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The effects of methylphenidate on cerebral responses to conflict anticipation and unsigned prediction error in a stop-signal task

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Abstract

To adapt flexibly to a rapidly changing environment, humans must anticipate conflict and respond to surprising, unexpected events. To this end, the brain estimates upcoming conflict on the basis of prior experience and computes unsigned prediction error (UPE). Although much work implicates catecholamines in cognitive control, little is known about how pharmacological manipulation of catecholamines affects the neural processes underlying conflict anticipation and UPE computation. We addressed this issue by imaging 24 healthy young adults who received a 45 mg oral dose of methylphenidate (MPH) and 62 matched controls who did not receive MPH prior to performing the stop-signal task. We used a Bayesian Dynamic Belief Model to make trial-by-trial estimates of conflict and UPE during task performance. Replicating previous research, the control group showed anticipation-related activation in the presupplementary motor area and deactivation in the ventromedial prefrontal cortex and parahippocampal gyrus, as well as UPE-related activations in the dorsal anterior cingulate, insula, and inferior parietal lobule. In group comparison, MPH increased anticipation activity in the bilateral caudate head and decreased UPE activity in each of the aforementioned regions. These findings highlight distinct effects of catecholamines on the neural mechanisms underlying conflict anticipation and UPE, signals critical to learning and adaptive behavior.

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Keywords

fMRI; stimulant; psychostimulant; Ritalin; inhibitory control; interference; dACC; insula; Bayesian

Introduction

Our ability to detect and respond to rapid changes in the environment is critical to learning and survival (Brown and Brüne, 2012). This fundamental process relies in part on the neural computation of conflict and unsigned prediction error (UPE), or the absolute difference between the expected and actual outcome of an event (Behrens et al., 2007; Yu and Dayan, 2005). By way of anticipating conflict and responding to prediction error, we allocate resources for cognitive control and adjust behavior according to outcomes. Earlier studies have described the cerebral processes that anticipate conflict, monitoring and preparing to react to stimuli that cue competing responses (Choi et al., 2012a; Drabant et al., 2011; Fan et al., 2007; Frith et al., 1991; Greenberg et al., 2015; Hu et al., 2015b; Lütcke et al., 2009). Previous work in both monkeys and humans has also identified neural signals related to UPE (Hayden et al., 2011; Ide et al., 2013), particularly in the dorsal anterior cingulate cortex (dACC), insula, and inferior parietal lobule (IPL), areas dense with catecholaminergic innervation (Berger et al., 1974; Brown et al., 1979; Lewis et al., 1979; Porrino and Goldman-Rakic, 1982). There is also abundant evidence that catecholamines strongly modulate activity in these and other cerebral regions (Assadi et al., 2009; Da Silva Alves et al., 2011; Florin-Lechner et al., 1996; O'Daly et al., 2014) for behaviors that require the computation of conflict and UPE. Generally, cortical dopaminergic and noradrenergic inputs enhance maintenance of stimulus representations, promote vigilance, and allow for behavioral flexibility when environmental stimuli change rapidly (Arnsten, 1997; Aston-Jones et al., 1999; Kahnt et al., 2015; Trantham-Davidson et al., 2004).

Animal studies provide strong evidence suggesting that catecholamines are specifically involved in the computation of conflict and prediction error. Schultz et al. have demonstrated that dopaminergic neurons increase phasic firing for stimuli that are learned to be associated with an impending reward, and decrease phasic firing when the predicted reward fails to be delivered (Schultz, 1998; Schultz et al., 1997). A recent study showed that pairing a reward with optogenetic stimulation of dorsal midbrain dopaminergic neurons was sufficient to produce reinforcement learning behaviors, demonstrating a causal link between dopamine (DA) and prediction error computation (Steinberg et al., 2013). On the other hand, this phenomenon may not be dependent on reward, and may be important for any stimulus-outcome contingency where UPE signals would be needed for learning (Aquila, 2014; Horvitz, 2000; Redgrave et al., 2008). In addition, noradrenergic neurons of the locus coeruleus fire in response to unpredicted but not predicted behaviorally relevant stimuli (Aston-Jones et al., 1994; Dayan and Yu, 2006; Foote et al., 1980), facilitating rapid changes in behavior following errors (Aston-Jones and Cohen, 2005; Bouret and Sara, 2005; Nieuwenhuis et al., 2005). Together, DA and norepinephrine (NE) may work in parallel to signal errors and guide flexible goal-directed behavior (Jocham and Ullsperger, 2009). However, while catecholamines have a strong influence on neural activity related to conflict

and prediction error and have been theorized to play a role in their computation (Friston et al., 2014; Yu and Dayan, 2005), little is known about how pharmacological manipulation of catecholamines affects neural processing of conflict and UPE.

Methylphenidate (MPH) is an indirect catecholamine agonist, increasing DA and NE concentrations in the synaptic cleft by blocking transporter reuptake (for reviews, see: Challman and Lipsky, 2000; Leonard et al., 2004). In healthy adults, MPH alters cerebral responses to a diverse array of cognitive processes supported by catecholamines, such as error processing (Dodds et al., 2008; Moeller et al., 2014), uncertainty during decision making (Schlösser et al., 2009), and attentional demands when tracking infrequent stimuli (Pauls et al., 2012). These different processes are all related to conflict anticipation and the computation of UPE. In order to compute the magnitude of the difference between an expected and observed outcome accurately, one must (a) remain vigilant/attentive to task demands, continuously encoding relevant stimulus properties; (b) use observed stimulus information to make probabilistic estimates about the likelihood of future stimulus occurrence; and (c) rapidly detect and respond to surprising stimuli that violate predictions (Petzschnier et al., 2015; Shenoy et al., 2010; Yu and Dayan, 2005). Given that MPH appears to play a role in these behavioral contingencies, it is plausible that MPH would also affect the brain's computation of conflict and UPE.

The goal of the present study was to assess whether MPH administration changes the neural responses to conflict anticipation and UPE. To this end, we utilized the stop-signal task (SST; Logan et al., 1984) during functional magnetic resonance imaging (fMRI) of healthy adults who received an oral dose of MPH and in a control group that did not receive MPH. Although this was not a placebo-controlled within-subject study, our previous work showed that the between-subject comparisons have yielded results that were robust for various analyses and consistent across different control groups (Farr et al., 2014a, 2014b). Because behavioral performance in the SST can be explained in terms of Bayesian optimal decision making (Shenoy and Yu, 2011; Shenoy et al., 2010), we used a Bayesian dynamic belief model (Yu and Cohen, 2009) to make trial-by-trial estimates of prediction error, as in our previous work (Ide et al., 2013). We hypothesized that MPH would alter the cerebral responses to conflict anticipation and UPE during SST performance.

Methods and materials

The study was performed under protocols approved by the Yale Human Investigation and MRI Safety Committees. Full details of the study procedures can be found in a previously published report (Farr et al., 2014a), of which a summary is presented here. Twenty-four participants (16 females; $M_{\text{age}} \pm SD$ 24 $\pm$ 0.8 years) received a single 45 mg oral dose of MPH one hour prior to the fMRI scan (MPH group). Although participants did not know whether they would be receiving MPH or placebo, all participants received MPH. Data of a cohort of 62 healthy participants (38 females; $M_{\text{age}} \pm SD$ 25 $\pm$ 0.5 years; Farr et al., 2012; Li et al., 2008, 2010) scanned under identical imaging protocols but without being given MPH were used for comparison (noMPH group 1). Because of an unbalanced sample size in this comparison, we also performed a follow-up analysis and compared the MPH group with a subgroup of 24 of the 62 participants who did not receive any medications and were matched in

demographics both individually and as a group (noMPH group 2). All participants were free from medical, neurological, and psychiatric illnesses, denied use of illicit substances, and tested negative in urine toxicology screens on the day of fMRI.

Behavioral task

During fMRI, participants performed the SST (Logan et al., 1984) as in our previous work (Hendrick et al., 2010; Ide and Li, 2011; Li et al., 2006, 2008; Zhang and Li, 2012). There were two trial types: go and stop, randomly intermixed. A small dot appeared on the screen to engage attention at the beginning of a go trial. After a randomized time interval (fore-period) between 1 and 5 s, the dot turned into a circle (the go signal), prompting the subject to quickly press a button. The circle vanished at a button press or after 1 s had elapsed, whichever came first, and the trial terminated. A premature button press prior to the appearance of the circle also terminated the trial. Approximately three quarters of all trials were go trials. The remaining one quarter were stop trials. In a stop trial, an additional X, the stop signal, appeared after and replaced the go signal. The subjects were told to withhold their button press upon seeing the stop signal. The stop-signal delay (SSD)—the time interval between the go and stop signal—started at 200 ms and varied from one stop trial to the next according to a staircase procedure, increasing and decreasing by 67 ms each after a successful or failed stop trial (De Jong et al., 1990; Levitt, 1971). There was an intertrial interval of 2 s. Subjects were instructed to respond to the go signal quickly while keeping in mind that a stop signal could come up in a small number of trials. In the scanner, each subject completed four 10 min runs of the task. Depending on the actual stimulus timing (trials varied in fore-period duration) and speed of response, the total number of trials varied slightly across subjects in an experiment. With the staircase procedure, we anticipated that the subjects would succeed in withholding their response in approximately half of the stop trials. The stop-signal reaction time (SSRT) was computed by subtracting the critical SSD, or the estimated SSD required for a subject to get half of stop trials correct, from the median go reaction time (Li et al., 2008).

Trial-by-trial Bayesian estimate of the likelihood of a stop signal

As in our previous work (Hu et al., 2015a; Ide et al., 2013, 2015), we used a dynamic Bayesian model (Yu and Cohen, 2009) to estimate the prior belief of an impending stop signal on each trial, based on prior stimulus history. The model assumes that subjects believe that stop-signal frequency r_k on trial k has probability α of being the same as r_{k-1} , and probability $(1-\alpha)$ of being resampled from a prior distribution $\pi(r_k)$. Subjects are also assumed to believe that trial k has probability r_k of being a stop trial, and probability $1-r_k$ of being a go trial. Based on these generative assumptions, subjects are assumed to use Bayesian inference to update their prior belief of seeing a stop signal on trial k , $p(r_k|s_{k-1})$ based on the prior on the last trial $p(r_{k-1}|s_{k-1})$ and last trial's true category ($s_k=1$ for stop trial, $s_k=0$ for go trial), where $s_k=\{s_1, \dots, s_k\}$ is short-hand for all trials 1 through k . Specifically, given that the posterior distribution was $p(r_{k-1}|s_{k-1})$ on trial $k-1$, the prior distribution of stop signal in trial k is given by:

$$p(r_k|s_{k-1}) = \alpha p(r_{k-1}|s_{k-1}) + (1 - \alpha) \pi(r_k),$$

where the prior distribution $\pi(r_k)$ is assumed to be a beta distribution with prior mean pm , and shape parameter $scale$, and the posterior distribution is computed from the prior distribution and the outcome according to the Bayesian rule:

$$p(r_k|s_k) \propto P(s_k|r_k)p(r_k|s_{k-1}).$$

The Bayesian estimate of the probability of trial k being a stop trial, which we call $P(\text{stop})$, given the predictive distribution $p(r_k|s_{k-1})$ is expressed by:

$$P(s_k=1|s_{k-1}) = \int P(s_k=1|r_k)P(r_k|s_{k-1})dr_k = \int r_k P(r_k|s_{k-1})dr_k = (r_k|s_{k-1})$$

In other words, the probability $P(\text{stop})$ of a trial k being a stop trial is simply the mean of the predictive distribution $p(r_k|s_{k-1})$. The assumption that the predictive distribution is a mixture of the previous posterior distributions and a generic prior distribution is essentially equivalent to using a causal, exponential, linear filter to estimate the current rate of stop trials (Yu and Cohen, 2009). In summary, for each subject, given a sequence of observed go/stop trials, and the three model parameters $\{\alpha, pm, scale\}$, we estimated $P(\text{stop})$ for each trial.

Imaging protocol and spatial preprocessing of brain images

Conventional T1-weighted spin-echo sagittal anatomical images were acquired for slice localization using a 3T scanner (Siemens Trio). Anatomical images of the functional slice locations were obtained with spin-echo imaging in the axial plan parallel to the Anterior Commissure-Posterior Commissure (AC-PC) line with TR=300 ms, TE=2.5 ms, bandwidth=300 Hz/pixel, flip angle=60°, field of view=220×220 mm, matrix=256×256, 32 slices with slice thickness=4 mm and no gap. A single high-resolution T1-weighted gradient-echo scan was obtained. One hundred and seventy-six slices parallel to the AC-PC line covering the whole brain were acquired with TR=2530 ms, TE=3.66 ms, bandwidth=181 Hz/pixel, flip angle=7°, field of view=256×256 mm, matrix=256×256, 1 mm³ isotropic voxels. Functional blood oxygenation level dependent (BOLD) signals were then acquired with a single-shot gradient-echo echo-planar imaging (EPI) sequence. Thirty-two axial slices parallel to the AC-PC line covering the whole brain were acquired with TR=2000 ms, TE=25 ms, bandwidth=2004 Hz/pixel, flip angle=85°, field of view=220×220 mm, matrix=64×64, 32 slices with slice thickness=4 mm and no gap. There were three hundred images in each session for a total of four sessions.

Data were analyzed with Statistical Parametric Mapping (SPM8, Wellcome Department of Imaging Neuroscience, University College London, UK). In the preprocessing of BOLD data, images of each participant were realigned (motion corrected) and corrected for slice timing. A mean functional image volume was constructed for each participant for each run from the realigned image volumes. These mean images were co-registered with the high-resolution structural image and then segmented for normalization to an MNI (Montreal Neurological Institute) EPI template with affine registration followed by nonlinear transformation (Ashburner and Friston, 1999; Friston et al., 1995). Finally, images were smoothed with a Gaussian kernel of 8 mm at full width at half maximum. Images from the

first five TRs at the beginning of each trial were discarded to enable the signal to achieve steady-state equilibrium between radio frequency pulsing and relaxation.

Generalized linear models

Our goal was to identify neural correlates associated with the effect of MPH on conflict anticipation and prediction error of a stop signal in healthy adults. We distinguished four trial outcomes: go success (GS), go error (GE), stop success (SS), and stop error (SE) for two generalized linear models (GLM). Because $P(\text{stop})$ is updated on a trial-by-trial basis, we posited that activities related to stop signal anticipation should arise at trial onset, whereas activities related to UPE arise at signal onset. Because the onsets of fixation point and go signal were on average 3 s apart, and the canonical hemodynamic response peaks at 6–10 s, it was not feasible to include both events in a single model to identify activations specific to each event (Huettel and McCarthy, 2000, 2001; Soon et al., 2003). It is suggested that an average lag of 6 s between two successive events is required to allow near-full separation (Huettel et al., 2009). Therefore, in the current study, we constructed two separate models, each describing the events of interest with fixation point (F model) and go signal (G model) onsets (Hu and Li, 2012; Hu et al., 2015b).

In the first GLM, the F (for *fixation* point at trial onset) model, we modeled BOLD signals by convolving the onsets of the fixation point—the beginning—of each trial with a canonical hemodynamic response function (HRF) and the temporal derivative of the canonical HRF (Friston et al., 1995). Realignment parameters in all six dimensions were entered in the model. We included the following variables as parametric modulators in the model: $P(\text{stop})$ of GS trials, SSD of SS trials, $P(\text{stop})$ of SS trials, SSD of SE trials, and $P(\text{stop})$ of SE trials, in that order. Inclusion of these variables as parametric modulators improves model fit (Büchel et al., 1998; Hu and Li, 2012) and, specifically, the parametric modulator of $P(\text{stop})$ would allow us to examine the neural correlates of conflict anticipation. Serial autocorrelation of the time series was corrected by a first-degree autoregressive or AR(1) model (Della-Maggiore et al., 2002; Friston et al., 2000). The data were high-pass filtered (1/128 Hz cutoff) to remove low-frequency signal drifts. In the first-level analysis, we obtained for each participant a contrast “1” on the parametric modulators “ $P(\text{stop})$ ” weighted by the proportion of trial number each of GS, SS, and SE trials to examine how deviations from the average BOLD amplitude are modulated by trial-by-trial estimate of the likelihood of a stop signal ((Wilson et al., 2009; (St Jacques et al., 2011). That is, this contrast identified voxels with activation increasing with the likelihood that a stop signal would appear.

In the second GLM, the G (for *go* signal onset) model, we modeled the BOLD signals by convolving the onsets of the go signal of each trial with a canonical HRF and its temporal derivative. We obtained for each participant a contrast of $P(\text{stop})$ on GS trials subtracting $P(\text{stop})$ on SS and SE trials, denoted as $P(\text{stop})_G - P(\text{stop})_{SS+SE}$ to examine the difference between go and stop trials of how deviations from the average BOLD amplitude are modulated by trial-by-trial estimate of the likelihood of a stop signal (Ide et al., 2013). This contrast captured UPE signals because on Go trials, $\text{UPE} = |0 - P(\text{stop})| = P(\text{stop})$, and on Stop trials, $\text{UPE} = |1 - P(\text{stop})| = 1 - P(\text{stop})$. That is, this contrast identified voxels with activation

increasing with the likelihood—a Bayesian belief—that a stop signal would appear in a go trial rather than in a stop trial, reflecting the discrepancy between anticipation and the actual outcome. In other words, this Bayesian surprise signal, or UPE related to stimulus outcome, should be positively correlated with $P(\text{stop})$ on go trials, and negatively correlated with $P(\text{stop})$ on stop trials.

In the second-level analysis, all images were evaluated at a voxel-wise threshold of $p < 0.005$, combined with a cluster size threshold of 29 contiguous voxels (783 mm^3). This combined threshold was estimated with a Monte-Carlo simulation using AlphaSim (Douglas Ward, http://afni.nimh.nih.gov/pub/dist/doc/program_help/AlphaSim.html) to give an overall threshold of $p < 0.05$, corrected for multiple comparison across the entire brain. One-sample t -tests were performed on this contrast to obtain the group effect of the MPH group, noMPH group 1 ($n=62$), and noMPH group 2 ($n=24$). Two-sample t -tests between MPH and noMPH groups identified differences in voxel-wise responses to conflict anticipation and UPE as a result of MPH.

Results

Behavioral performance in the SST, including Go RT (629.7 ± 95.8 vs. 653.8 ± 120.0 ms, $p=0.38$, MPH vs. noMPH group 1; 629.7 ± 95.8 vs. 647.4 ± 135.7 ms, $p=0.61$, MPH vs. noMPH group 2) and SSRT (225.7 ± 32.7 vs. 217.2 ± 4.1 ms, $p=0.22$, MPH vs. noMPH group 1; 225.7 ± 32.7 vs. 209.1 ± 36.6 ms, $p=0.06$, MPH vs. noMPH group 2), did not differ between the MPH and noMPH groups. The lack of significant between-group behavioral differences replicated previous work (Farr et al., 2014a). MPH also did not alter the sequential effect (Hu et al., 2015b; Ide et al., 2013), as quantified by a correlation between $P(\text{stop})$ and Go RT ($z=0.16 \pm 0.11$ vs. 0.21 ± 0.14 , $p=0.10$, MPH vs. noMPH group 1; $z=0.16 \pm 0.11$ vs. 0.23 ± 0.16 , $p=0.08$, MPH vs. noMPH group 2).

We first examined regional activations specific to conflict anticipation in each group (Figure 1). In a one-sample t -test, the noMPH group 1 ($n=62$) showed significant anticipation-related activation in the presupplementary motor area (pre-SMA), angular gyrus, right anterior insula, thalamus, and frontopolar cortex, and significant deactivation in ventromedial prefrontal cortex, caudate, parahippocampal gyrus, superior frontal gyrus, posterior SMA, right somatomotor cortex, precuneus, and bilateral visual cortex, replicating our recent work in a larger cohort (Hu et al., 2015b). The noMPH group 2 ($n=24$) showed similar but more restricted patterns of activation to conflict anticipation compared to the noMPH group 1 (see Figure 1). The MPH group showed significant activation to conflict anticipation in right dorsal caudate, right anterior insula, pre-SMA, right superior frontal gyrus (SFG), left somatomotor cortex, and significant deactivation in ventromedial prefrontal cortex/ventral striatum and bilateral visual cortex.

In two-sample t -tests, voxel-wise analysis revealed significantly higher activation to conflict anticipation in the MPH group compared with both noMPH groups in the bilateral caudate head and dorsal thalamus (Figure 2).

We then examined regional activations specific to UPE in each group (Figure 3). In a one-sample *t*-test, several cortical regions were significantly associated with UPE in noMPH group 1, including dACC extending into the supplementary motor area (SMA) and pre-SMA, inferior parietal lobule (IPL), right insular cortex, right superior temporal gyrus (STG), and bilateral SFG. The noMPH group 2 demonstrated highly similar patterns of cerebral activation related to UPE (see Figure 3). These results largely replicated our previous work (Ide et al., 2013). The MPH group showed no significant UPE-related activations at the same threshold.

In two-sample *t*-tests, voxel-wise analysis did not reveal any differences between MPH and noMPH group 1 or between MPH and noMPH group 2 at the same threshold. Thus, we conducted post hoc analyses to focus on cerebral regions that responded to UPE in the noMPH groups. Because patterns of activity were largely similar between the two control groups that did not receive MPH, we isolated regions identified in the larger group (noMPH group 1) and extracted contrast values from these regions for all three groups (Figure 4). We then used two-sample *t*-tests to compare the contrast values between MPH and noMPH group 1, as well as between MPH and noMPH group 2. Compared with noMPH group 1, the MPH group showed significantly reduced cerebral activation in the dACC, STG, IPL, and insula ($p < 0.05$). Compared with noMPH group 2, the MPH group showed significantly less cerebral activation in similar regions and also bilateral SFG ($p < 0.05$).

Discussion

Combining model-based analysis and fMRI of the SST, we report that in healthy young adults, MPH administration is associated with increased cerebral responses to conflict anticipation and reduced responses to UPE. Specifically, the MPH group showed significantly higher activation to conflict anticipation than controls did in the bilateral caudate head. Further, while a control group without receiving MPH displayed significant responses to UPE in the dACC, insula, and IPL, the MPH group showed no significant activity related to UPE in any region in whole-brain analysis. These findings highlight the distinct effects of a catecholaminergic agent on the neural processes underlying conflict anticipation and UPE.

Effects of MPH on conflict anticipation

The bilateral caudate head showed significantly higher activation to conflict anticipation following MPH administration compared with control groups not receiving MPH. An integral part of corticostriatal-midbrain circuits supporting conflict detection and cognitive control, the caudate head is heavily modulated by midbrain dopaminergic inputs (for reviews, see: Cools, 2008; Haber, 2014).

Animal studies demonstrated that a majority of caudate neurons increase their firing when anticipating a salient visual target (Lauwereyns et al., 2002) and in response to MPH injection (Claussen and Dafny, 2012; Yang et al., 2006). Human fMRI studies have linked these two findings, showing that MPH increases caudate activation during tasks requiring conflict anticipation. For instance, on a choice reaction-time task, MPH increased caudate activation on trials where subjects needed to anticipate a directional cue (Müller et al.,

2005). MPH also increased caudate responses during the go/no-go task, specifically when individuals successfully anticipated infrequent no-go trials (Kasparbauer et al., 2015). However, Nandam et al. (2014) used a similar task and found that MPH decreased caudate responses to no-go trials; this may be due to the fact that the cluster was located posterior to the caudate region reported here. It is also possible that because the no-go response was modeled at signal onset, the finding resembles a prediction error signal rather than anticipatory processes. The current findings thus support the body of work implicating the striatum and catecholaminergic function in cognitive control. By using a more quantitatively precise approach to estimate conflict anticipation, we have isolated neural responses that are specific to this critical component of cognitive control and modulated by MPH.

More broadly, the caudate supports behavioral anticipation in a wide variety of contexts. The caudate responds to the anticipation of a reward in relation to increased striatal dopaminergic signaling (Da Silva Alves et al., 2011; Dreher et al., 2009), to reduced delay discounting (Benningfield et al., 2014), and to stress (Kumar et al., 2014). Caudate activation has also been related to personality traits such as neuroticism and anxiety when anticipating threatening or emotional stimuli (Brühl et al., 2011; Choi et al., 2012a; Drabant et al., 2011). Finally, the caudate responds to the anticipation of both positive and negatively valenced experiences (Greenberg et al., 2015). While one study showed caudate activation in anticipation of pleasurable music, a recent meta-analysis identified the caudate as being commonly activated in response to pain across 19 fMRI studies (Palermo et al., 2015; Salimpoor et al., 2011). It remains to be seen how catecholaminergic agents influence caudate and other regional responses during these behavioral contingencies.

MPH effects on anticipation-related caudate activity during cognitive control may help to explain the drug's beneficial properties in clinical populations such as individuals with attention deficit hyperactivity disorder (ADHD). Reductions in volume and D₂/D₃ binding potential of the caudate head are a prominent feature in ADHD (Hynd et al., 1993; Montes et al., 2010; Volkow et al., 2007). On tasks requiring conflict anticipation, individuals with ADHD show poor performance, but after MPH administration, performance improves in association with larger changes in caudate D₂/D₃ binding potential (Fried et al., 2014; Rosa-Neto et al., 2005). Thus, MPH-induced changes in caudate catecholaminergic function may contribute to an improved ability to anticipate stimuli for cognitive demands (Cherkasova et al., 2014; Wang et al., 2013). Anticipation-related activation in the caudate is also altered in other clinical populations that implicate catecholaminergic dysfunction. Pathological gamblers and individuals with schizophrenia show blunted caudate responses to reward anticipation (Choi et al., 2012b; Mucci et al., 2015), whereas adolescents with social phobia and bulimia nervosa display increased caudate activation during reward anticipation (Bohon and Stice, 2012; Guyer et al., 2012). In order to develop effective treatments, more work is needed to link caudate catecholaminergic function directly with anticipation behaviors in these psychiatric conditions.

Effects of MPH on UPE

With reduced UPE-related activity following MPH administration, the dACC and the insula are notable for error/surprise processing and responses to prediction error (Bossaerts, 2010;

Garrison et al., 2013; Holroyd and Coles, 2002; Silvetti et al., 2013; Uddin, 2015; Ullsperger et al., 2010). As major nodes of the “salience network,” these regions are strongly modulated by DA and NE (Chandler et al., 2014; Cole et al., 2013; Hermans et al., 2011; Seeley et al., 2007) and are amenable to the influence of MPH. Indeed, previous studies have shown that MPH attenuates dACC/insular activity in the context of surprise or error. For instance, compared with placebo, acute MPH challenge is associated with blunted insular response to surprising stimuli (Ivanov et al., 2014; Pauls et al., 2012). MPH also reduces neural responses to error in the insula and dACC during reversal learning (Dodds et al., 2008) and Stroop tasks (Moeller et al., 2014). The current data thus corroborate these findings and demonstrate that catecholaminergic function of the dACC and insula may comprise Bayesian inference and the response to violations of expected outcomes.

As part of the ventral attention network, the IPL responds to stimulus detection (Bunge et al., 2002; Corbetta and Shulman, 2002). Compared with placebo, MPH reduced inferior parietal response in healthy adults searching for visuospatial targets (Mehta et al., 2000; Udo De Haes et al., 2007). Further, Schlösser et al. (2009) reported that MPH attenuates IPL response to uncertainty on a task where participants used sensory evidence to make decisions. Positron emission tomography imaging has revealed increased DA release in IPL during SST performance compared with a baseline go-only task (Albrecht et al., 2014). These findings suggest that manipulation of catecholamines may alter IPL activity during tasks that require rapid detection of infrequent and behaviorally relevant stimuli.

Observations of reduced error-related neural activity have also been made with acute administration of other catecholaminergic agents such as methamphetamine (Bernacer et al., 2013; see, however, Menon et al., 2007). The current findings along with these earlier studies are in line with the literature in animals suggesting a role of DA (Schultz, 1998, 2002; Schultz et al., 1997) and NE (Aston-Jones et al., 1994; Foote et al., 1980) in prediction error computation, as discussed earlier. Individuals with reduced catecholaminergic functioning such as healthy older adults or those with Parkinson’s disease show impaired predictive learning, a deficit that can be ameliorated with L-DOPA (Chowdhury et al., 2013; Frank et al., 2004; Galea et al., 2012; Knowlton et al., 1996; Schonberg et al., 2010). Genetic differences also appear to play a role in learning behaviors and brain responses to error (Klein et al., 2007). Individuals with genes that code for high tonic DA levels (Catechol-O-Methyltransferase Met/Met carriers) and increased D₄ receptor expression (DRD4 single-nucleotide polymorphism-521 CC carriers) in the prefrontal cortex show reduced prefrontal responses to novel stimuli and error processing (Krämer et al., 2007; Marco-Pallarés et al., 2010). Thus, the current findings support the general role of DA and NE in prediction error computation, and highlight cerebral regions that are involved in UPE and modulated by catecholamine manipulation.

Although little research exists on how MPH specifically affects the neural correlates of UPE, additional clues can be derived from studies of the mismatch negativity (MMN), which represents a response to an “oddball” amidst familiar stimuli (Sams et al., 1985). However, studies of catecholamine involvement in the MMN have shown mixed results. In healthy adults, NE alpha-2 antagonists decreased MMN amplitude, whereas DA D₂ antagonists increased MMN amplitude (Kähkönen et al., 2001; Mervaala et al., 1993). Individuals with

Parkinson's disease showed attenuated MMN, presumably due to catecholamine depletion (Pekkonen et al., 1995). Yet other studies found no significant difference in MMN following D₁ or D₂ receptor stimulation (Leung et al., 2007), after tyrosine/phenylalanine depletion to reduce DA neurotransmission (Leung et al., 2010), or after apomorphine and clonidine challenge to alter NE and DA function (Hansenne et al., 2003). Further, MPH did not significantly alter the MMN in children diagnosed with ADHD (Winsberg et al., 1997). An important distinction is that in the oddball tasks used to probe MMN, the surprising stimulus is behaviorally irrelevant, whereas in the SST, the infrequent stop signal is critical for successful task performance. This might explain different findings on catecholamine involvement in the MMN and clarify the role of catecholamines in the processing of salient, behaviorally relevant stimuli (Aston-Jones et al., 1994; Bromberg-Martin et al., 2010; Foote et al., 1980; Horvitz, 2000). Therefore, these reports, along with the present data, highlight that catecholamines may influence neural responses to surprise, but perhaps especially in situations where the surprising stimuli are behaviorally relevant. Another issue is that some of the MMN studies used small sample sizes and reported high intersubject variability (for reviews, see: Garrido et al., 2009; Pekkonen, 2000). Larger scale studies should be conducted for a more thorough evaluation on how DA and NE affect neural processing of behaviorally relevant/irrelevant surprising stimuli.

A question remains over why catecholamine-enhancing drugs tend to decrease, rather than increase, error-related brain activity. Some have suggested that because DA and NE increase the signal-to-noise ratio of neuronal activity (Hirata et al., 2006; Kiyatkin and Rebec, 1996), perhaps MPH makes the brain more efficient, decreasing the energy required for task performance (Swanson et al., 2011). Indeed, MPH decreases brain glucose metabolism during cognitive task performance in a large swath of the cerebral cortex, including the dACC/superior frontal cortex, parietal cortex, and bilateral insula (Volkow et al., 2008). Another possibility is that administering MPH to healthy adults results in a maladaptive DA "overdose" (Cools, 2006; Cools and D'Esposito, 2011), in line with reports that MPH normalizes brain activity during response inhibition in populations with DA deficiency, such as ADHD (Rubia et al., 2011; Vaidya et al., 1998) and cocaine-use disorders (Li et al., 2010; Moeller et al., 2014; Matuskey et al., 2013). This hypothesis is also in accordance with the opposing effects of MPH on the BOLD signal during a go/no-go task, depending on DA transporter genotype (Kasparbauer et al., 2015). On no-go compared with go trials, MPH increased the BOLD signal in carriers of the 9R allele for *SLC6A3*, but decreased the BOLD signal in carriers of the 10/10 allele; these genotypes are associated with lower and higher striatal DA transporter availability, respectively. More research is needed to elucidate the precise mechanisms behind MPH effects on cerebral activations.

Conclusions and limitations

There are several limitations to the current study. First and most importantly, we did not have a placebo control for the individuals who received MPH. Therefore, the placebo effect is a potential confound for the differences that we observed between the MPH and noMPH groups. Although previous studies suggest that MPH and placebo show different, distinguishable effects on cerebral activations (Marquand et al., 2011, 2012; Volkow et al., 2008), the current results need to be replicated in a placebo-controlled study. Second, this

study was conducted with a relatively small sample of 24 individuals receiving MPH, limiting the power of our analyses. The small sample size perhaps explained why a direct voxel-wise comparison between MPH and noMPH groups did not reveal significant findings related to UPE. Lastly, there may be factors contributing to individual differences in the cerebral responses to MPH that we did not assess and could not account for. Thus, future research with a more comprehensive evaluation of participants' genetic make-up (Krugel et al., 2009) and personality traits (Cooper et al., 2014; Pickering and Pesola, 2014; Skatova et al., 2013; Smillie et al., 2011; Zhang et al., 2015) is an important next step.

In summary, MPH increased caudate activation to conflict anticipation and reduced cerebral activations to UPE in the SST. These data have implications for the role of catecholamines in the brain's ability to adapt flexibly to a rapidly changing environment. A key question that remains is whether these effects are mediated primarily by dopaminergic or noradrenergic signaling. Understanding the precise contributions of DA and NE to conflict anticipation and to error prediction and learning is an important task for future studies and may have implications for both basic and clinical neuroscience (Corlett et al., 2007; Griffiths et al., 2014; Huys et al., 2014; Song and Fellous, 2014; Yoder et al., 2009).

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Figure 1.

Cerebral activations to conflict anticipation in healthy adults who did or did not receive oral methylphenidate (MPH). Significant activations shown for the (a) noMPH group 1, (b) noMPH group 2, and (c) MPH group at the AlphaSim $p < 0.05$ corrected threshold.

Figure 2.

Contrast values for conflict anticipation for each group. Significant clusters were derived from the voxel-wise two-sample *t*-test of MPH group>noMPH group 1 at the AlphaSim $p<0.05$ corrected threshold (nearly identical results were identified in the MPH>noMPH group 2 comparison). The MPH group showed significantly higher activations to conflict anticipation than healthy adults who did not receive MPH in the caudate head and dorsal thalamus (shown in bottom right inset). ** $p<0.01$; *** $p<0.001$.

Figure 3. Cerebral activations to unsigned prediction error (UPE) in healthy adults who did or did not receive oral MPH. Significant activations shown for the (a) noMPH group 1, (b) noMPH group 2, and (c) MPH group at the AlphaSim $p < 0.05$ corrected threshold.

Figure 4.

Contrast values for UPE for each group. Voxel-wise two-sample *t*-tests did not reveal significant results. Therefore, clusters were derived from the one-sample *t*-test results for the larger control group (noMPH group 1), and post hoc *t*-tests were performed. The MPH group showed significantly lower cerebral activations to UPE than did healthy adults who did not receive MPH. R: right; L: left; ACC: anterior cingulate cortex; STG: superior temporal gyrus; IPL: inferior parietal lobule; SFG: superior frontal gyrus. * $p < 0.05$; ** $p < 0.01$.