schematic representation of the trial structure.

Functional data were analyzed in FSL using a standard processing pipeline (Jenkinson et al., 2012; Smith et al., 2004; Woolrich et al., 2009). Data from each run was preprocessed using the following steps. Motion correction was performed via MCFLIRT (Jenkinson et al., 2002). Functional scans were brain-extracted using BET (Smith, 2002). The data were smoothed with a 5 mm full-width at half-maximum Gaussian kernel and high-pass filtered with a 100 second cutoff to compensate for signal drift. No low-pass filtering or slice-timing correction was applied.

The four functional runs for each participant were then concatenated into a single file. A mean functional volume was computed for each run, over time. Spatial transformations to bring all runs into alignment with the mean image of the first run were computed using the mean volumes from each of the other scans (two through four) and applied to all volumes. The intensity of each voxel was normalized independently by adjusting the mean intensity of the voxel across each run to match the intensity of the mean volume of the first run.

A general linear model (GLM) analysis was then performed on the concatenated data files using FSL FEAT (Woolrich et al., 2001). Four explanatory variables (regressors) were modeled by convolving each event with a double-gamma hemodynamic response function: the period of active problem solving, the feedback-anticipation phase (between response and feedback), the feedback delivery phase on correct trials, and the feedback delivery phase on incorrect trials. No-response trials where the participant failed to respond within the four-second problem-solving period and received the feedback 'TOO SLOW' were included in the model of the feedback delivery phase for incorrect trials.

The GLM contrast of interest was between positive and negative feedback delivery. A comparison of parameter estimate (COPE) value, in arbitrary units, was computed for each voxel for this contrast. Larger COPE values correspond to a greater difference between positive and negative feedback delivery than smaller COPEs. The resulting COPE maps were projected into the volumetric space of the participant's first anatomical scan (i.e., the same space as the transformed volumetric ROIs) using a transformation matrix previously computed with FLIRT. The average COPE score within each bilateral ROI was then computed. These average COPE scores were used in subsequent correlational analyses.

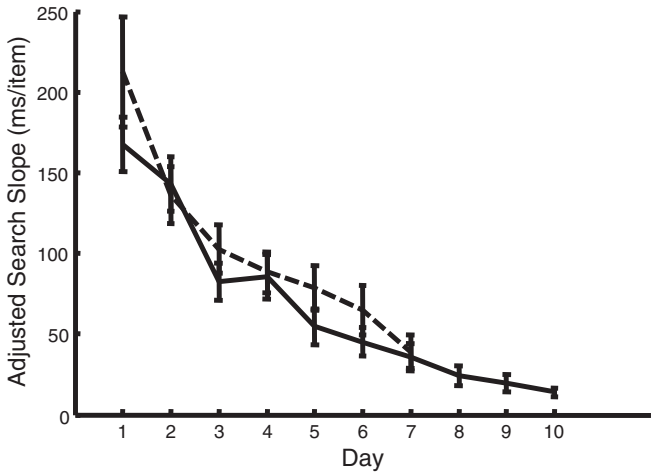

Fig. 3. Learning in the main group (solid line) and holdout group (dashed line). Performance improved significantly over time for members of both groups.

Results

Participants

In the main experimental sample of 36 participants, not all participants completed all parts of the experiment, so the *N*s of different analyses vary slightly. The exact number of participants is listed in each subsection when fewer than 36. All 24 holdout sample participants are included in each holdout analysis.

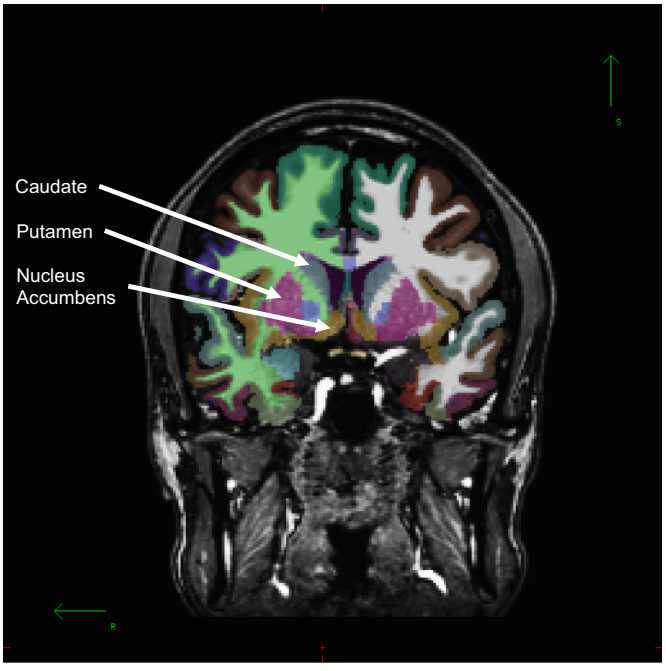

Fig. 4. Example FreeSurfer segmentation of a representative participant, showing the three striatal ROIs on a coronal slice (radiological coordinates).

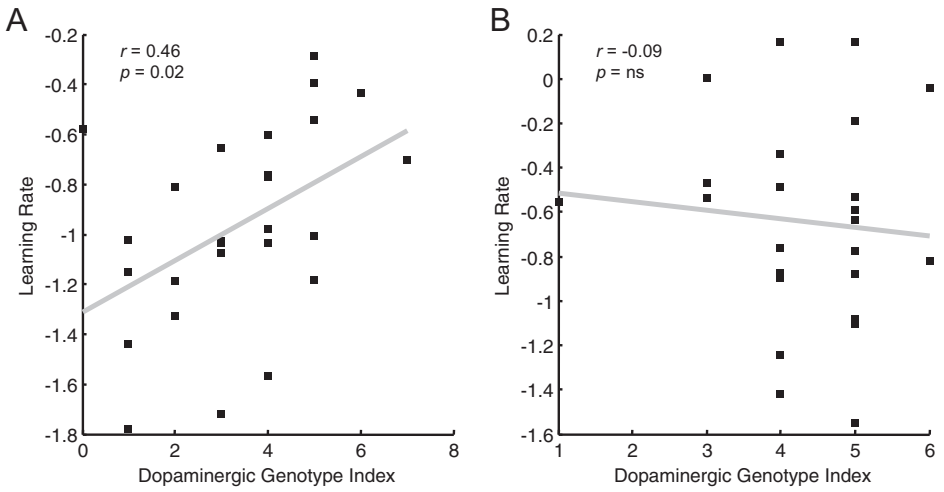

Fig. 5. Gene–behavior correlations: overall genotype index. Panel A shows the experimental group. In the experimental group, there was a significant correlation in the opposite direction of the experimental prediction: individuals with genetic markers of enhanced dopaminergic function learned more slowly (i.e., had less negative slopes) than those with markers of attenuated dopaminergic function. Panel B shows the holdout group. In the holdout group, there was no significant correlation between genetic markers of dopaminergic function and learning rate.

Visual search training

The main experimental group demonstrated significant conjunction learning: the average slope of the power functions describing participants' learning rates was significantly smaller than zero, $t(35) = -9.43$, $p < 0.001$, Cohen's $d = 3.19$ (see Fig. 3).

The distribution of learning rates was normal. One outlier participant's rate of learning was more than three standard deviations

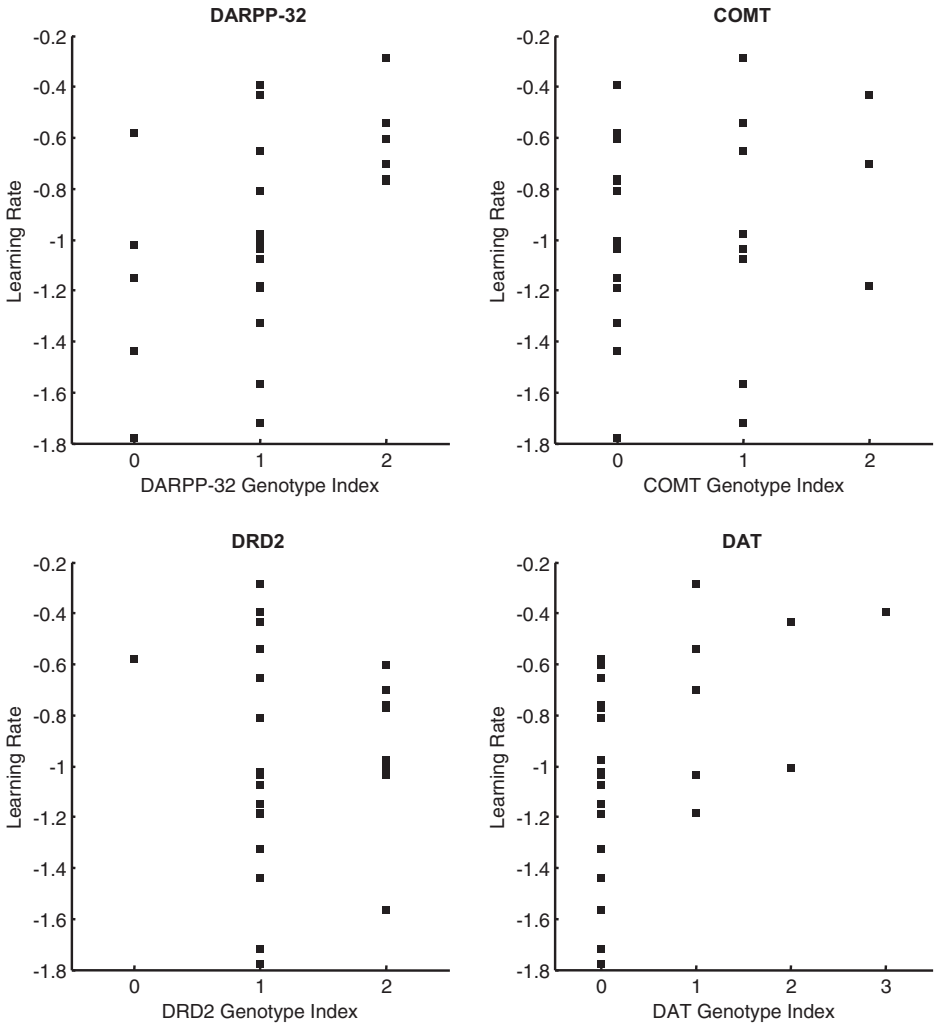

Fig. 6. Individual gene–behavior correlations in the experimental group. Only DARPP-32 was significantly related to learning rate (at an uncorrected statistical threshold).

faster than all others'. This person was removed from all subsequent analyses to avoid outlier-driven correlations.

As in the main sample, participants in the holdout sample showed significant learning over time. Slopes of the power functions fitted to participants' adjusted search slopes over time were significantly less than zero, on average, $t(23) = -6.58$, $p < 0.001$, Cohen's $d = 2.74$ (see Fig. 3). As in the main experimental sample, the distribution of learning rates in the holdout sample was normal. There were no outliers.

Genotyping

There were 27 participants in the main experimental sample and 24 in the holdout sample who provided cheek swabs for genetic analysis. All genotyping was performed by staff at the Norris Cotton Cancer Center of Dartmouth-Hitchcock Hospital.

Across both groups, concentrations of DNA in each extracted buccal swab sample ranged from 0.6 to 33.3 ng/μl. All genetic markers were successfully assayed for each participant.

Dopaminergic genotype indices in both the main experimental group and the holdout group were normally distributed.

There was a significant difference in the mean dopaminergic genotype index between the main experimental group and the control group, according to an independent-samples t-test, $t(49) = 2.45$, $p = 0.02$, Cohen's $d = 0.70$. Members of the experimental group scored lower, on average (M = 3.3) than the holdout group (M = 4.3).

MRI

No members of the holdout sample took part in the MRI portion of the experiment. There were 31 members of the main experimental sample who participated in the post-training MRI session. Performance on the math task was well maintained at 50% accuracy by the adaptive staircase procedure. Participants gave correct responses on 50.6% of trials (SD across participants = 1.3%). The two subtypes of incorrect trials divided into 30.4% of trials where participants delivered an incorrect response (SD = 11.9%) and 19.0% of trials where they did not respond (SD = 12.0%). The fMRI analysis collapsed across these two subtypes of incorrect trials, yielding 49.4% of trials in the 'incorrect' analysis condition.

Automated FreeSurfer segmentation successfully created custom ROI masks for each individual participant in their native anatomical volumetric space (see Fig. 4).

Average comparison of parameter estimate (COPE) values for the contrast of correct vs. incorrect feedback delivery were normally distributed. One participant had outlier COPE values more than three standard deviations above the mean in the putamen, and was excluded from all subsequent analyses (across all ROIs) to prevent outlier-driven correlations.

Gene–behavior correlations

There were 26 participants in the main experimental group for the analysis of gene–behavior correlations. In this sample, there was a

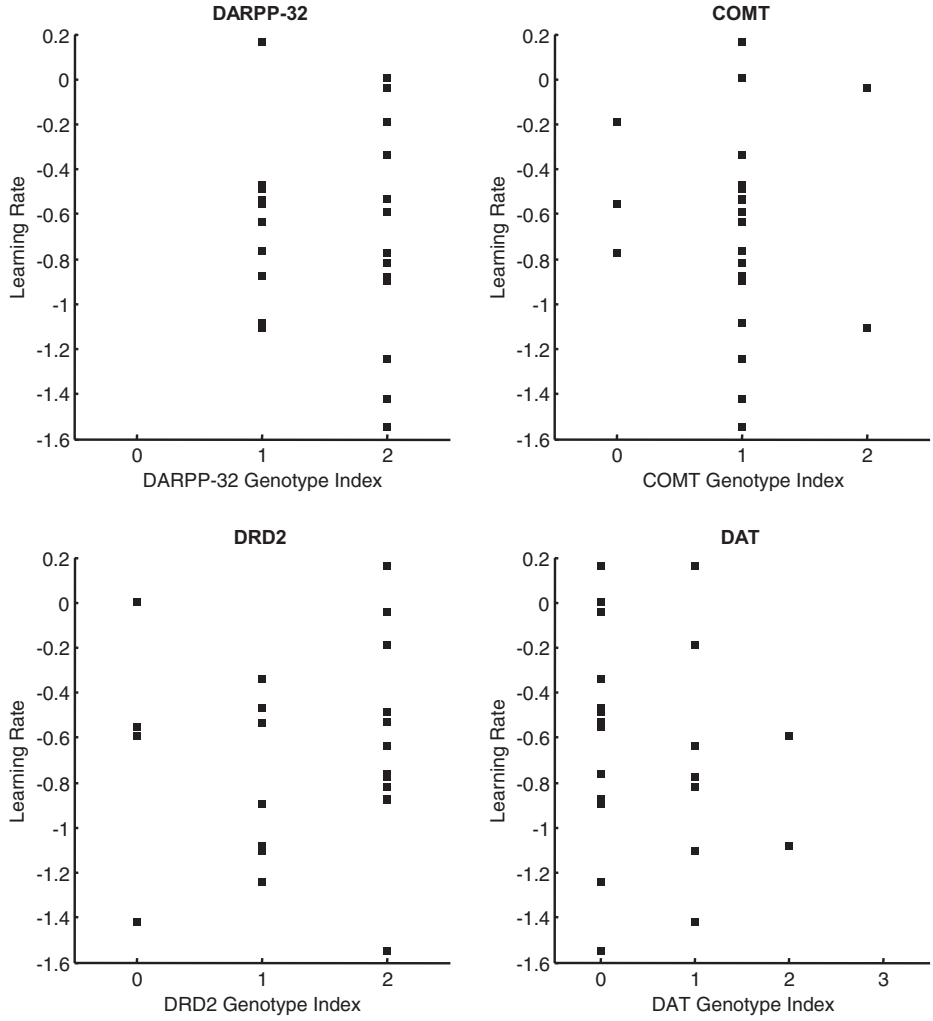

Fig. 7. Individual gene–behavior relationships in the holdout group. No genotypic marker was significantly related to learning rate.

significant correlation between dopaminergic genotype score and learning rate in the opposite direction of the hypothesized effect. Participants with genotypic markers of enhanced dopaminergic neurotransmission learned more slowly than participants with markers of attenuated dopaminergic transmission, $r = 0.46$, $p = 0.02$ ($r^2 = 0.21$) (see Fig. 5A).

This surprising index-level relationship prompted us to investigate the influence of individual genes within the index on learning rate post-hoc. Since genetic data for each individual gene contained only a few levels (i.e., number of risk alleles: 0, 1, or 2), and because there were, in many cases, greatly different numbers of participants from one level to another, a parametric statistical test was contraindicated. Therefore, we assessed these relationships using Kruskal–Wallis tests: a nonparametric alternative to a one-way ANOVA that generates a chi-squared statistic. Post-hoc Kruskal–Wallis tests showed a significant relationship between DARPP-32 genotype and learning rate (only if an uncorrected statistical threshold was used): $\chi^2(2,23) = 7.20$, $p = 0.03$ (see Fig. 6). No other individual gene was significantly related to learning rate (COMT: $\chi^2(2,23) = 0.64$, $p = 0.73$; DRD2: $\chi^2(2,23) = 1.62$, $p = 0.45$; DAT: $\chi^2(3,22) = 5.86$, $p = 0.12$) (see Fig. 6).

However, in the holdout sample, there was no such relationship between dopaminergic genotype index and learning rate, $r = -0.09$, $p =$ ns (see Fig. 5B). Neither did any significant correlation exist between genotype and behavior for any single gene assayed (DARPP-32: $\chi^2(1,22) = 0.61$, $p = 0.43$; COMT: $\chi^2(2,21) = 0.33$, $p = 0.85$; DRD2: $\chi^2(2,21) = 1.30$, $p = 0.52$; DAT: $\chi^2(2,21) = 0.89$, $p = 0.64$) (see Fig. 7).

Gene–brain correlations

There were 26 participants who provided usable data in both the genotyping and scanning portions of the experiment.

In the absence of a holdout sample, we used the Bonferroni-corrected α levels of 0.0167 to reduce the likelihood of a false positive due to multiple comparisons of brain activity and genotype in three ROIs. With this corrected threshold, there were no significant correlations between genotype index score and the difference in activity between correct and incorrect feedback delivery in any ROI. However, at an uncorrected α level of 0.05, putamen activity would have been significantly correlated with genotype such that individuals with a higher genotypic index of dopaminergic neurotransmission would have shown a greater difference between correct and incorrect feedback delivery, $r = 0.42$, $p = 0.03$ ($r^2 = 0.18$). Neither caudate nor nucleus accumbens activity approached a significant correlation with genotype: caudate, $r = -0.11$, $p =$ ns; accumbens, $r = -0.03$, $p =$ ns. These results appear in Fig. 8.

An exploratory analysis of individual genes' contributions to the marginally significant relationship between genotype and putamen activity was attempted in order to identify possible individual genetic contributors to between-subject differences in putamen activity. Kruskal–Wallis tests were used due to the non-normal distribution of the genetic data. There was no significant relationship between genotype and putamen activity for any particular assay (DARPP-32: $\chi^2(2,23) = 3.24$, $p = 0.20$; COMT: $\chi^2(2,23) = 5.32$, $p = 0.07$; DRD2: $\chi^2(2,23) = 1.84$, $p = 0.40$; DAT: $\chi^2(3,22) = 4.38$, $p = 0.22$). These results are shown in Fig. 9.

Brain–behavior correlations

There were 29 participants in the analysis of brain–behavior correlations. The difference in activity between correct and incorrect feedback delivery in the caudate nucleus was significantly correlated with learning rate, $r = -0.48$, $p = 0.008$ ($r^2 = 0.23$) (see Fig. 10). Participants with a larger difference in caudate activity level between correct and incorrect feedback delivery trials in the math task learned faster in the visual search task than those with smaller activity differences. There was no significant correlation in either of the other two ROIs: nucleus accumbens, $r = -0.21$, $p =$ ns and putamen, $r = 0.28$, $p =$ ns (see Fig. 10).

Brain–brain correlations

To estimate the amount of variance shared between the responses of the three striatal ROIs, cross-correlations were performed. The COPE values obtained in the two dorsal striatal ROIs (i.e., caudate and putamen) were significantly correlated ($r = 0.48$, $p = 0.007$, $r^2 = 0.23$). Likewise, activity in the caudate nucleus and nucleus accumbens was highly correlated ($r = 0.72$, $p < 0.001$, $r^2 = 0.52$).

Since the three striatal ROIs showed inter-correlated activity, correlations between average COPE values for the combined region of caudate, putamen, and nucleus accumbens versus learning rate or genotype were attempted. There was no significant correlation between either total striatal activity and learning rate ($r = -0.04$, $p = 0.83$), or between total striatal activity and genotype ($r = 0.26$, $p = 0.20$). It is worth noting that this analysis gives disproportionate weight to anatomically large portions of the striatum over small ones, since it uses a voxelwise average measure across ROIs of various sizes.

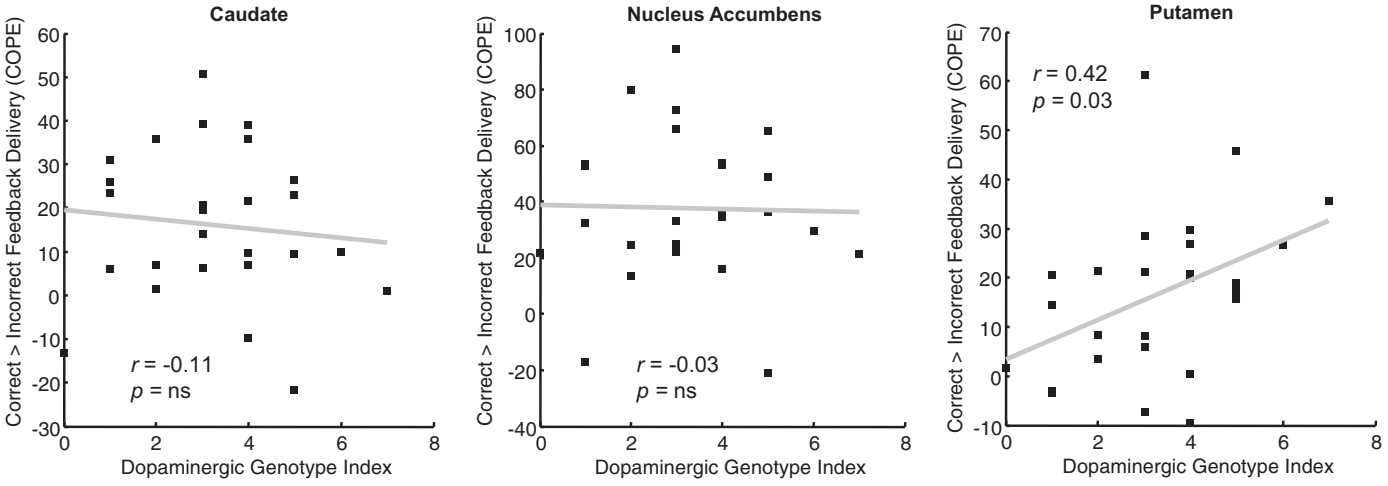

Fig. 8. Brain–genotype correlations. Using Bonferroni-corrected α levels to reduce the likelihood of a false positive due to multiple comparisons, no significant relationships exist between dopaminergic genotype index and brain activity. Putamen activity would have been significantly correlated using an uncorrected α of 0.05. (COPE values = arbitrary units).

Discussion

The results of this experiment provide evidence that individual differences in the responsivity of the caudate nucleus to cognitive feedback are associated with individual differences in visual feature conjunction learning on a visual search task. This result is consistent with the hypothesis that dopaminergic signaling facilitates conjunction learning, and its specificity suggests a particular neural mechanism whereby dopaminergic reinforcement could affect perception of feature conjunctions, described in detail below. However, our failure to find other dopaminergic correlates of conjunction learning rate suggests that the hypothesis of dopaminergic facilitation of conjunction learning might be more narrowly true than first thought.

The specificity of the effect to the caudate nucleus, and not other striatal ROIs, suggests that there is more to the story than just dopamine. The other striatal ROIs tested here also receive dopaminergic inputs from the VTA/SNpc, and the responses of the VTA and SNpc are thought to be relatively undifferentiated (i.e., when they respond, the VTA and SNpc flood all of their target areas with dopamine, not specific areas). Indeed, the substantial shared variance we observed in the activation of the three striatal ROIs is consistent with the idea that the majority of the activity observed in the three areas is driven by a common input.

However, these three striatal regions also receive differentiated excitatory inputs from other regions of the brain (Calabresi et al., 2007). Different parts of the striatum belong to different corticostriatal loops, receiving excitatory afferents from a particular region of cortex, and returning efferents back to nearby cortical neurons via a thalamic relay (Alexander et al., 1986). Unlike the other striatal ROIs studied, the caudate nucleus belongs specifically to a corticostriatal loop containing visual and oculomotor regions known to be involved in the conjunction learning search task, such as the frontal eye fields (FEF) (Alexander et al., 1986; Frank et al., 2014). Thus, if any studied ROI were to be expected to be especially responsive in individuals who are quick learners on the visual conjunction search task, it would be the caudate nucleus. The differences in caudate BOLD activity we observed might reflect differences in levels of long term potentiation within different participants' caudate nuclei, or could be due to stronger or more frequent excitation of the caudate nucleus from cortical afferents originating in FEF and other known components of the caudate corticostriatal loop.

It is important to consider, though, that the activity measured in the caudate nucleus was evoked in response to a completely different task that did not involve visual search or visual feature conjunctions. Instead, activity was measured in response to a mental math task that was more cognitive than perceptual in nature. Why, then, would activity measured during such a different task predict conjunction learning in visual search? The most obvious answer to this question is that the people who registered a larger difference in caudate activity for positive versus negative feedback have consistently lower thresholds for dopaminergic inputs to evoke activity in the caudate nucleus, independent of task-

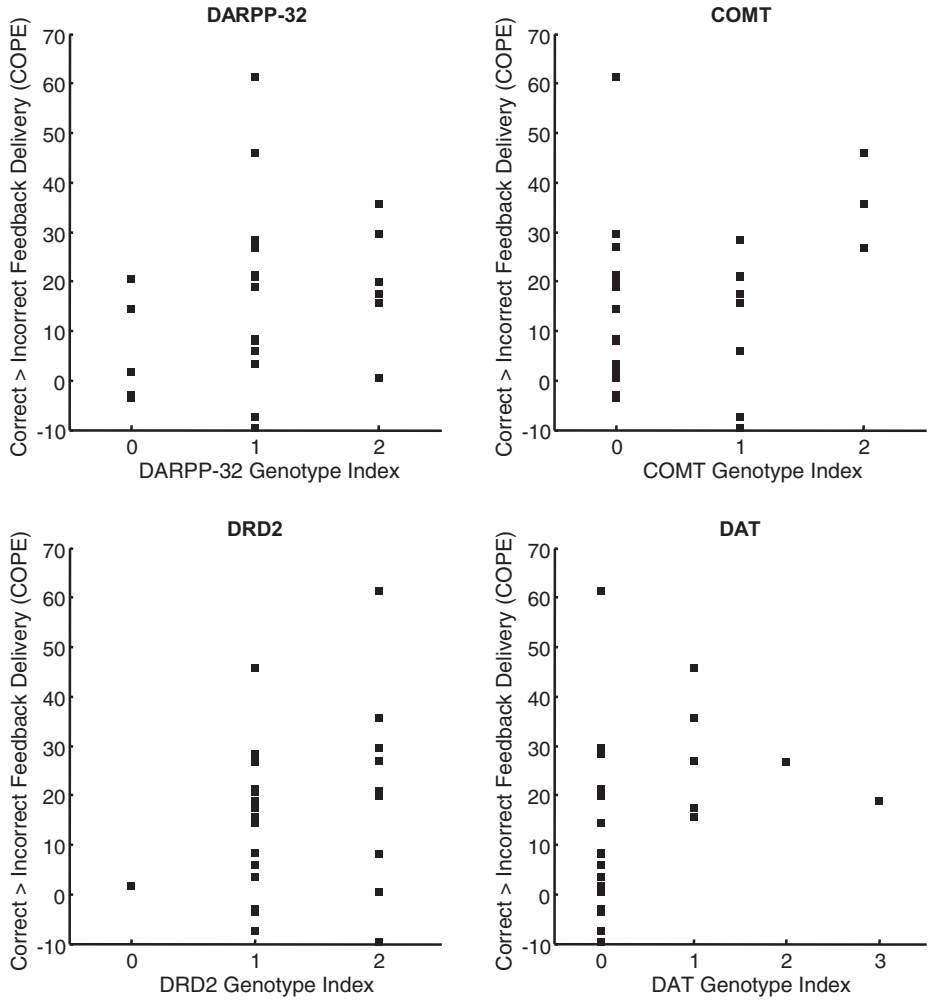

Fig. 9. Relationship between putamen activity and individual genetic markers. No individual genetic marker was significantly associated with putamen activity. (COPE values = arbitrary units).

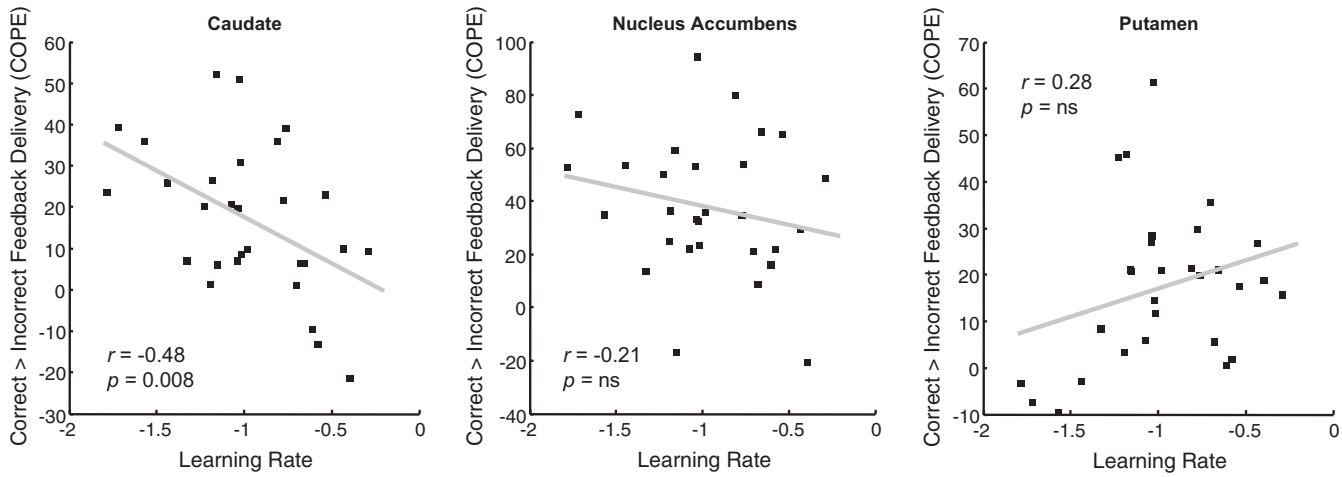

Fig. 10. Brain–behavior correlations. More negative learning rates correspond to faster learning. The difference in caudate activity between correct and incorrect feedback delivery was significantly correlated with learning rate: greater differences in correct and incorrect feedback delivery predicted faster learning. Neither the putamen nor nucleus accumbens showed a significant correlation. (COPE values = arbitrary units).

demands, than those who register smaller differences. In other words, the caudate nucleus may be more excitable in some participants than others, across various different tasks.

Some of the individual differences we observed in caudate activity could also relate to differences in participants' pattern of expectancies across trials, which we cannot resolve in the present dataset. Reward expectancy has been shown to influence the magnitude of dopaminergic responses: unexpected rewards tend to trigger a larger dopamine release than expected rewards. Within our positive-feedback trials, a range of expectancies likely existed prior to each onset of feedback, ranging from completely expected positive feedback (e.g., when participants were absolutely certain a response was correct) to completely unexpected positive feedback (e.g., when participants merely guessed and obtained a correct answer by chance). The present dataset lacks an objective trialwise measure of participants' expectancies. It is our hope that future experiments will remedy this limitation by employing methods such as Post-Decision Wagering (PDW), where participants place monetary bets on the likelihood that their answers are correct after they make each response (Persaud et al., 2007). PDW thus provides an objective measure of participants' confidence in each of their responses. Such confidence estimates could be used in future experiments to model expectancy as an additional regressor in GLM analyses of feedback-driven brain activity. Likewise, future experiments that do not employ a fixed-duration response period could eliminate the possible difference between trials where participants expect standard negative feedback versus the 'too slow' feedback presented when no response was registered within the four-second response period, which could have generated a different type of psychological expectancy on some trials in this study.

The results of the genotyping portion of the experiment are equivocal. In the main experimental sample, a significant correlation between dopaminergic genotype and learning rate was observed. However, this effect was in the opposite direction of the experimental prediction, and completely failed to emerge in members of an independent holdout sample. This failure to replicate the effect suggests that the finding in the main experimental group might have been a false positive.

Similarly ambiguous results were obtained for gene–brain correlations. Using α levels corrected for multiple comparisons, no correlations reached significance. However, putamen activity would have been significantly correlated with genotype using an uncorrected threshold of 0.05. No individual genetic marker predicted putamen activity; a significant correlation only emerged when all of the genetic markers were pooled into a single index score. Whether or not this result reflects a weak true positive effect for which there was insufficient experimental power in the present design or a false positive due to exploratory multiple comparisons is impossible to say on the basis of the current dataset. It is, however, consistent with findings from a larger study of the relationship between dopaminergic genotype (indexed using a different but partially-overlapping set of genetic markers) and individual differences in individuals' putamen activity evoked by monetary rewards (Stice et al., 2012). Thus, this trend in our results merits follow-up investigation with a larger, more powerful experimental sample.

In sum, the present genotyping results do not support any conclusions either for or against the hypothesis that individual differences in dopaminergic genotype influence conjunction learning rate. However, the mixed results observed do provide a justification for future studies with more participants and greater experimental power, supplying a proof-of-concept dataset showing that genotypic differences can be practicably measured, and might be correlated with neural or behavioral metrics.

Overall, the results of this experiment support the hypothesis that the dopaminergic system is involved in conjunction learning. Specifically, individual differences in feedback-related activity within the caudate nucleus, a part of the oculomotor corticostriatal loop, are correlated with individual differences in conjunction learning rate. By linking conjunction learning to a neural system heavily implicated in associative learning, this result suggests a possible relationship between conjunction learning and associative learning, raising the possibility that conjunction learning in the visual domain is a special type of associative learning. This possibility provides an interesting starting point for future investigation.

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References

Alexander, G., DeLong, M., Strick, P., 1986. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu. Rev. Neurosci. 9, 357–381.

Bakin, J.S., Weinberger, N.M., 1996. Induction of a physiological memory in the cerebral cortex by stimulation of the nucleus basalis. Proc. Natl. Acad. Sci. U. S. A. 93, 11219–11224.
Bao, S., Chan, V.T., Merzenich, M.M., 2001. Cortical remodelling induced by activity of ventral tegmental dopamine neurons. Nature 412, 79–83. http://dx.doi.org/10.1038/35083586.
Beer, A.L., Vartak, D., Greenlee, M.W., 2013. Nicotine facilitates memory consolidation in perceptual learning. Neuropharmacology 64, 443–451. http://dx.doi.org/10.1016/j.neuropharm.2012.06.019.
Björklund, A., Dunnett, S.B., 2007. Dopamine neuron systems in the brain: an update. Trends Neurosci. 30, 194–202. http://dx.doi.org/10.1016/j.tins.2007.03.006.
Bromberg-Martin, E.S., Matsumoto, M., Hikosaka, O., 2010. Dopamine in motivational control: rewarding, aversive, and alerting. Neuron 68, 815–834. http://dx.doi.org/10.1016/j.neuron.2010.11.022.
Calabresi, P., Picconi, B., Tozzi, A., Di Filippo, M., 2007. Dopamine-mediated regulation of corticostriatal synaptic plasticity. Trends Neurosci. 30, 211–219. http://dx.doi.org/10.1016/j.tins.2007.03.001.
Cass, W.A., Gerhardt, G.A., 1995. In vivo assessment of dopamine uptake in rat medial prefrontal cortex: comparison with dorsal striatum and nucleus accumbens. J. Neurochem. 65, 201–207.
Cohen, M.X., Young, J., Baek, J.-M., Kessler, C., Ranganath, C., 2005. Individual differences in extraversion and dopamine genetics predict neural reward responses. Cogn. Brain Res. 25, 851–861. http://dx.doi.org/10.1016/j.cogbrainres.2005.09.018.
D'Ardenne, K., McClure, S.M., Nystrom, L.E., Cohen, J.D., 2008. BOLD responses reflecting dopaminergic signals in the human ventral tegmental area. Science 319, 1264–1267. http://dx.doi.org/10.1126/science.1150605.
Dreher, J.-C., Kohn, P., Kolachana, B., Weinberger, D.R., Berman, K.F., 2009. Variation in dopamine genes influences responsivity of the human reward system. Proc. Natl. Acad. Sci. U. S. A. 106, 617–622. http://dx.doi.org/10.1073/pnas.0805517106.
Duncan, R., Boynton, G., 2003. Cortical magnification within human primary visual cortex correlates with acuity thresholds. Neuron 38, 659–671.
Fischl, B., Salat, D.H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., van der Kouwe, A., Killiany, R., Kennedy, D., Klaveness, S., Montillo, A., Makris, N., Rosen, B., Dale, A.M., 2002. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron 33, 341–355.
Fischl, B., Salat, D.H., van der Kouwe, A.J.W., Makris, N., Ségonne, F., Quinn, B.T., Dale, A.M., 2004. Sequence-independent segmentation of magnetic resonance images. NeuroImage 23 (Suppl. 1), S69–S84. http://dx.doi.org/10.1016/j.neuroimage.2004.07.016.
Frank, M.J., Moustafa, A.A., Haughey, H.M., Curran, T., Hutchison, K.E., 2007. Genetic triple dissociation reveals multiple roles for dopamine in reinforcement learning. Proc. Natl. Acad. Sci. U. S. A. 104, 16311–16316. http://dx.doi.org/10.1073/pnas.0706111104.
Frank, S.M., Reavis, E.A., Tse, P.U., Greenlee, M.W., 2014. Neural mechanisms of feature conjunction learning: enduring changes in occipital cortex after a week of training. Hum. Brain Mapp. 35, 1201–1211. http://dx.doi.org/10.1002/hbm.22245.
Frank, S.M., Reavis, E.A., Greenlee, M.W., Tse, P.U., 2015. Pretraining cortical thickness predicts subsequent perceptual learning rate in a visual search task. Cereb. Cortex 1–10 http://dx.doi.org/10.1093/cercor/bhu309.
Hahn, T., Heinzel, S., Dresler, T., Plichta, M.M., Renner, T.J., Markulin, F., Jakob, P.M., Lesch, K.-P., Fallgatter, A.J., 2011. Association between reward-related activation in the ventral striatum and trait reward sensitivity is moderated by dopamine transporter genotype. Hum. Brain Mapp. 32, 1557–1565. http://dx.doi.org/10.1002/hbm.21127.
International HapMap Consortium, T., 2003. The international HapMap project. Nature 426, 789–796.
Jenkinson, M., Bannister, P., Brady, M., Smith, S., 2002. Improved optimization for the robust and accurate linear registration and motion correction of brain images. NeuroImage 17, 825–841. http://dx.doi.org/10.1006/nimg.2002.1132.
Jenkinson, M., Beckmann, C.F., Behrens, T.E.J., Woolrich, M.W., Smith, S.M., 2012. FSL. NeuroImage 62, 782–790. http://dx.doi.org/10.1016/j.neuroimage.2011.09.015.
Kilgard, M.P., Merzenich, M.M., 1998. Cortical map reorganization enabled by nucleus basalis activity. Science 279, 1714–1718. http://dx.doi.org/10.1126/science.279.5357.1714.
Koch, K., Wagner, G., Dahnke, R., Schachtzabel, C., Güllmar, D., Reichenbach, J.R., Schlösser, R.G.M., 2010. Structure–function relationships in the context of reinforcement-related learning: a combined diffusion tensor imaging-functional magnetic resonance imaging study. Neuroscience 168, 190–199. http://dx.doi.org/10.1016/j.neuroscience.2010.03.026.
Krugel, L.K., Biele, G., Mohr, P.N.C., Li, S.-C., Heekeren, H.R., 2009. Genetic variation in dopaminergic neuromodulation influences the ability to rapidly and flexibly adapt decisions. Proc. Natl. Acad. Sci. U. S. A. 106, 17951–17956. http://dx.doi.org/10.1073/pnas.0905191106.
Nikolova, Y.S., Ferrell, R.E., Manuck, S.B., Hariri, A.R., 2011. Multilocus genetic profile for dopamine signaling predicts ventral striatum reactivity. Neuropsychopharmacology 36, 1940–1947. http://dx.doi.org/10.1038/npp.2011.82.
Norton, D.J., McBain, R.K., Ongür, D., Chen, Y., 2011. Perceptual training strongly improves visual motion perception in schizophrenia. Brain Cogn. 77, 248–256. http://dx.doi.org/10.1016/j.bandc.2011.08.003.
Noudoost, B., Moore, T., 2011a. The role of neuromodulators in selective attention. Trends Cogn. Sci. 15, 585–591. http://dx.doi.org/10.1016/j.tics.2011.10.006.
Noudoost, B., Moore, T., 2011b. Control of visual cortical signals by prefrontal dopamine. Nature 474, 372–375. http://dx.doi.org/10.1038/nature09995.
Persaud, N., McLeod, P., Cowey, A., 2007. Post-decision wagering objectively measures awareness. Nat. Neurosci. 10, 257–261. http://dx.doi.org/10.1038/nn1840.
Pleger, B., Ruff, C.C., Blankenburg, F., Klöppel, S., Driver, J., Dolan, R.J., 2009. Influence of dopaminergically mediated reward on somatosensory decision-making. PLoS Biol. 7, e1000164. http://dx.doi.org/10.1371/journal.pbio.1000164.
Reavis, E.A., Frank, S.M., & Tse, P.U. (In Preparation). Feature conjunction learning in visual search: Evidence for an associative learning process.
Roelfsema, P.R., van Ooyen, A., Watanabe, T., 2010. Perceptual learning rules based on reinforcers and attention. Trends Cogn. Sci. 14, 64–71. http://dx.doi.org/10.1016/j.tics.2009.11.005.
Rokem, A., Silver, M.A., 2010. Cholinergic enhancement augments magnitude and specificity of visual perceptual learning in healthy humans. Curr. Biol. 20, 1723–1728. http://dx.doi.org/10.1016/j.cub.2010.08.027.
Rokem, A., Silver, M.A., 2013. The benefits of cholinergic enhancement during perceptual learning are long-lasting. Front. Comput. Neurosci. 7, 1–7. http://dx.doi.org/10.3389/fncom.2013.00066.
Santesso, D.L., Dillon, D.G., Birk, J.L., Holmes, A.J., Goetz, E., Bogdan, R., Pizzagalli, D.A., 2008. Individual differences in reinforcement learning: behavioral, electrophysiological, and neuroimaging correlates. NeuroImage 42, 807–816. http://dx.doi.org/10.1016/j.neuroimage.2008.05.032.
Schott, B.H., Minuzzi, L., Krebs, R.M., Elmenhorst, D., Lang, M., Winz, O.H., Seidenbecher, C.I., Coenen, H.H., Heinze, H.-J., Zilles, K., Düzel, E., Bauer, A., 2008. Mesolimbic functional magnetic resonance imaging activations during reward anticipation correlate with reward-related ventral striatal dopamine release. J. Neurosci. 28, 14311–14319. http://dx.doi.org/10.1523/JNEUROSCI.2058-08.2008.
Schultz, W., 2010. Multiple functions of dopamine neurons. F1000 Biology Reports 2, pp. 1–4. http://dx.doi.org/10.3410/B2-2.
Schultz, W., Dayan, P., Montague, P.R., 1997. A neural substrate of prediction and reward. Science 275, 1593–1599. http://dx.doi.org/10.1126/science.275.5306.1593.
Seitz, A.R., Dinse, H.R., 2007. A common framework for perceptual learning. Curr. Opin. Neurobiol. 17, 148–153. http://dx.doi.org/10.1016/j.conb.2007.02.004.
Seitz, A.R., Watanabe, T., 2005. A unified model for perceptual learning. Trends Cogn. Sci. 9, 329–334. http://dx.doi.org/10.1016/j.tics.2005.05.010.
Seol, G.H., Ziburkus, J., Huang, S., Song, L., Kim, I.T., Takamiya, K., Huganir, R.L., Lee, H.-K., Kirkwood, A., 2007. Neuromodulators control the polarity of spike-timing-dependent synaptic plasticity. Neuron 55, 919–929. http://dx.doi.org/10.1016/j.neuron.2007.08.013.
Shen, W., Flajolet, M., Greengard, P., Surmeier, D.J., 2008. Dichotomous dopaminergic control of striatal synaptic plasticity. Science 321, 848–851. http://dx.doi.org/10.1126/science.1160575.
Sherry, S.T., Ward, M.H., Kholodov, M., Baker, J., Phan, L., Smigielski, E.M., Sirotkin, K., 2001. dbSNP: the NCBI database of genetic variation. Nucleic Acids Res. 29, 308–311.
Simsek, M., Lawatia, K., Al-Adawi, S., Al-Sharbati, M., 2005. DAT1 VNTR allele frequencies in the Omani population. Hum. Biol. 77, 281–286.
Smith, S.M., 2002. Fast robust automated brain extraction. Hum. Brain Mapp. 17, 143–155. http://dx.doi.org/10.1002/hbm.10062.
Smith, S.M., Jenkinson, M., Woolrich, M.W., Beckmann, C.F., Behrens, T.E.J., Johansen-Berg, H., Bannister, P.R., De Luca, M., Drobnjak, I., Flitney, D.E., Niazy, R.K., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J.M., Matthews, P.M., 2004. Advances in functional and structural MR image analysis and implementation as FSL. NeuroImage 23 (Suppl. 1), S208–S219. http://dx.doi.org/10.1016/j.neuroimage.2004.07.051.
Stice, E., Yokum, S., Burger, K., Epstein, L., Smolen, A., 2012. Multilocus genetic composite reflecting dopamine signaling capacity predicts reward circuitry responsivity. J. Neurosci. 32, 10093–10100. http://dx.doi.org/10.1523/JNEUROSCI.1506-12.2012.
Townsend, J., Ashby, F., 1978. Methods of modeling capacity in simple processing systems. In: Castellan, N., Restle, F. (Eds.), Cognitive Theory vol. 3. Lawrence Erlbaum Associates, Hillsdale, NJ, pp. 199–239.
Turchi, J., Buffalari, D., Mishkin, M., 2008. Double dissociation of pharmacologically induced deficits in visual recognition and visual discrimination learning. Learn. Mem. 15, 565–568. http://dx.doi.org/10.1101/lm.966208.
Turchi, J., Devan, B., Yin, P., Sigrist, E., Mishkin, M., 2010. Pharmacological evidence that both cognitive memory and habit formation contribute to within-session learning of concurrent visual discriminations. Neuropsychologia 48, 2245–2250. http://dx.doi.org/10.1016/j.neuropsychologia.2010.02.003.
Uc, E.Y., Rizzo, M., Anderson, S.W., Sparks, J., Rodnitzky, R.L., Dawson, J.D., 2006. Impaired visual search in drivers with Parkinson's disease. Ann. Neurol. 60, 407–413. http://dx.doi.org/10.1002/ana.20958.
Van Asselen, M., Almeida, I., Andre, R., Januário, C., Gonçalves, A.F., Castelo-Branco, M., 2009. The role of the basal ganglia in implicit contextual learning: a study of Parkinson's disease. Neuropsychologia 47, 1269–1273. http://dx.doi.org/10.1016/j.neuropsychologia.2009.01.008.
Woolrich, M.W., Ripley, B.D., Brady, M., Smith, S.M., 2001. Temporal autocorrelation in univariate linear modeling of FMRI data. NeuroImage 14, 1370–1386. http://dx.doi.org/10.1006/nimg.2001.0931.
Woolrich, M.W., Jbabdi, S., Patenaude, B., Chappell, M., Makni, S., Behrens, T., Beckmann, C., Jenkinson, M., Smith, S.M., 2009. Bayesian analysis of neuroimaging data in FSL. NeuroImage 45, S173–S186. http://dx.doi.org/10.1016/j.neuroimage.2008.10.055.