A Match Made by Modafinil: Probability Matching in Choice Decisions and Spatial Attention

Joy J. Geng, Steffan Soosman, Yile Sun, Nicholas E. DiQuattro, Beth Stankevitch, and Michael J. Minzenberg

Abstract

■ When predicting where a target or reward will be, subjects tend to choose each location commensurate with the true underlying probability (i.e., to probability match). The strategy of probability matching includes sampling high and low probability locations on some proportion of trials. In contrast, models of probabilistic spatial attention hypothesize that on any given trial attention will either be weighted toward the high probability location or be distributed equally across all locations. Thus, the strategies of probabilistic sampling by choice decisions and spatial attention appear to differ with regard to low-probability events. This distinction is somewhat surprising because similar brain mechanisms (e.g., pFC-mediated cognitive control) are thought to be important in both functions. Thus, the goal of the current study was to examine the relationship between choice decisions and attentional selection within single trials to test for any strategic differences, then to determine whether that relationship is malleable to manipulations of catecholamine-modulated cognitive control with the drug modafinil. Our results demonstrate that spatial attention and choice decisions followed different strategies of probabilistic information selection on placebo, but that modafinil brought the pattern of spatial attention into alignment with that of predictive choices. Modafinil also enhanced learning of the probability distribution, evidenced by earlier learning of the probability distribution. Together, these results suggest that enhancing cognitive control mechanisms (e.g., through prefrontal cortical function) leads spatial attention to follow choice decisions in selecting information according to rule-based expectations. ■

INTRODUCTION

Probabilistic information is ubiquitous in our natural environments and provides an important cue for selection of both sensory inputs and behavioral outputs. For example, mechanisms of spatial attention are known to bias sensory selection toward locations that are more likely to contain task-relevant information. These probabilities can be implicitly present or symbolically cued, but the outcome is similar: Targets in the more likely location are detected or recognized faster and more accurately (e.g., Brascamp, Blake, & Kristjánsson, 2011; Druker & Anderson, 2010; Fecteau, Korjoukov, & Roelfsema, 2009; Geng & Behrmann, 2002, 2005, 2006; Behrmann & Tipper, 1999; Chun & Jiang, 1998; Posner, Snyder, & Davidson, 1980; Biederman, Glass, & Stacy, 1973). These probabilistic cues are used to selectively facilitate information processing in regions of the visual field that are likely to contain useful information because doing so helps overcome natural limitations in sensory processing (Reeves & Sperling, 1986; Neisser & Becklen, 1975; Kahneman, 1973; Sperling, 1960).

Although many studies have now shown that probabilistic cueing is an effective way to selectively bias attention, the exact mechanisms of how attention is weighted on a trial-by-trial basis are still unresolved. In contrast, the probabilistic sampling strategy for choice behaviors (e.g., in foraging tasks) that require discrete responses are quite clear; subjects tend to follow a pattern of probability matching in which each alternative is sampled on a proportion of trials equal to the true probability of the reward being there (e.g., Kable & Glimcher, 2009; Koehler & James, 2009; Sugrue, Corrado, & Newsome, 2004; Wolford, Miller, & Gazzaniga, 2000; Baum, 1979; Estes, 1976; Herrnstein, 1970, 1974; Gardner, 1958). Probability matching is sometimes thought to be a suboptimal strategy because fewer rewards are collected than under a strategy of maximization whereby the highest probability location is sampled exclusively. However, it has been argued that probability matching can be "optimal" during the exploration of an environment because it builds rules about the topography of rewards, is more likely to find patterns when present, and is sensitive to dynamic changes in statistical structure (e.g., Behrens, Hunt, Woolrich, & Rushworth, 2008; Gaissmaier & Schooler, 2008; Cohen, McClure, & Yu, 2007; Wolford et al., 2000). There are conditions when the high probability location may be sampled more frequently than the true probability, but these situations are the exception rather than the norm, particularly under experimental conditions where the strategy to maximize is not emphasized with large rewards, learning, or feedback (e.g., Kasanova, Waltz, Strauss, Frank, & Gold, 2011; Koehler & James, 2009; Gaissmaier & Schooler, 2008; Fantino & Esfandiari, 2002;

University of California, Davis

Shanks, Tunney, & McCarthy, 2002; Wolford et al., 2000; Friedman & Massaro, 1998; Baum, 1979; Herrnstein, 1970).

There are two strategies by which probabilistic cues can be used by the attentional system to bias perception; these are distinguished by the distribution of attention across alternative locations on a single trial. The first is a weighted resource strategy in which attention, within a single trial, is weighted according to the probability of the target being in that location (e.g., Anderson & Folk, 2010; Druker & Anderson, 2010; Vul, Hanus, & Kanwisher, 2009; Eckstein, Shimozaki, & Abbey, 2002; Sperling, 1986; Eriksen & Yeh, 1985; Shaw & Shaw, 1977). These weights may reflect the true probabilities or be biased toward maximizing attention on the highest probability location; for example, if the proportion of a target in two locations are .7 and .3, respectively, spatial attention would split between the two locations in a ratio of 7:3 up to 10:0. In the most extreme case of maximal weighting of the highest probability location, the other regions would only be attended if the target was absent from that location. Data from neurobiological and psychophysical methods frequently appear consistent with this strategy (e.g., Gould, Rushworth, & Nobre, 2011; Sylvester, Shulman, Jack, & Corbetta, 2007; Vossel, Thiel, & Fink, 2006; Ciaramitaro, Cameron, & Glimcher, 2001; Basso & Wurtz, 1997).

The second strategy is a variant of probability matching in which the distribution of attention is probabilistic between trials; for example, Jonides (1980) proposed a two-stage model in which attention is selectively focused on the high probability location, but only on a proportion of trials equal to the true probability of the target occurring there (e.g., .7 using the previous example). If the target is not in the high probability location, then the system defaults to a parallel processing mode in which attention is distributed over all possible locations equally. Critically, on the remaining proportion of trials (e.g., .3), the parallel processing mode is engaged from the beginning and attention is distributed equally across all locations (van der Heijden, 1989; Jonides, 1980, 1983).

The different attentional strategies are hard to distinguish because they make similar predictions for behavior that is averaged over multiple trials (e.g., Ciaramitaro et al., 2001). All would lead to shorter average RTs and higher average accuracy in response to targets in an explicitly cued location (e.g., Posner, 1980; Posner, Nissen, & Ogden, 1978) or a high probability location learning paradigms (e.g., Geng & Behrmann, 2005; Chun & Jiang, 1998; Miller, 1988). The critical difference between strategies is whether the overall pattern of performance is because of a weighted attentional bias on every trial or a focal attentional bias on the high probability location on a subset of trials. Interestingly, none of the models would hypothesize attention being weighted (partially or fully) in favor of a low probability over a higher probability location. Thus, the strategies for choice behaviors and spatial attention differ such that spatial attention is not hypothesized to ever be biased toward low probability locations, but choice behaviors sample low probability locations. In choice tasks, both high and low probability locations are sampled directly, but the frequency depends on the probability of reward.

In this study, we test whether differences in probabilistic strategies for spatial attention and choice decisions can be measured within the same trial, and moreover, whether the two processes can be brought into convergence by manipulating the neurochemical circuits that drive these processes. We used a novel task in which subjects were asked to first choose the location of an upcoming target and then subsequently detect the appearance of a target on the same trial. The target location was manipulated to favor one location over the other in the first half of the experiment and then to be unbiased in the second half. We used the drug modafinil (MOD) to evaluate the role of central catecholamine systems in the modulation of cognitive processes related to choice decisions and spatial attention.

MOD is an FDA-approved medication that shows low-potency inhibition of the plasma membrane transporters for norepinephrine (NET) and dopamine (DAT); at doses commonly used in clinical settings, it shows significant displacement of binding to the NET and DAT (e.g., Andersen et al., 2010; Volkow et al., 2009; Madras et al., 2006). It elevates extracellular levels of norepinephrine (NE) and dopamine (DA) in a widespread manner but particularly strongly in the frontal cortex. We have previously found evidence to suggest that MOD may optimize task-relevant pFC-based circuits by optimizing the modes of signaling activity in the locus coeruleus (LC; Minzenberg, Watrous, Yoon, Ursu, & Carter, 2008) and by strengthening task-active neuronal ensembles in pFC (e.g., Minzenberg & Carter, 2008; Cohen et al., 2007; Yu & Dayan, 2005). This effect of LC modulation on pFC function could be mediated via increased release in terminal fields in pFC of both NE (e.g., Berridge & Abercrombie, 1999; Florin-Lechner, Druhan, Aston-Jones, & Valentino, 1996) and also DA, given that transport of extracellular DA in pFC primarily occurs via the NET, and at high rates of NE release, increased competition of NE with DA for NET binding leads to increased extracellular DA (e.g., Carboni & Silvagni, 2004).

MOD improves numerous cognitive functions, especially those that are highly dependent on control processes and pFC function In healthy humans, these include improvements in stop-signal RT, planning, rapid switching of attention, working memory, and proactive cognitive and inhibitory control (e.g., Marchant et al., 2009; Winder-Rhodes et al., 2009; Minzenberg et al., 2008; Cohen et al., 2007; Morgan, Crowley, Smith, LaRoche, & Dopheide, 2007; Piérard et al., 2006; Waters, Burnham, O'connor, Dawson, & Dias, 2005; Yu & Dayan, 2005; Ward, Harsh, York, Stewart, & McCoy, 2004; Turner et al., 2003; Béracochéa et al., 2001). Probabilistic learning depends on the ability to integrate target locations over time, which relies on pFC functions (Huettel, Mack, & McCarthy, 2002), and

therefore, we expected MOD to enhance pFC function and facilitate representation of the underlying spatial probability structure.

We hypothesized that spatial attention and choice decisions would rely on separate strategies during "baseline" conditions (i.e., naive subjects on placebo), as predicted by existing models of spatial attention and decision-making. However, we further hypothesized that spatial attention might be brought into convergence with a strategy of probability matching, specifically when the low probability location is chosen, when cognitive control mechanisms were enhanced by MOD.

The critical trials to evaluate the strategy of spatial attention occurred when the low probability location was chosen to contain the target. On these trials, subjects chose the less likely location, but they did so in violation of the global probabilities. There are three different predictions for the RT data: First, if attention adheres to a strategy of weighted resource distribution, then attention would remain biased toward the high probability location; thus, spatial attention would be opposite to the chosen location. Second, if attentional priority is set according to the two-stage model of Jonides (1980), then attention should either be biased toward the high probability location or be evenly distributed (i.e., unbiased) across the two locations. However, a third possibility is that attentional priority would be set by the choice decision. If this occurs, then attention would be biased toward the low probability location in direct opposition to the global statistical likelihoods. Note that the third alternative is not predicted by any current models of attention (see above) but would be consistent with neural models that hypothesize an important role of pFC in setting attentional priority (e.g., DiQuattro & Geng, 2011; Kennerley & Wallis, 2009; Rossi, Pessoa, Desimone, & Ungerleider, 2009; Gazzaley et al., 2007; Everling, Tinsley, Gaffan, & Duncan, 2006; Wallis, Anderson, & Miller, 2001; Shimamura, 2000; Duncan, 1986).

METHODS

Subjects

Twenty-six healthy adults (16 women; age = 39.7 ± 4.5 years, range = 23–42 years) participated. All were right-handed, had normal or corrected-to-normal vision, were free of medical (including neurological) illness by report, and lacked psychiatric disorders as determined by the Structured Clinical Interview for DSM-IV Disorders, Nonpatient version. The experimental procedures were approved by the internal review board at the University of California, Davis. The experiment was conducted with the informed written consent of each subject. All subjects were instructed to maintain their usual quantities and patterns of nicotine and caffeine intake, without changes on or between test days, to avoid neural/cognitive effects because of changes in intake from their baseline. All included subjects tested negative for drugs of abuse in their urine on each testing day. The test-to-test interval was 12.7 ± 12.0 days (range = 2–43 days).

Task

Each trial began with bilateral question marks appearing in two blue squares (Figure 1). The question marks prompted subjects to indicate their choice location (left or right) for an upcoming target. These choices were an explicit measure of the subjects' expectation for where the next target would appear. For data analyses, "left" and "right" responses were recoded according to the whether the location had a "high" or "low" probability to contain the target. These prompts were on for an unlimited duration until the subject responded. The "j" key indicated a left choice and the "k" key, a right choice. After a jittered ISI ranging between 1000 and 1800 msec (at 200-msec intervals), a target circle appeared in one of the two locations for 100 msec. The unpredictable ISI was critical for reducing the number of anticipatory button presses, given the predictability of the presence of the target. We did not include "catch" trials because that would reduce the reinforcement validity of the "choice" portion of the task. We conducted additional analyses to test for any anticipatory responses (i.e., RTs less than 100 msec)

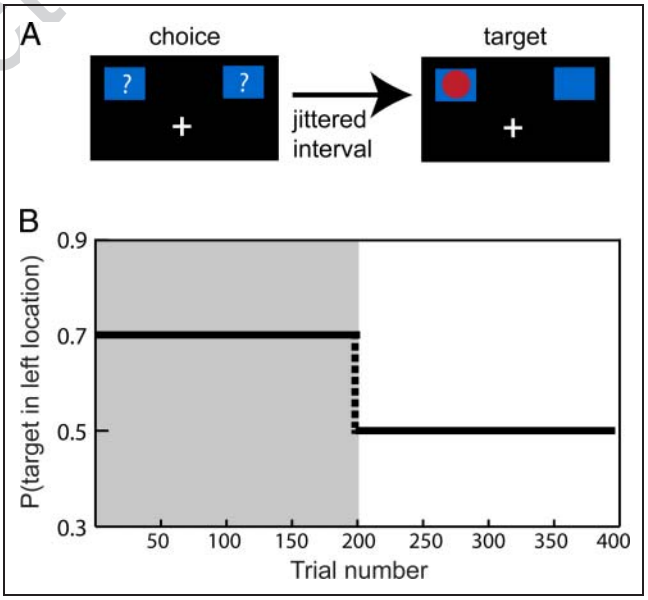

Figure 1. Illustration of trial procedure and experimental design. (A) On each trial, subjects were prompted to indicate a two-alternative-forced-choice response predicting the location of the target. After a varying interval, subjects indicated the appearance of a target with a single button response. The target was biased to appear in one or the other location on 70% of trials in the first half of the experiment (200 trials) and appeared in the two locations randomly in the second half. (B) Illustration of the probability structure throughout each experimental session. The first half was the biased probability block (shaded gray). The location of the target was counterbalanced between subjects and across experimental sessions.

and eliminated those from further analysis. Subjects were instructed to press the "space" bar as rapidly as possible to indicate detection of the target.

During the first half of the experiment, the target was implicitly biased to appear in one location such that 70% of targets appeared in one location and 30% in the other. No mention of this spatial probability was made to the subjects at any point of the experiment. The "high probability" location was counterbalanced across subjects in the first session (i.e., either modafinil or placebo) and reversed in the second. The reversal minimized cross-session learning effects regarding the specific mapping of location and target probabilities. Any carryover effects would therefore be because of an abstract learning of spatial probabilities being present rather than the direct knowledge of the target being in a single location. In the second half of the experiment, the target appeared randomly in each location (i.e., 50% of targets in each location). The random block was included to allow us to measure the "decay" of probabilistic expectations. In analyses, the locations were still referred to as being "high" or "low" probability in reference to the likelihood of the target being in that same location in the previous block. Subjects were not informed of the probability distributions during the first and second halves of the experiment. A self-paced rest period occurred every 100 trials, resulting in a total of four experimental blocks. At the end of the experiment, we assessed their knowledge of the probability structure informally but found no reliable ability to report the spatial probability structure from any particular time period. We were only able to assess knowledge of the probability distribution after the entire experiment to avoid (to the best of our ability) any changes in strategic search for structure in subsequent sessions; in any case, explicit knowledge of spatial probabilities has little impact on behavior (e.g., Fecteau et al., 2009; Geng & Behrmann, 2005; Chun & Jiang, 1998, 2003). In these prior studies, which used similar spatial probabilistic manipulations, behavior preceded knowledge such that subjects showed a bias in responses based on probabilities regardless of whether or not they expressed conscious awareness of it.

Procedure

A crossover design was employed such that each subject received PLC before one experimental session and 200 mg oral MOD before the other session. Drug administration was double-blind, with treatment order randomized and counterbalanced by a research pharmacist using a computer algorithm; the pharmacist also packaged the MOD and PLC in identical appearing capsules for administration and was otherwise uninvolved in the study. Testing was conducted approximately 2–3 hr after MOD administration, during peak plasma levels of the drug (Robertson & Hellriegel, 2003). Subjects first completed a training block (approximately 20 trials) to familiarize them with the task. They then completed a total of 400 trials in four blocks. A self-paced rest occurred after each block. Eye movements were not monitored, although subjects were instructed to fixate the central fixation cross. All investigators remained blind to treatment order for individual subjects until all data was acquired for that subject, and treatment order information was then necessary to sort data for inferential testing. The primary analyses were conducted within each session alone to draw inferences from data uncontaminated by carryover interactions; thus, the manipulation of drug (PLC, MOD) was a between-subject factor in these analyses. Separate within-subject analyses were conducted to directly examine the relationship between performance between sessions in relation to drug dosage.

Logistic Model for Choice Data

The choice data were fit to a logistic function, which provided a model of capacity-limited learning. Data from each participant was fit to a four parameter logistic function described by $[Y = A/(1 + \exp(-B*(x - C))) + D]$, where A is a scaling factor that represents the upper limit, B is the growth rate, C indicates the time of maximum change in learning, and D is the lower asymptote. The best fit function was determined by the Levenberg–Marquardt with line search algorithm using MATLAB (2009a, Mathworks, MA). The starting points for the individual subject PLC and MOD fits were derived without constraint from the best fit parameters for the group means. Data from one subject could not be fit by a logistic function (only a single exponential) and was therefore excluded from this analysis. The root-mean-square error from the fitted logistic functions to the individual data was entered into a Drug × Session ANOVA; there were no significant main effects nor an interaction [all $F(1, 23) < .18$, $p > .67$; mean and *SEM*: PLC (Session 1) = .037 ± .004, PLC (Session 2) = .034 ± .004, MOD (Session 1) = .036 ± .005, MOD (Session 2) = .035 ± .005]. This indicated that the derived parameters from the models fit the data from all conditions equally well.

RESULTS

The primary goals of this study were to examine strategic differences in how choices and spatial attention sample probabilistic information and to determine whether the two strategies could be brought into convergence by manipulating cognitive function through neuromodulation with the drug modafinil (MOD). To do so, we first characterized the profile of choice decisions as a function of block probability and drug manipulation. We then describe the pattern of RTs in response to the target as a function of block probability, drug manipulation, and also the preceding choice. RTs to targets in alternative locations have long been used as a measure of the distribution of spatial attention; here, we use it to assess the

relative weighting of internal choices and external global probabilities on sensory selection.

Choice Decisions: Session 1

Data from Session 1 were analyzed alone to avoid any potential carryover effects in the data from session to session; these data represented the most straightforward comparison of the effects of modafinil on performance. Each trial began with a choice screen in which subjects indicated where they thought the target would appear on that trial (see Figure 1). We expected choices to follow a "foraging" strategy where selection of each location was matched to the true underlying probability of the target being in that location. Such a strategy would result in the high and low probability locations being chosen on a proportion of .7 and .3 trials, respectively. We further expected that learning of the probability structure (as indicated by probability matching) would be enhanced on MOD, consistent with previous evidence that MOD improves cognitive control and memory functions associated with the pFC.

To quantify learning of the spatial probability, we first calculated the proportion of "high probability" choices over a 50 trial moving window (i.e., the first data point corresponds to the proportion of "high probability" choices over Trials 1–50, and the second data point, the proportion of high probability choices over Trials 2–51; Figure 2A). Note that because the probability of choice was calculated over bins of 50 trials, there was an apparent decline in matching at the end of the biased block in Figure 2A, but this is because of the inclusion of trials from the random block in those bins. Only the first 150 bins included trials exclusively from the biased probability block.

We next characterized the shape of the learning curve, by fitting the first 150 bins of data for each subject using a four-parameter logistic function. The logistic function was described by $[Y = A/(1 + \exp(-B*(x - C))) + D]$, where A is a scaling factor that represents the upper limit, B is the growth rate, C indicates the time of maximum change in learning, and D is the lower asymptote (see Methods for description of model fits to individual data). The logistic function models capacity-limited exponential growth. This is an appropriate model of our data because it characterizes the time to learn the implicit spatial probability bounded by a plateau in behavior (e.g., when probability matching is reached). The parameter for the maximum change in learning (C) characterizes the time bin when the proportion of high probability choices plateaus; this was used to test the hypothesis that

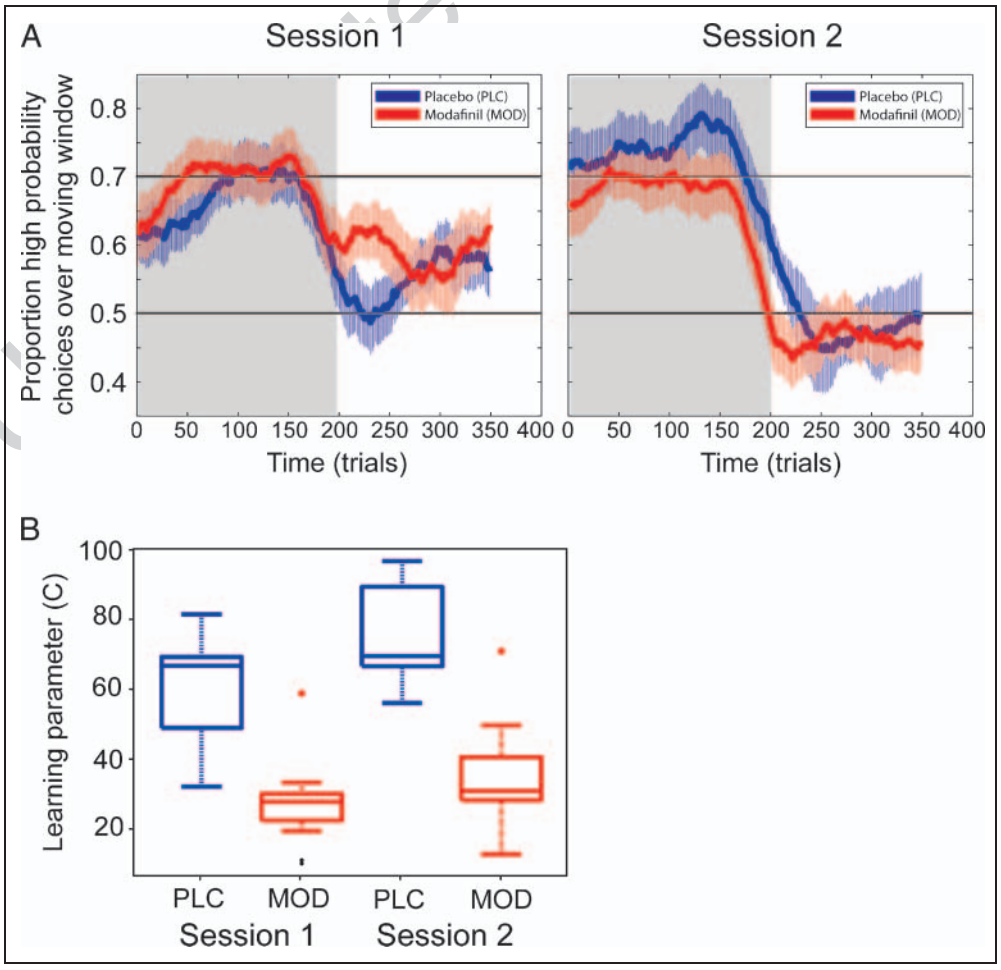

Figure 2. (A) Choice decisions over time as a function of dose-ordering and drug. Each data bin calculates the proportion of high probability choices within a 50 trial window. Left, contains data from Session 1; right, contains data from Session 2. Placebo (PLC) data are in blue and modafinil (MOD), in red. Error bars are *SEM*. Shaded gray area contains trials from the biased probability block. The apparent decline in probability matching at the end of the biased probability block is because of the inclusion of trials from the random probability (involving a moving window of 50 trials; see text). (B) Boxplot of median and 95% confidence intervals for the *C* parameter from the fitted logistic model. The *C* parameter represented the time bin of maximal learning when the proportion of high probability choices reached plateau (i.e., matched probabilities).

participants on MOD would learn to probability match earlier than those on PLC. The *C* parameter was the most accurate measure of when matching was achieved and was more sensitive to the structure of learning than any direct comparison of time bins between conditions (e.g., because such *t* tests would be insensitive to patterns of change over time and require correction for many multiple comparisons).

Model fits for the learning parameter *C* were entered into a two-sided nonpaired *t* test with the factor of drug (MOD, PLC); equal variance between groups was not assumed. This between-group analysis of just the first session data revealed a highly significant difference in the point of maximal learning in the drug and placebo groups [$t(22.2) = 5.9, p < .0001$; Figure 2B]. These data suggested that learning of the target spatial probability occurred earlier on MOD than PLC.

Learning occurred more rapidly on MOD, but this is only meaningful if there were no group differences in initial performance. Although the model parameter *D* is the lower asymptote (i.e., the theoretical intercept), the actual model values were outside the bounds of the data. Therefore, to test for differences in the start point of performance, we compared data from the first 50 trials of the experiment (Bin 1) directly as a function of drug (MOD, PLC) using a two-sided nonpaired *t* test. There was no statistical difference in the start point of learning [$t(19.6) = 0.10, p = .92$; mean values: PLC = 0.62, MOD = 0.61], demonstrating that there were no spurious differences between groups in initial performance. This suggests that the MOD group began to probability match earlier because they learned the probability structure more rapidly. Additional comparisons of the other model parameters A, B, and D, for completeness produced no significant differences between groups (all *t* values less than 1.4, *p* values greater than 1.6); thus, the only meaningful difference between model fits was in the learning parameter *C*.

In addition, the MOD group appeared to perseverate their choice strategy into the random probability block (Figure 2). To examine this effect, we tested if the probability of choosing the high probability location was greater than .5 (chance) at the three central time bins. We conducted three one-sample *t* tests on data bins from the central portion of the block (when transitional effects would have had time to subside) that also contained data from completely independent trials: bin 225 (i.e., trials 225–274), bin 275 (i.e., trials 275–324), and bin 325 (trials 325–375). For the MOD group, the first bin was significantly different from .5 [$t(11) = 2.9, p < .05$ with Bonferroni correction] and the other two were not [both $t(11) < 1.6, p > .13$, without correction]. All three bins were not significantly different from .5 in the PLC group [$t(13) < 1.7, p > .1$, without correction]. The direct comparison of the MOD and PLC groups at time bin 225 was marginally significant [$t(24) = 2.0, p = .06$]. This suggests that subjects on MOD tended to continue to choose the high probability location at a rate greater than chance, although the statistics of the target location were now truly random. This pattern of perseveration was somewhat surprising and suggests that MOD did not optimize behavior, but rather caused subjects to have a stronger bias toward finding statistical structure in the data, even when it did not exist.

Choice Decisions: Session 2

In Session 1, MOD had a local effect that increased seeking of probabilistic structure, which resulted in earlier learning when the spatial probabilities were present, but a bias in choosing the previous high probability location when probabilities were random. We next examined data from Session 2 to see if (a) the effect of MOD was similar when it was experienced subsequent to PLC and (b) whether there were any carryover effects of MOD into Session 2, although it occurred an average of 12.7 ± 12.0 days (range = 2–43 days) after Session 1. Notably, the high probability location changed from session to session, precluding the ability of subjects to reinstate the exact same expectations.

To answer the first question, the data from the first 50 trial time bin and the model *C* parameters between sessions were entered into paired *t* tests for the PLC-first subjects only; drug was now a within-subject factor. There was no difference in the initial probability of choosing the high probability location in the first 50 trials [$t(12) = 1.6, p = .14$; PLC = 0.62, MOD = 0.67], but learning of the target probability occurred earlier on MOD compared with PLC [$F(1, 12) = 17.7, p < .005$; PLC = 62.6, MOD = 34.7]. These results were similar to those from the between-subject analysis of data from Session 1 only (see above); interestingly, the point of maximal learning in the two MOD groups was remarkably similar (MOD Session 1 subjects = 27.4; MOD Session 2 subjects = 34.7; compare red lines in left and right panels of Figure 2A). The effects of MOD on learning were similar when MOD was experienced first and following PLC. Additional comparisons of the other model parameters *A*, *B*, and *D* resulted in no significant differences between groups (all *t* values less than 1.4, *p* values greater than .9). As with the data from Session 1, the only meaningful difference between model fits was in the learning parameter *C*.

With regard to the second question, there were clear carryover effects on performance in the PLC condition when MOD was experienced in Session 1. First, there was a significant difference in the initial probability of choosing the high probability location [$t(11) = 2.3, p < .05$; PLC = 0.61, MOD = 0.71]. Subjects that experienced MOD in Session 1 began the Session 2 with greater sensitivity to the probabilistic structure, despite the high probability location switching to the opposite location. In fact, the rate of choice for the high probability location, even in the first 50 trials reached the level of probability matching, suggesting that learning occurred almost immediately. Although there appears to be an additional

increase in the proportion of high probability over the course of the block, the increase in high probability choices was not significantly different from .7 (i.e., subjects as a group did not overmatch). Although statistically nonsignificant, there were individual differences in the trend toward overmatching (i.e., five subjects chose the high probability location on more than 80% of trials). Individual differences in probability matching (and maximization) are known to exist (e.g., Kasanova et al., 2011; Wozny, Beierholm, & Shams, 2010; Frank, Doll, Oas-Terpstra, & Moreno, 2009; Miller, Valsangkar-Smyth, Newman, Dumont, & Wolford, 2005; Shanks et al., 2002; Friedman & Massaro, 1998), but our sample size was too small to tease out any such subgroup differences.

As before, we also tested for evidence of a continued tendency to choose the high probability location in the random block by conducting one-sample t tests at time bins 225, 275, and 325 (see above). Contrary to the Session 1, there were no significant differences for the PLC group [all $t(13) < 1.2$, $p > .23$] nor for the MOD group [all $t(13) < 1.4$, $p > .17$]. There was no evidence for any perseveration of high probability choices into the random block, perhaps suggesting that subjects accumulated information about the changing probabilities over the two sessions and adjusted their sensitivity to changes in the probability structure (e.g., Behrens, Woolrich, Walton, & Rushworth, 2007).

Target Detection: Session 1

The previous results demonstrated that MOD facilitated learning that led to probability matching. We next examined RTs to the targets that followed choice. Fewer than .04 ± .01% of the data in the PLC condition and .03 ± .01% of the data in the MOD condition were excluded based on the criteria of being less than 100 msec or 2 standard deviations above or below the individual subject mean. We excluded these trials as anticipations and errors, respectively.

First, to confirm that that there was an effect of the spatial probability on target detection, RTs were entered into a mixed-effects ANOVA with factors spatial probability (high, low), block (biased, random), and drug (PLC, MOD). The main effect of spatial probability was significant, $F(1, 24) = 23.5$, $p < .0001$; there was also an interaction between spatial probability and block, $F(1, 24) = 9.7$, $p < .005$, which was because of a bigger difference between high and low probability target RTs in the biased compared with the random probability blocks (low minus high probability RT means: 61 msec [biased], 42.8 msec [random]). This pattern was expected and confirmed that attention was biased toward the high probability location overall, and more so during the biased probability block. However, the critical question was whether this general pattern of attentional priority at the high probability location was modulated by the trial-by-trial choice decision.

To determine the effect of the choice on subsequent attentional selection, we calculated an RT "validity effect" score. Validity was defined by the subtraction of RTs to targets in the chosen location (i.e., "valid" targets) from RTs to targets in the unchosen location (i.e., "invalid" targets). Positive values indicated that attention was biased toward the same location that was chosen to contain the target; negative values indicated that attention was biased opposite to the chosen location; and zero values indicated that attention was distributed equally to both locations. Note that validity is defined relative to the choice and not the external probabilities.

The validity scores from Session 1 were entered into a mixed-design ANOVA with within-subject factors of choice location (high, low) and block (biased, random) and the between-subject factor of drug (PLC, MOD). There was a main effect of choice location, $F(1, 24) = 13.2$, $p < .005$, and an interaction between choice location and drug, $F(1, 24) = 4.9$, $p < .05$. The interaction was because of a significant difference between validity scores on PLC [$t(13) = 3.5$, $p < .01$, with Bonferroni correction], but no difference on MOD [$t(11) = 1.6$, $p = .14$; Figure 3A]. Thus, the strategies for spatial attention differed for trials with high and low probability choices on PLC, but were the same for subjects on MOD. There was also an expected significant two-way interaction between choice location and block, $F(1, 24) = 6.2$, $p < .05$, which reflected reduced differences in validity scores in the random probability block. There was no three-way interaction between choice location, block, and drug, $F(1, 24) = 1.8$, $p = .19$ (see Figure 3A).

The validity scores from the biased probability block were of primary interest and therefore additional planned comparisons were conducted on data from this block alone (i.e., excluding data from the random block). The results were consistent with those reported above: The validity score for low probability choices on PLC was significantly smaller than any of the other three conditions [paired t test: $t(13) = 2.9$, $p < .05$; independent samples t test against the two MOD conditions: both $t(17.8) > 1.8$, $p < .05$]; none of the other comparisons were significant. The fact that the validity score following low probability choices on PLC was significantly less than in any other condition (see Figure 3A) was critical because it indicated that the strategy for spatial attention on low probability choices was different than the strategy following high probability choices, and moreover, that this strategy changed on MOD such that spatial attention now followed choice.

The fact that spatial attention did not follow low probability location choices on PLC was consistent with both the weighted resource and the two-stage models of spatial attention reviewed in the Introduction. Therefore, to more specifically test between these models we conducted a post hoc one-sample t test of just the low probability choices on PLC. Recall that the weighted resource model predicted a negative validity effect and

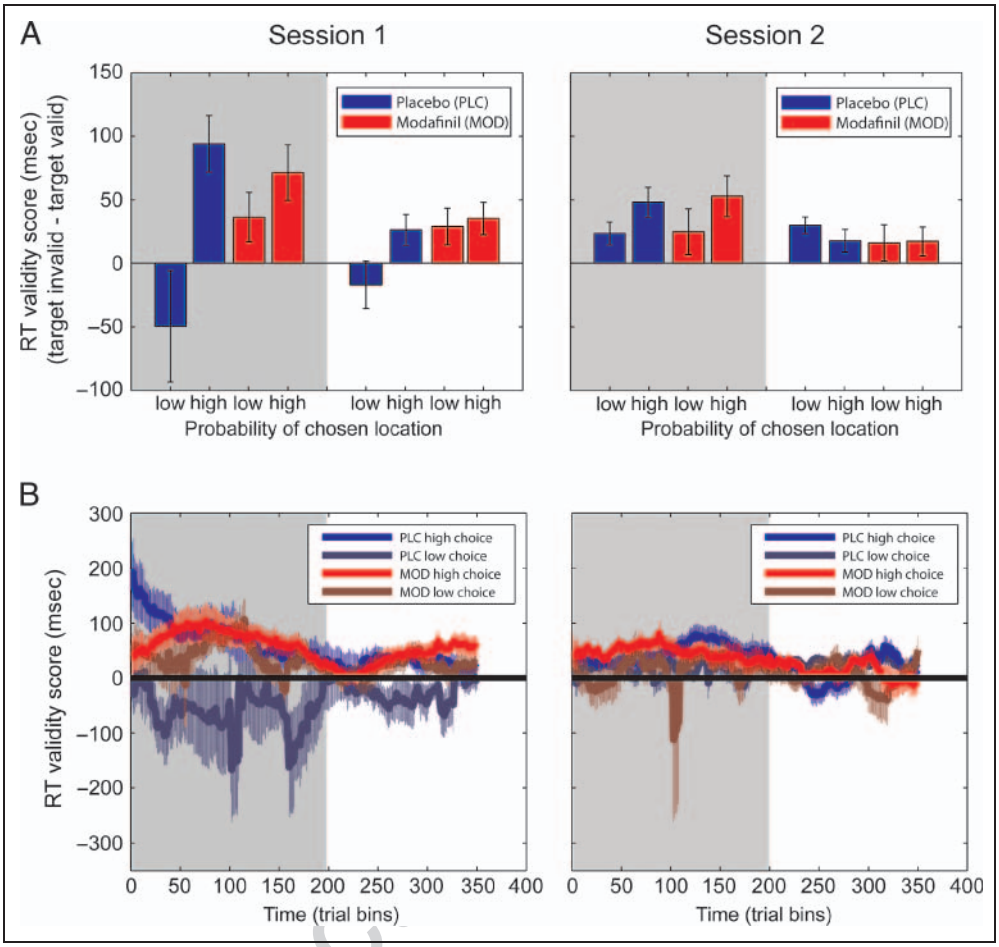

Figure 3. (A) RT validity effects in target detection as a function of the same-trial choice. Panels divided by session and drug similar to Figure 2. Positive values indicate cases in which spatial attention was biased toward the chosen location. Error bars are *SEM*. Notably the validity effect for low probability choices in the Session 1 placebo data are significantly different than all other conditions in the same session. (B) RT validity effect plotted over time. Each data point is a validity score over a 50-trial moving window.

the two-stage model, a null effect on trials with low probability choices. The t test was not significantly different from zero [$t(13) = 1.1$, $p = .14$]. This supported the two-stage model and suggested that, on average, attention was evenly distributed between the two locations when the low probability location was chosen. However, to once again look at individual differences in the use of probabilistic strategies (see choice data above) we further examined the individual data and found a mixture of scores (seven subjects with scores less than −25 msec; five with scores between −25 and 25 msec; and two above 25 msec); this suggested that subjects may have used different strategies.

To be sure that the average validity scores, particularly on low probability choice trials, were not simply because of slower learning of the probability structure (as seen in the choice results), we calculated the validity effect over time. We again used a moving window of 50 trials and calculated a validity score within each window of time (Figure 3B). The validity scores did not appear to change even after subjects had demonstrated knowledge of the global probabilities by choosing the high probability location at a rate commensurate with the true probability (cf. Figures 2A and 3B). Specifically, the low probability choice scores were consistently negative and below the others (on average, only six scores were positive and five of those occurred in first 15/150 time bins; in contrast, 147/150 data bins were positive for the low choice trials on MOD and 150/150 on high choice trials in both drug conditions). This evidence suggests that the attentional strategy for low probability choices on PLC was not an artifact of slower learning (as indicated by choice performance), but a real difference in the strategic use of probabilistic information (on PLC). Thus, spatial attention was not biased toward the chosen low probability location on PLC but was on MOD. This suggests that the increased sensitivity to the spatial structure on MOD caused attention to shift strategies and weight the chosen low probability location against the more probable location.

Target Detection: Session 2

The analyses of RT data from Session 2 was identical to that of Session 1. Fewer than .02 ± .01% of the data in the PLC condition and .04 ± .02% of the data in the MOD condition were excluded based on the criteria of being less than 100 msec or 2 standard deviations above or below the individual subject mean. As before, we excluded these trials as anticipations and errors, respectively.

Similar to Session 1, the main effect of spatial probability on RTs was significant in a mixed-effects ANOVA with factors spatial probability (high, low), block (biased, random), and drug [MOD, PLC; Session 2: $F(1, 24) = 5.4, p < .05$]. There was also an interaction between spatial probability and block [Session 2: $F(1, 24) = 18.7, p < .0005$] because of the expected reduction of the probability in the random blocks (low minus high probability RT means: 33.2 msec [biased], −2.4 msec [random]).

In contrast to the results from Session 1, there were no effects of drug (MOD, PLC) in the analysis of RT validity scores. The same three-way mixed-design ANOVA used for Session 1 data only revealed a main effect of block, $F(1, 23) = 5.0, p < .05$, and an interaction between block and choice location, $F(1, 23) = 9.0, p < .01$; note that data from one subject was excluded because of missing values in the low choice location condition). The interaction was because of greater differences in validity scores for low versus high probability choices in the biased compared with the random blocks (see Figure 3A). Interestingly, there was no effect of drug, all effects $F(1, 23) < 0.5, p > .5$, indicating that the directionality of the validity scores were the same in the PLC and MOD groups (i.e., all positive). Consistent with these results, the validity scores for all conditions were positive over the course of the experiment (Figure 3B). The contrast between PLC performance in Sessions 1 and 2 suggest that MOD had a long-lasting carryover effects on performance even after any direct effects of MOD had dissipated. As with the prior analyses on choice decisions, this result suggests that experiencing MOD lead to long-term changes in subject sensitivity to the presence of global probabilities, which impacted behavioral measurements of attentional allocation and choice behaviors.

DISCUSSION

The goals of the current study were to examine the relationship between strategies of choice decisions and spatial attention within the same trial and then to determine whether that relationship was malleable to manipulations of catecholamine-modulated cognitive control with the drug modafinil. We developed a novel paradigm in which we measured choice decisions and spatial attention on every trial during a double-blind administration of PLC and MOD across sessions.

The first result of interest was that MOD enhanced learning of the spatial probability structure as indicated by choice decisions. The inflection point in learning (representing the point at which probability matching was stably achieved) occurred earlier on MOD than PLC. This result was present both in the between group comparison within Session 1 when all subjects were naive to the experimental design, as well as between sessions for the PLC-first subjects. Unlike the PLC-first group, however, subjects that experienced MOD first began Session 2 with a significantly greater proportion of high probability choices that was already near matching. The asymptote in their learning curve was therefore less interpretable with regard to data from other sessions but suggests the enhanced learning on MOD in Session 1 was metacognitive and translated into performance enhancements during Session 2. This is particularly interesting because the exact high probability location switched between sessions.

The short-term effect of MOD on choice decisions within a single session, observed while the drug was present in the brain, likely occurred as a result of increased extracellular neurotransmitters (from NET and DAT inhibition) leading to increased activation of catecholamine receptors and on-line signaling in postsynaptic neurons. This could accelerate the attainment of matching by strengthening the representation of the probabilistic strategy in pFC through a plasticity-based mechanism (e.g., Soltani & Wang, 2010; Loewenstein & Seung, 2006) effected by moderate tonic and high-phasic LC activity (Eckhoff, Wong-Lin, & Holmes, 2009). This is consistent with our prior evidence for augmentation of task-related pFC activity and LC–pFC coupling during cognitive control processes in subjects given this same single-dose of MOD (Minzenberg et al., 2008). One caveat is that because the effect of MOD impacts both NET and DAT, it is unclear at this time whether the behavioral effects we found were due primarily to NE or DA-mediated processes in pFC or both.

The second result of interest involved the pattern of RT performance in the target detection task on PLC and associated changes in behavior on MOD. To quantify the location of spatial attention, we calculated an RT validity effect based on the difference between RT following targets in the chosen versus unchosen locations. A positive validity score meant that attention was allocated to the chosen location, a negative score that attention was in the opposite location, and a zero validity score indicated that attention was evenly distributed between the two locations. In the PLC condition, we expected a positive validity score on high probability choice trials and either a negative or null validity score on low probability choice trials; such results would be consistent with the weighted resource models and the two-stage probability matching model, respectively (see Introduction). Our predictions for the effect of MOD on spatial attention were less clear from the outset.

The data from naive subjects on PLC on high probability choice trials were as expected: There was a significant positive validity effect such that targets in the chosen location were detected faster than targets in the unchosen location. Interestingly, the validity effect was negative overall when the low probability location was chosen, but this pattern did not differ statistically from zero. These results suggest that on average, attention was equally distributed to the two alternative locations when a low probability choice was made, consistent with the Jonides

(1980) model. However, individual variability in the direction of validity effects leave open the possibility that some subjects may have used a strategy of weighted resource distribution that favored the high probability location. Individual differences in probabilistic strategy use have been reported in a perceptual and decision tasks and subsequent experiments investigating such differences in attention are needed (e.g., Kasanova et al., 2011; Wozny et al., 2010; Frank et al., 2009; Miller et al., 2005; Shanks et al., 2002; Friedman & Massaro, 1998).

In contrast, to the PLC results, the validity effect for low probability choices on MOD was positive. This result was not predicted by any of the existing models of attention and indicated that attention was systematically biased toward the low probability location. Although MOD improves vigilance (e.g., Finke et al., 2010; Lanni et al., 2008), and there is evidence that MOD moderately enhances attention from a meta-analysis of varied neuropsychological tasks (e.g., Repantis, Schlattmann, Laisney, & Heuser, 2010), it was not clear what effect MOD would have on selective spatial attention. One possibility was that MOD would augment the strategy of weighted resource distribution and maximize the attentional bias toward the high probability location. Another alternative was that it would not change the strategy of probabilistic selection but only affect the speed of detection. However, our results support a third possibility where cognitive control processes caused spatial attention to follow the choice strategy of probability matching to exploit finer-grained expectancies of both high and low probability target locations.

It is unlikely that the change in the distribution of spatial attention was due only to earlier learning of the spatial probability because the pattern of spatial attention did not change over the course of the experiment (see Figure 3B). Instead, it appears that MOD modulated the strategy of spatial attention on a trial-by-trial basis to be consistent with the current choice. We could not rule out the possibility that the change in spatial attention and pattern of choices seen in the MOD condition were controlled by independent mechanisms, but it is clear that MOD changed the strategy of spatial attention to be more in line with the trial-by-trial choice decision of where the target would appear.

We hypothesized that this effect of MOD occurred because of greater engagement of cognitive control mechanisms implemented in pFC that that represent predictive and rule-based knowledge (e.g., Bubic, von Cramon, & Schubotz, 2010; Miller, 2000). These pFC changes would be expected to bias cortical functioning in areas subserving attentional priority through mechanisms of gain modulation in individual or ensembles of neurons (e.g., Rossi et al., 2009; Desimone & Duncan, 1995). Catecholamine influences can mediate such biases via afferents to pFC from the LC–NE system (e.g., Aston-Jones & Cohen, 2005) and the mesocortical DA system (Seamans & Yang, 2004). Alternatively, attentional biases could arise from direct ascending input to other attentional control regions (e.g., the parietal cortex), which receives dense input from the LC (Morrison & Foote, 1986); in this case, pFC could still provide a control signal through descending input to brainstem nuclei where these neurotransmitter systems originate to putatively provide the "knowledge" of which stimuli are proper targets to amplify processing via increased gain.

Although we can only speculate on the exact mechanisms by which MOD affected behavior in this task, the results clearly show that the setting of attentional priority based on internal (choice) versus external (statistical) information depends on processes that mediate the learning of probabilistic information and rule representations. pFC is a clear candidate region for mediating these effects (see above), but there are other possible systems such as DA-dependent striatal-based learning or striatal–frontal interactions (e.g., Frank et al., 2009; Shulman et al., 2009; Volkow et al., 2009; Lanni et al., 2008; Miller & Cohen, 2001). pFC-based control functions to guide exploratory behavior and resolve uncertainty are proposed to compete with a striatal control system; which system prevails may depend on the degree of uncertainty present (e.g., Doll, Jacobs, Sanfey, & Frank, 2009; Daw, Niv, & Dayan, 2005). Moreover, the balance between strategies of selection based on uncertainty has been attributed to the LC–NE system (e.g., Doya, 2002; Ishii, Yoshida, & Yoshimoto, 2002), and we therefore cannot differentiate between pFC and striatal effects on performance in our task at this time.

Interestingly, in addition to a local effect on choice and attention, MOD in Session 1 produced carryover effects on performance in Session 2. The carryover effects in choice and spatial attention are intriguing and suggest a second drug effect on a distinct, more sustained neurobiological process. MOD has a half-life of 15 hr and was undoubtedly washed out of subjects well before the second test session several days later (mean = 12.7 days later). This strongly suggests the induction of a more sustained phase of neural plasticity in target neurons, which could include later consolidation processes, such as that mediated by "late-phase LTP" that requires new protein synthesis (e.g., Frey, 2001) and possibly gene transcription (e.g., Kandel, 2001). These processes are sensitive to catecholamine modulation, as studies that deliver catecholamine receptor-binding agents in either neocortical or limbic cortical areas within several hours after a learning session indicate a profound influence of these drugs on subsequent memory performance (e.g., Izquierdo et al., 2006).

Another (compatible) account for this sustained MOD effect is dependent on hippocampal–neocortical interactions involved in establishing a stable long-term memory trace (Buzsáki, 1996). It has been argued that cognitive control processes supported by pFC are critical to both the flexible reconfiguration and stabilization of distributed memory traces to integrate sensory experience with

overarching goals of the organism (e.g., Mercado, 2008; Miller, Freedman, & Wallis, 2002). This account suggests that the long-lasting effect of MOD was mediated by strengthening pFC-dependent control processes via enhanced signaling at catecholamine receptors in pFC (e.g., Verguts & Notebaert, 2009).

One interesting avenue of further study will be to determine whether individual differences in cognitive control correlate with changes in behavior following MOD. Our population of subjects was more heterogeneous than the typical study of college students, and they may been more affected by MOD (Finke et al., 2010). Follow-up studies are needed to determine the effect of individual differences in cognitive control on patterns of spatial attention, including sensitivity to agents such as MOD.

In summary, the first result of interest from this study was that MOD enhanced learning of the spatial probability structure that governed the target location. Subjects on MOD began to probability match earlier; moreover, the enhanced learning carried-over to Session 2 when subjects were on PLC. The second primary finding was that the strategy for spatial attention changed on MOD. The pattern of RT validity effects for naive subjects on PLC were consistent with existing models: spatial attention was evenly distributed on low probability choice trials (possibly with some individuals being biased toward the high probability location). However, on MOD, the pattern switched such that spatial attention was now biased toward the low probability choice. This was not predicted by existing models of spatial attention and suggest that catecholaminergic-dependent cognitive control processes can override the default probabilistic pattern of spatial attention.

Acknowledgments

We would like to thank Kevin Grimm and two anonymous reviewers for their comments. This work was supported by the Hellman Foundation to J. J. G., the Clinical Scientist Development Award from Doris Duke Charitable Foundation to M. M., and the University of California, Davis.

Reprint requests should be sent to Joy J. Geng, Center for Mind and Brain, University of California, Davis, Davis, CA 95618, or via e-mail: jgeng@ucdavis.edu.

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