Published in final edited form as:

Psychopharmacology (Berl). 2012 March ; 220(1): 109–115. doi:10.1007/s00213-011-2462-6.

Effect of d-amphetamine on post-error slowing in healthy volunteers

Margaret C. Wardle, Amy Yang, and Harriet de Wit

Department of Psychiatry and Behavioral Neuroscience, University of Chicago, 5841 S. Maryland Ave, MC 3077, Chicago, IL 60637, USA

Harriet de Wit: hdew@uchicago.edu

Abstract

Rationale—Post-error slowing has long been considered a sign of healthy error detection and an important component of cognitive function. However, the neuropharmacological processes underlying post-error slowing are poorly understood.

Objectives—This study investigated the effect of the dopamine agonist d-amphetamine on post-error slowing and secondarily, the potential mediator of drug-induced euphoria and potential moderators of personality and baseline task performance.

Methods—Healthy male and female participants ($N=110$) completed four study sessions, at which d-amphetamine (placebo 5, 10, 20 mg) was administered under double-blind, counter-balanced conditions. At each session, participants completed subjective drug effect assessments and a working memory task (N -back) to measure post-error slowing. They completed the Multidimensional Personality Questionnaire (MPQ) during screening.

Results—Amphetamine (20 mg) reduced post-error slowing, consistent with a dampened behavioral reactivity to errors. This was not related to drug-induced euphoria. Although higher scores on MPQ constraint were related to less post-error slowing under placebo conditions, neither personality nor baseline cognitive performance moderated the effects of amphetamine on post-error slowing.

Conclusions—The finding that amphetamine reduced post-error slowing supports the idea that dopamine plays a role in error stimulus processing. The finding is discussed in relation to an existing literature on the mechanisms and function of behavioral and electrophysiological indices of error sensitivity.

Keywords

Amphetamine; Dopamine; Post-error slowing; Error monitoring; Error-related negativity

Introduction

Error detection and behavioral adjustment after errors play a critical role in human cognitive performance. Responses in timed tasks are typically slower immediately after an error, a phenomenon known as post-error slowing (Rabbitt 1966). There are several theories about the neurocognitive processes that produce post-error slowing, but it is generally thought to be an adaptive part of the error response, as it is associated with reduced probability of committing a subsequent error (Holroyd et al. 2005; Laming 1979). Post-error slowing has been proposed to correspond to a negative deflection on the electroencephalogram occurring approximately 100 ms after an error (Falkenstein et al. 1991), referred to as error-related negativity (ERN). ERN has been interpreted as neurophysiological evidence of the error detection system and a precursor to the observable behavior of post-error slowing (Gehring et al. 1993). Although ERN and post-error slowing have both been hypothesized to depend on dopamine, there are few examinations of the effect of dopaminergic manipulations on the behavioral response of post-error slowing. Thus, in the current study, we examine the effect of d-amphetamine, a dopaminergic agonist, on post-error slowing and secondarily explore the effect of two individual differences that may index baseline dopaminergic functioning.

Although there is debate about the exact neurocognitive processes underlying ERN and post-error slowing, it appears likely that dopamine is involved in both electrophysiological (ERN) and behavioral (post-error slowing) responses to error. The anterior cingulate cortex, where ERN is thought to originate (Carter et al. 1998; Dehaene et al. 1994), is rich in dopaminergic innervation (Paus 2001). Patients with neuropsychiatric disorders characterized by dopaminergic dysfunction (e.g., Parkinson's disease) exhibit abnormal error monitoring (Ruchsow et al. 2004; Schachar et al. 2004; Stemmer et al. 2007; Thakkar et al. 2008; Vlamings et al. 2008). Children with ADHD also have impaired error monitoring and correction (Schachar et al. 2004), and methylphenidate, which increases dopamine in the brain, partially reverses these deficits (Jonkman et al. 2007). Thus, both electrophysiological (ERN) and behavioral (post-error slowing) measures of error monitoring may be markers of dopaminergic dysfunction in psychiatric disorders. Pharmacological manipulations affecting the dopamine system may provide a better understanding of the mechanisms underlying ERN and post-error slowing, giving valuable insight into the nature of these disorders and their treatments.

Two previous studies have used pharmacological challenges to investigate error processing. The dopamine antagonist haloperidol attenuates ERN amplitude and decreases post-error reaction time in healthy volunteers, suggesting decreased sensitivity to errors on both electrophysiological and behavioral measures (Zirnheld et al. 2004). In one study, amphetamine increased ERN after errors in a conflict resolution task (de Bruijn et al. 2004) but did so *without* affecting the behavioral measure of post-error slowing, suggesting that electrophysiological and behavioral responses to error are dissociable. However, de Bruijn et al. imposed a comparatively short reaction time (RT) limit in their task, which may have masked amphetamine effects on slowing. Thus, the effect of the dopamine agonist amphetamine on post-error slowing remains uncertain.

In the current study, we examined the effect of amphetamine on post-error slowing in a working memory task with a longer RT window, thus extending the results of de Bruijn et al. to a different type of task and higher RT ceiling. Secondly, we also examined whether the drug's effect on post-error slowing was mediated by its ability to induce positive mood. This was based on the idea that post-error slowing may represent an emotional response to error (Bush et al. 2000) and evidence that positive mood leads to greater post-error slowing, better performance adjustment, and more task engagement (Smallwood et al. 2009).

We also investigated individual differences in personality and cognition that may affect either overall post-error slowing or moderate the effects of amphetamine on post-error slowing. The relationships between personality and ERN or post-error slowing are complex. The trait of “high drive for reward,” which is related to positive emotionality and has been linked to dopamine function (Depue et al. 1994), is associated with greater ERN (Tops and Boksem 2010), but paradoxically, negative emotionality also appears to be associated with greater ERN, perhaps through alternate cognitive mechanisms such as fear of social evaluation (Tops and Boksem 2010). Constraint, which is the inverse of impulsivity, is also implicated in both dopaminergic functioning and affects ERN/post-error slowing (Tops and Boksem 2010). Thus, we examined relationships between a comprehensive measure of personality and post-error slowing. Additionally, because past studies have shown that dopaminergic drug effects may depend on baseline cognitive ability (which may partially index individual differences in dopaminergic functioning; de Wit et al. 2002; Mattay et al. 2000, 2003), we also looked at whether baseline performance on the *N*-back was related to post-error slowing.

Thus, the aims of the study were threefold. First, we examined whether post-error slowing occurred in a standardized working memory task and whether moderate doses of amphetamine affected post-error slowing and/or the performance on this task. Based on the ERN results obtained by de Bruijn et al. for amphetamine, we expected amphetamine to increase post-error slowing, indicating greater sensitivity to errors. Second, we sought to determine whether the effects of amphetamine on post-error slowing were mediated by amphetamine's euphoric effects. Third, we conducted exploratory analyses of the effects of personality and baseline performance on post-error slowing under placebo conditions and in response to amphetamine to characterize the effect of individual differences that may be related to dopamine function. Together, this study could help us understand the neuropharmacological basis of post-error slowing and particularly, illuminate the role of dopamine in this error response behavior.

Methods

Participants

Healthy male and female Caucasians aged 18–35 years were recruited by posters, advertisements, and word-of-mouth referrals. Only Caucasians participated because this study was part of a larger genetic study. Participants were excluded if they had a past year Axis I DSM-IV disorder (American Psychiatric Association 2000), history of substance dependence, history of personal or legal problems related to drug use, or any current or past medical conditions contraindicating d-amphetamine. To avoid withdrawal from nicotine or

caffeine during sessions, participants who smoked more than ten cigarettes per week or consumed more than three cups of coffee per day were excluded. Candidates had to speak English and have at least high school education. Body mass index (BMI) limitations were 19–26 kg/m². Women not on oral contraceptives participated only during the follicular phase. This study was approved by the University of Chicago Institutional Review Board and performed in accordance with the Helsinki Declaration of 1975.

Study design

This within-subjects design consisted of four sessions separated by at least 72 h, at which participants received capsules containing placebo, d-amphetamine 5, 10, or 20 mg in counter-balanced order under double-blind conditions. Subjects completed the working memory (*N*-back) task (Callicott et al. 1999) at each session 90 min after ingesting the capsules.

Procedure

During an initial orientation, the participants signed the consent form, completed personality questionnaires including the abbreviated Multidimensional Personality Questionnaire (MPQ; Patrick et al. 2002) and practiced the study tasks. They were instructed to abstain from taking drugs, including alcohol, for 24 h before each session, to fast from midnight the night before the sessions, and not to consume more or less nicotine or caffeine than the usual 24 h before and 12 h after the start of each session.

Each of the four experimental sessions were conducted from 9:00 a.m. to 1:00 p.m. Participants were tested individually in a comfortably furnished room. Before the session, the participants gave urine and breath samples to verify abstinence and consumed a standardized snack. They then completed baseline measures of blood pressure, heart rate, and subjective mood. These measures were repeated every 30 min throughout the study. At 9:30 a.m., they ingested a capsule containing d-amphetamine (5 or 10 or 20 mg) or placebo with a glass of water. The d-amphetamine (Mallinkrodt, MO, USA) was placed in size 00 capsules with dextrose filler. Placebo capsules contained dextrose only. For blinding purposes, the participants were informed that the capsule might contain a stimulant, sedative, or placebo. At 11:00 a.m., 90 min after capsule administration when plasma concentrations of d-amphetamine are expected to peak, subjects performed several tasks including the *N*-back task on a Windows platform PC. At 1:00 p.m. participants left the laboratory. After completing all four sessions, the participants were debriefed and paid.

Measures

Personality—Personality traits were obtained through the brief version of the MPQ (Patrick et al. 2002). The MPQ consists of three superfactors: positive emotionality, negative emotionality, and constraint. Positive emotionality assesses characteristics conducive to joyous and rewarding engagement with social and work environments, while negative emotionality measures proneness to anxiety, anger, and negative emotional and behavioral engagement. Constraint measures tendencies to inhibit and restrain impulse expression, unconventional behavior, and risk taking.

Subjective mood—The subjective mood effects of amphetamine were assessed using a research version of the Profile of Mood States (POMS; Johanson and Uhlenhuth 1980). This questionnaire consists of 72 adjectives commonly used to describe momentary mood states. The subjects rate from 0 (not at all) to 5 (extremely); the extent to which each adjective describes how they feel at that moment. The items on the POMS have been factor analyzed to yield eight-mood-state scales: anger, anxiety, confusion, depression, elation, fatigue, friendliness, and vigor. Elation was our primary measure of amphetamine's euphoric effects.

Cognitive measures—Participants performed 0-, 1-, 2-, and 3-back versions of the *N*-back. The task consisted of 120 trials on which a number between 1 and 4 was presented randomly in one corner of a large diamond-shaped square on a white background. The participants pressed a key that matched the target stimulus as follows: for $n=0$ (i.e., 0-back), they were to press the key corresponding to the number currently on the screen, giving a simple choice reaction time test. For $n=1$ (i.e., 1-back), the participants pressed the key corresponding to the number presented on the trial before the current one, and for $n=2$, two trials before the current one, and 3-back three trials before, producing a working memory test of increasing difficulty. Twenty-item blocks of 1-back, 2-back, and 3-back were presented in randomized order. The 1-, 2-, and 3-back blocks were always followed by a 0-back block, giving six blocks total and interspersing cognitively demanding working memory blocks with relatively easy choice reaction time blocks to decrease participant fatigue. Instructions were provided before each block. The participants were given 1,500 ms to respond on each trial, and trials on which they failed to respond in time were considered time-outs. After each response, they were immediately informed whether their response was correct or not. Response feedback (“correct” or “incorrect”) was displayed for 500 ms in the center of the screen, followed immediately by the next trial. Time-out trials received no feedback but were immediately followed by the next trial.

Primary outcome measures derived from the *N*-back task were overall performance, measured as the percentage of correct responses and RT of all correct responses, and post-error slowing, measured as the RT for all correct responses following a correct response (post-correct RT) relative to the RT for all correct responses immediately following an error (post-error RT). The relative ease of the 0-, 1-, and 2-back conditions led to comparatively few incorrect responses within the 0-back ($n=16$ with any errors), 1-back ($n=2$), and 2-back ($n=26$) blocks, thus both the accuracy and post-error slowing analyses were limited to the 3-back block.

Statistical analysis

We first confirmed the presence of post-error slowing in our task using a paired sample *t* test of post-error and post-correct RTs under placebo, then examined our first hypothesis about the effects of amphetamine on performance and post-error slowing using repeated measures (RM) ANOVA on accuracy and reaction times in the 3-back block using Drug (placebo 5, 10, 20 mg) and reaction time type (post-correct, post-error; only reaction type RMANOVA) as within-subject factors. We then examined potential mediation of post-error slowing by drug-induced changes in mood, using peak drug-induced changes in elation scores at the 20-mg dose as a covariate in the post-error slowing RMANOVA. Peak drug-induced elation

was quantified by taking the difference between POMS elation scores at peak and at baseline for the 20 mg and placebo sessions, then subtracting placebo peak change scores from 20-mg peak change scores. Lastly, we conducted exploratory analyses examining the effect of personality (the three super factors of the MPQ) and baseline accuracy on post-error slowing. We examined the relationship between these individual differences and post-error slowing under placebo conditions by correlating each measure with the degree of post-error slowing under placebo. We examined possible moderation of amphetamine's effects on post-error slowing by mean centering (Delaney and Maxwell 1981) each individual difference measure and including each in turn as a covariate in the post-error slowing RMANOVA.

Results

Participants

A total of 198 subjects participated, and of these 177 had complete *N*-back data for all sessions. However, careful inspection indicated that 67 subjects did not perform the task as required: Instead of continuing to respond to each stimulus by indicating the value of the *n*th stimulus before, these subjects waited for *n* stimuli to pass before making another response. This was evident in the data pattern: each response is interspersed with *n* time-outs, where *n* corresponds to the *n* on the *N*-back. Data from these participants were excluded from all analyses, leaving a total *N* of 110 for analyses of amphetamine's effects on task accuracy.

Analysis of post-error slowing requires comparison of correct responses occurring immediately after both correct and incorrect responses. Although the 3-back provided the greatest number of errors, only 58 subjects made at least 3 correct after error and correct after correct responses even during the 3-back block (often because correct and incorrect responses were interspersed with time-outs) on the placebo and 20-mg sessions. We performed imputation of correct after error and correct after correct data for the few of those 58 who were missing only 1 of either the 5- or 10-mg session, producing a final *n*=55 for the post-error slowing analysis. Based on preliminary analyses of only the subjects with complete post-error slowing data, we used a linear dose-response imputation model (so a missing 5-mg session was imputed as the mean of that participant's placebo and 10-mg scores). Subjects with more than one missing session or who missed the placebo or 20-mg session were not included in the analysis. Table 1 summarizes the demographics of the full set of 110 participants who performed the task as required. On average, the participants were in their early 20s and had completed some college. The subjects included in the post-error slowing analysis did not significantly differ from those not included on any demographics.

Post-error slowing under placebo

Analysis of 3-back responses confirmed that under placebo conditions, participants responded more slowly after an error than after a correct response ($t[54]=-2.26$, $p=0.03$), demonstrating post-error slowing on our working memory task. Further, participants who were more accurate on the task also exhibited more post-error slowing ($r=0.26$, $p=0.05$).

Effects of amphetamine

Amphetamine did not affect 3-back accuracy, $F(3, 327)=0.48$, $p=0.70$, $\eta^2=0.004$, and it decreased post-error RTs without changing post-correct RTs (drug $\times$ RT type interaction, $F[3, 162]=3.06$, $p=0.03$, $\eta^2=0.05$; post hoc RMANOVA on post-error RTs only, $F[3, 162]=6.41$, $p<0.001$, $\eta^2=0.11$, post hoc RMANOVA on post-correct RTs only was nonsignificant). Figure 1 illustrates these findings.

Exploratory analysis of mediator and individual differences

To determine whether the drug's effects on mood mediated its effects on post-error slowing, we included the change in POMS elation score as a covariate in the post-slowing RMANOVA. While 20 mg d-amphetamine significantly increased mean POMS elation over placebo ($t[53]=3.60$, $p=0.001$), amphetamine-induced changes in elation did not account for the observed changes in post-error slowing, as these were still significant even when change in elation was included as a covariate (adjusted drug $\times$ RT type interaction, $F[3, 156]=2.68$, $p=0.05$, $\eta^2=0.05$).

Examining individual differences, after excluding data from two subjects with incomplete responses, we first examined personality (positive emotionality, negative emotionality, and constraint) in relation to post-error slowing under placebo conditions. Only constraint was significantly correlated with post-error slowing, such that higher constraint scores predicted less post-error slowing in the placebo session ($r=-0.45$, $p=0.001$). We then included each of these personality variables as covariates in the post-error RMANOVA, but there was no relationship between any of the personality measures and the effect of amphetamine on post-error slowing. Baseline performance on the *N*-back (percent correct under placebo conditions) was correlated with greater post-error slowing under placebo conditions, as noted above, but did not moderate the effect of amphetamine on post-error slowing.

Discussion

Our main finding in this experiment was that d-amphetamine selectively reduced post-error reaction times, without affecting either RT's after correct trials or overall accuracy on the task. The observation that amphetamine, a drug that increases dopamine function, decreased the slowing that typically occurs following an error suggests that the dopamine system is involved in behavioral responses to error. However, the findings are apparently inconsistent with reports that amphetamine increased ERN, an event-related potential (ERP) marker thought to be associated with post-error slowing. It is possible that ERN and post-error slowing reflect different underlying processes. We also found that individuals high on the personality measure of constraint exhibited less overall post-error slowing under placebo conditions, suggesting that post-error slowing may be related to a personality style corresponding to inhibition. However, this personality trait did not moderate the effects of amphetamine on post-error slowing.

Post-error slowing is a complex behavioral index about which there are several major theories: (1) Post-error slowing may be the result of error detection and subsequent adjustment to a more careful response style (Holroyd and Coles 2002); (2) it may represent a

RT penalty resulting from the coactivation of two conflicting (correct and incorrect) responses (Yeung et al. 2004); (3) it may represent an emotional response to error (Bush et al. 2000); and (4) it may represent attentional capture by motivationally relevant and infrequently presented stimuli (Notebaert et al. 2009). Our finding that d-amphetamine selectively reduced post-error slowing is consistent with evidence that structures modulating dopamine output play a key role in processing errors (Chevrier and Schachar 2010) and can be viewed in the context of several of these theories.

Consistent with the first theory, amphetamine might change the ability to detect error signals through non-contingent release of dopamine. Errors in reward prediction are coded by phasic increases in midbrain dopamine activity when ongoing events are better than expected and decreases when ongoing events are worse than expected (Ridderinkhof et al. 2004; Schultz 2002). Thus, drugs that noncontingently release dopamine may interfere with detection of or reactions to negative events like errors. However, this hypothesis is not consistent with de Bruijn et al. who reported that amphetamine increased an electrophysiological marker of error monitoring. Examining the second theory, conflict monitoring, amphetamine generally enhances cognitive ability, so amphetamine might reduce post-error slowing by reducing the RT penalty associated with activation of two conflicting responses. This would be consistent with de Bruijn et al., assuming that amphetamine simultaneously improves monitoring of conflict (ERN) while decreasing the consequences of conflict (post-error slowing). In relation to the idea that post-error slowing is related to positive affect, we found that the mood-enhancing effect of amphetamine was not related to its effects on post-error slowing, nor was post-error slowing related to personality measures of positive or negative emotionality. Examining the final theory, amphetamine might have reduced automatic orientation to infrequently occurring motivationally relevant stimuli, perhaps by decreasing the motivational salience of errors. The fact that we observed changes in post-error slowing without a change in accuracy supports the view that post-error slowing is not simply an error correction phenomenon. Further, some researchers have found that the P3 component of the ERP, a response associated with attention and expectancy, is more tightly correlated with post-error slowing than the ERN (Castellar et al. 2010). If ERN is not in fact closely related to post-error slowing, this would explain the contrast between our results and those of de Bruijn and suggest that these various responses to error do not share a single neuropharmacological basis. A study designed to measure the effect of amphetamine on post-error slowing, ERN, and the P3 ERP simultaneously would help to clarify this point.

In exploratory analyses of sources of individual differences that might relate to both dopaminergic functioning and post-error slowing, we found that post-error slowing was correlated with the personality dimension constraint, but not with positive emotionality, negative emotionality, or baseline performance. The constraint factor encompasses tendencies toward behavioral restraint versus impulsivity and venturesomeness and has been related to behavioral inhibition (Patrick et al. 2002). In our study, the subjects who scored high on the constraint scale exhibited less post-error slowing. This finding is in support of the theory of Pailing et al. that more consistent reaction times (and hence a smaller difference in post-correct and post-incorrect RTs) may actually reflect a more controlled response strategy (Pailing et al. 2002). We did not find an association between reaction

times and positive or negative emotionality. While positive and negative emotionality have been associated with ERN amplitudes (Luu et al. 2000; Pailing et al. 2002), they have not been reliably linked to behavioral indices (Hajcak et al. 2004; Luu et al. 2000).

One important limitation of the current study was the use of the *N*-back task rather than a more frequently utilized conflict resolution or choice reaction time task, such as the Eriksen Flanker Task (EFT). We did find significant post-error slowing on this task and found this post-error slowing was correlated with better performance at a between-subject level, suggesting that post-error slowing is adaptive on the *N*-back task and extending this literature to a new task. However, whether the cognitive and neural processes involved in post-error slowing on the *N*-back are the same as those established in the more extensively studied EFT (Holroyd et al. 2005) is still open to question. We also did not examine post-error slowing on this task on a trial-by-trial basis to determine whether greater post-error slowing on was associated with more accurate performance at a within-subject level. We were further limited in the number of participants with complete post-error data, due to the common phenomenon of participants “skipping” or timing out on many trials at the 3-back level. This suggests that although this task is usable for post-error analysis, it is not ideal. Another limitation was the relatively young and high-functioning nature of our sample, which may have produced ceiling effects on accuracy and restricted our range on the personality variables. While studies have shown that a moderate dose of amphetamine improves working memory and attention in adults, importantly, studies that looked at individual variation suggest amphetamine improves performance only in participants whose initial performance is relatively poor (de Wit et al. 2002; Mattay et al. 2000). Although we found no moderation of amphetamine's effects on post-error slowing by baseline performance, our study may have produced different findings if we had a broader range of subjects with lower baseline cognitive function. Similarly, if constraint is considered a measure of impulsivity, our findings that higher constraint (lower impulsivity) related to reduced post-error slowing is in conflict with findings in ADHD children and adults, who show reduced post-error slowing compared to their non-ADHD peers (Sergeant and Van der Meere 1988; Wiersema et al. 2005). However, this relationship may not be linear across the entire range of impulsivity, and our sample did not contain individuals with clinically significant levels of impulsivity.

Despite these limitations, the current study supports the conclusion that post-error slowing is subject to dopaminergic manipulation and is correlated with individual differences in personality, suggesting post-error slowing reflects activity in a broader dopaminergic system with implications for behavior both inside and out of the laboratory.

Acknowledgments

A. Yang was supported by NIDA DA021336 (PI: A.A. Palmer), H. deWit by DA02812 (PI: H. deWit), and M. Wardle by T32 DA007255.

References

American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th edn, text revision. American Psychiatric Association; 2000.

- Bush G, Luu P, Posner MI. Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn Sci.* 2000; 4:215–222. [PubMed: 10827444]
- Callicott JH, Mattay VS, Bertolino A, Finn K, Coppola R, Frank JA, Goldberg TE, Weinberger DR. Physiological characteristics of capacity constraints in working memory as revealed by functional MRI. *Cerebr Cortex.* 1999; 9:20–26.
- Carter CS, Braver TS, Barch DM, Botvinick MM, Noll D, Cohen JD. Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science.* 1998; 280:747–749. [PubMed: 9563953]
- Castellar EN, Kühn S, Fias W, Notebaert W. Outcome expectancy and not accuracy determines posterror slowing: ERP support. *Cogn Affect Behav Neurosci.* 2010; 10:270–278. [PubMed: 20498350]
- Chevrier A, Schachar RJ. Error detection in the stop signal task. *NeuroImage.* 2010; 53:664–673. [PubMed: 20600968]
- de Bruijn ERA, Hulstijn W, Verkes RJ, Ruigt GSF, Sabbe BGC. Drug-induced stimulation and suppression of action monitoring in healthy volunteers. *Psychopharmacology (Berl).* 2004; 177:151–160. [PubMed: 15578258]
- de Wit H, Engasser JL, Richards JB. Acute administration of d-amphetamine decreases impulsivity in healthy volunteers. *Neuropsychopharmacology.* 2002; 27:813–825. [PubMed: 12431855]
- Dehaene S, Posner MI, Tucker DM. Localization of a neural system for error detection and compensation. *Psychol Sci.* 1994; 5:303–305.
- Delaney HD, Maxwell SE. On using analysis of covariance in repeated measures designs. *Multivar Behav Res.* 1981; 16:105–123.
- Depue RA, Luciana M, Arbisi P, Collins P, et al. Dopamine and the structure of personality: relation of agonist-induced dopamine activity to positive emotionality. *J Pers Soc Psychol.* 1994; 67:485–498. [PubMed: 7965602]
- Falkenstein M, Hohnsbein J, Hoormann J, Blanke L. Effects of cross modal divided attention on late ERP components. II. Error processing in choice reaction tasks. *Electroencephalogr Clin Neurophysiol.* 1991; 78:447–455. [PubMed: 1712280]
- Gehring WJ, Goss B, Coles MG, Meyer DE, et al. A neural system for error detection and compensation. *Psychol Sci.* 1993; 4:385–390.
- Hajcak G, McDonald N, Simons RF. Error-related psychophysiology and negative affect. *Brain Cogn.* 2004; 56:189–197. [PubMed: 15518935]
- Holroyd CB, Coles MGH. The neural basis of human error processing: reinforcement learning, dopamine, and the error-related negativity. *Psychol Rev.* 2002; 109:679–709. [PubMed: 12374324]
- Holroyd CB, Yeung N, Coles MGH, Cohen JD. A mechanism for error detection in speeded response time tasks. *J Exp Psychol Gen.* 2005; 134:163–191. [PubMed: 15869344]
- Johanson CE, Uhlenhuth EH. Drug preference and mood in humans: d-amphetamine. *Psychopharmacology (Berl).* 1980; 71:275–279. [PubMed: 6779335]
- Jonkman LM, van Melis JJM, Kemner C, Markus CR. Methylphenidate improves deficient error evaluation in children with ADHD: an event-related brain potential study. *Biol Psychol.* 2007; 76:217–229. [PubMed: 17904268]
- Laming D. Choice reaction performance following an error. *Acta Psychol (Amst).* 1979; 43:199–224.
- Luu P, Collins P, Tucker DM. Mood, personality, and self-monitoring: negative affect and emotionality in relation to frontal lobe mechanisms of error monitoring. *J Exp Psychol Gen.* 2000; 129:43–60. [PubMed: 10756486]
- Mattay VS, Callicott JH, Bertolino A, Heaton I, Frank JA, Coppola R, Berman KF, Goldberg TE, Weinberger DR. Effects of dextroamphetamine on cognitive performance and cortical activation. *NeuroImage.* 2000; 12:268–275. [PubMed: 10944409]
- Mattay VS, Goldberg TE, Fera F, Hariri AR, Tessitore A, Egan MF, Kolachana B, Callicott JH, Weinberger DR. Catechol O-methyltransferase val 158-met genotype and individual variation in the brain response to amphetamine. *Proc Natl Acad Sci USA.* 2003; 100:6186–6191. [PubMed: 12716966]

- Notebaert W, Houtman F, Van Opstal F, Gevers W, Fias W, Verguts T. Post-error slowing: an orienting account. *Cognition*. 2009; 111:275–279. [PubMed: 19285310]
- Pailing PE, Segalowitz SJ, Dywan J, Davies PL. Error negativity and response control. *Psychophysiology*. 2002; 39:198–206. [PubMed: 12212669]
- Patrick CJ, Curtin JJ, Tellegen A. Development and validation of a brief form of the Multidimensional Personality Questionnaire. *Psychol Assess*. 2002; 14:150–163. [PubMed: 12056077]
- Paus T. Primate anterior cingulate cortex: where motor control, drive and cognition interface. *Nat Rev Neurosci*. 2001; 2:417–424. [PubMed: 11389475]
- Rabbitt PM. Errors and error correction in choice-response tasks. *J Exp Psychol*. 1966; 71:264–272. [PubMed: 5948188]
- Ridderinkhof KR, Ullsperger M, Crone EA, Nieuwenhuis S. The role of the medial frontal cortex in cognitive control. *Science*. 2004; 306:443–447. [PubMed: 15486290]
- Ruchow M, Br H, Wiesend C, Grön G, Spitzer M, Kiefer M. The effect of erroneous responses on response monitoring in patients with major depressive disorder: a study with event-related potentials. *Psychophysiology*. 2004; 41:833–840. [PubMed: 15563336]
- Schachar RJ, Chen S, Logan GD, Ornstein TJ, Crosbie J, Ickowicz A, Pakulak A. Evidence for an error monitoring deficit in attention deficit hyperactivity disorder. *J Abnorm Child Psychol*. 2004; 32:285–293. [PubMed: 15228177]
- Schultz W. Getting formal with dopamine and reward. *Neuron*. 2002; 36:241–263. [PubMed: 12383780]
- Sergeant JA, Van der Meere J. What happens after a hyperactive child commits an error? *Psychiatry Res*. 1988; 24:157–164. [PubMed: 3406236]
- Smallwood J, Fitzgerald A, Miles LK, Phillips LH. Shifting moods, wandering minds: negative moods lead the mind to wander. *Emotion*. 2009; 9:271–276. [PubMed: 19348539]
- Stemmer B, Segalowitz SJ, Dywan J, Panisset M, Melmed C. The error negativity in nonmedicated and medicated patients with Parkinson's disease. *Clin Neurophysiol*. 2007; 118:1223–1229. [PubMed: 17398147]
- Thakkar KN, Polli FE, Joseph RM, Tuch DS, Hadjikhani N, Barton JJS, Manoach DS. Response monitoring, repetitive behaviour and anterior cingulate abnormalities in autism spectrum disorders (ASD). *Brain*. 2008; 131:2464–2478. [PubMed: 18550622]
- Tops M, Boksem MAS. Absorbed in the task: personality measures predict engagement during task performance as tracked by error negativity and asymmetrical frontal activity. *Cogn Affect Behav Neurosci*. 2010; 10:441–453. [PubMed: 21098805]
- Vlamings PHJM, Jonkman LM, Hoeksma MR, van Engeland H, Kemner C. Reduced error monitoring in children with autism spectrum disorder: an ERP study. *Eur J Neurosci*. 2008; 28:399–406. [PubMed: 18702711]
- Wiersema J, Van Der Meere J, Roeyers H. ERP correlates of impaired error monitoring in children with ADHD. *J Neural Transm*. 2005; 112:1417–1430. [PubMed: 15726277]
- Yeung N, Botvinick MM, Cohen JD. The neural basis of error detection: conflict monitoring and the error-related negativity. *Psychol Rev*. 2004; 111:931–959. [PubMed: 15482068]
- Zirnheld PJ, Carroll CA, Kieffaber PD, O'Donnell BF, Shekhar A, Hetrick WP. Haloperidol impairs learning and error-related negativity in humans. *J Cogn Neurosci*. 2004; 16:1098–1112. [PubMed: 15298795]

Fig. 1.

Mean (SEM) post-correct and post-error reaction times for all amphetamine doses illustrating the reduction of post-error reaction times in the 3-back condition by 20 mg amphetamine ($N=55$). * $p<0.05$, different from placebo

Table 1

Participant demographics

Description	Analyzed (N=110) N (%) or mean (SD)
Gender (male/female)	55/55 (50%)
Age	22.97 (2.99)
Education completed	
High school/GED	3 (2.7%)
Some college	41 (37.3%)
Bachelor's	60 (54.5%)
Post-bachelor's	6 (5.5%)