Dopamine D_2 Receptor Modulation of Human Response Inhibition and Error Awareness

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Abstract

■ Response inhibition, comprising action cancellation and action restraint, and error awareness are executive functions of considerable clinical relevance to neuropsychiatric disorders. Nevertheless, our understanding of their underlying catecholamine mechanisms, particularly regarding dopamine, is limited. Here, we used the dopamine D_2 agonist cabergoline to study its ability to improve inhibitory control and modulate awareness of performance errors. A randomized, double-blind, placebo-controlled, crossover design with a single dose of cabergoline (1.25 mg) and placebo (dextrose) was employed in 25 healthy participants. They each performed the stop-signal task, a well-validated measure of action cancellation, and the Error Awareness Task, a go/no-go measure of action restraint and error awareness, under each drug condition. Cabergoline was able to selectively reduce stop-signal RT, compared with placebo, indicative of enhanced action cancellation ($p < .05$). This enhancement occurred without concomitant changes in overall response speed or RT variability and was not seen for errors of commission on the Error Awareness Task. Awareness of performance errors on the go/no-go task was, however, significantly improved by cabergoline compared with placebo ($p < .05$). Our results contribute to growing evidence for the dopaminergic control of distinct aspects of human executive ability, namely, action cancellation and error awareness. The findings may aid the development of new, or the repurposing of existing, pharmacotherapy that targets the cognitive dysfunction of psychiatric and neurological disorders. They also provide further evidence that specific cognitive paradigms have correspondingly specific neurochemical bases. ■

INTRODUCTION

Inhibiting inappropriate actions and recognizing errors in performance are critical aspects of human cognition. Unfortunately, these abilities are impaired in a range of neuropsychiatric disorders. Response inhibition deficits are seen in schizophrenia (Bellgrove et al., 2006), cocaine dependence (Garavan & Hester, 2007), attention-deficit hyperactivity disorder (ADHD; Crosbie & Schachar, 2001), Parkinson disease (Aron & Poldrack, 2006), and obsessive–compulsive disorder (Volkow, Wang, Fowler, & Ding, 2005). Similarly, diminished error awareness has been demonstrated in schizophrenia (Carter, MacDonald, Ross, & Stenger, 2001), cocaine dependence (Kaufman, Ross, Stein, & Garavan, 2003), Huntington disease (Hoth et al., 2007), Parkinson disease (Jocham & Ullsperger, 2009), and ADHD (Rubia, Smith, Brammer, Toone, & Taylor, 2005). An increasing recognition that deficits in these cognitive processes can influence clinical outcome (Field & O'Keefe, 2004; Mintz, Addington, & Addington, 2004) has driven efforts to better understand their neurochemistry.

Response inhibition has been examined in both animals and humans using behavioral paradigms such as the go/no-go (GNG) task and stop-signal task (SST). These tasks represent distinct behavioral forms of response inhibition, with the GNG requiring "action restraint" and the SST requiring "action cancellation" (Eagle, Bari, & Robbins, 2008). The validity of action restraint and action cancellation, being dissociable constructs, has received support from experimental studies suggesting that they have distinct neurochemical bases (Eagle, Bari, et al., 2008). Although specific roles for noradrenaline (Chamberlain et al., 2006) and serotonin (Harrison, Everitt, & Robbins, 1999) have been recognized, studies on dopamine have been proved as more controversial.

Initially, a role for dopamine in action cancellation was rejected. This followed rodent studies in which the systemic administration of the dopamine reuptake inhibitor GBR-12909 and the nonspecific dopamine receptor antagonist flupenthixol both failed to influence the primary index of SST inhibitory efficiency, the stop-signal RT (SSRT; Eagle, Tufft, Goodchild, & Robbins, 2007). Later work showed, however, that the infusion of a selective D_1 antagonist, SCH 23390, into the rat striatum improved SSRT, whereas infusion of a selective D_2 antagonist, sulpiride, impaired SSRT (Eagle, Wong, et al., 2008). Furthermore, in

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healthy volunteers, administration of amphetamine, a dopamine and noradrenaline reuptake inhibitor, increased D_2 gene expression and also improved SSRT (Hamidovic, Dlugos, Skol, Palmer, & de Wit, 2009).

With respect to action restraint, neither L-dopa administration nor phenylalanine/tyrosine depletion influenced GNG performance in healthy volunteers (Vrshek-Schallhorn, Wahlstrom, Benolkin, White, & Luciana, 2006; Hershey et al., 2004). Frank and O'Reilly administered cabergoline (a selective D_2 agonist) or haloperidol (a selective D_2 antagonist) to healthy volunteers and proposed that inhibition, during a reward-learning GNG paradigm, was controlled via phasic and tonic modulation of D_1 and D_2 receptors within the direct and indirect pathways of the striatum (Frank & O'Reilly, 2006). However, Eagle, Bari, and Robbins challenged this, noting that what had been defined as improved action restraint was likely only a negative modulation of the go pathway rather than a positive modulation of the no-go pathway (Eagle, Bari, et al., 2008). The argument against a role for dopamine in action restraint received further support when D_1 and D_2 manipulations were unable to influence GNG in either rats or monkeys (Eagle et al., 2007; Inase, Li, & Tanji, 1997). Hence, in contrast to the SST, evidence for the dopaminergic modulation of GNG performance remains equivocal.

Error processing may also be sensitive to D_1 and D_2 modulation. Pharmacological studies of error processing have extended findings from electrophysiology, which showed that the early stages of error processing are preconscious and independent of any awareness of errors (O'Connell et al., 2007). This stage has a characteristic ERP, the error-related negativity (ERN), which may arise from the ACC via signaling from the mesencephalic dopamine system (Holroyd & Coles, 2002). A separate ERP known as the error positivity (Pe) is seen around 200 msec later and has been associated with the conscious awareness of errors (O'Connell et al., 2007). The role of dopamine during error processing has been investigated in Parkinson disease (Gauggel, Rieger, & Feghoff, 2004) and by using amphetamine (de Bruijn, Hulstijn, Verkes, Ruigt, & Sabbe, 2004) and haloperidol (de Bruijn, Sabbe, Hulstijn, Ruigt, & Verkes, 2006; Zirnheld et al., 2004). From these studies, Joacham et al. concluded that alterations in the balance between presynaptic and postsynaptic D_2 and D_1 modulated the amplitude of the ERN (Jocham & Ullsperger, 2009). Caffeine, which indirectly modulates dopamine via adenosine, influences the Pe (Tieges, Richard Ridderinkhof, Snel, & Kok, 2004); however, the Pe is unaffected by two indirect dopamine modulators, lorazepam and ethanol (Overbeek, 2005). Hester et al. demonstrated that methylphenidate (a dopamine and noradrenaline reuptake inhibitor) and atomoxetine (a noradrenaline reuptake inhibitor) improved error awareness behavior in healthy volunteers (Hester et al., 2012). Significantly, the pharmacological modulation of error awareness had distinct neuroanatomical correlates for methylphenidate (dorsal ACC, parietal cortex) versus atomoxetine (inferior frontal gyrus; Hester et al., 2012). These data suggest that there may be separate dopaminergic and noradrenergic mechanisms for error awareness (Hester et al., 2012).

Here, we used cabergoline, which has high affinity for postsynaptic D_2 receptors (0.4 nM) and almost no affinity for D_1 receptors (32,000 nM; Sharif et al., 2009), to examine the effects of D_2 receptor modulation on action cancellation, action restraint, and error awareness tasks in healthy adults. Participants performed an SST and the Error Awareness Task (EAT; Hester, Foxe, Molholm, Shpaner, & Garavan, 2005), a modified GNG task that allows participants to explicitly indicate their awareness of performance errors. Previous electrophysiological analysis has shown that error awareness on the EAT is positively correlated with the amplitude of the Pe (O'Connell et al., 2007). We hypothesized that cabergoline would improve action cancellation in the SST but not action restraint in the GNG task. Furthermore, given our previous finding that methylphenidate enhanced error awareness and other data showing D_2 modulation of error processing more broadly, we predicted that cabergoline would enhance error awareness relative to placebo.

METHODS

Participants

Twenty-five healthy male volunteers were recruited for this study via advertisement at the University of Queensland, Australia. All participants were right-handed and aged from 18 to 26 years (M = 21.6 years, SD = 2.06 years). Participants were excluded if they reported any history of psychiatric or neurological illness including head injury, previous usage of psychotropic medication, or significant illicit drug use (significant was defined as [a] use of any illicit substances within the last month; [b] >5 lifetime intake of any illicit drug except cannabis; [c] more than monthly cannabis intake, smoking [>5 cigarettes/week], or alcohol dependence [>24 units/week]). Participants were also excluded if there were any contraindications to cabergoline. Before commencing, all participants were screened by a consultant psychiatrist who also administered the M.I.N.I. Screen and the Kessler K10. Blood pressure (BP), heart rate, weight, and height were all recorded. Participants also completed the Conners' Adult ADHD Rating Scale (Patton, Stanford, & Barratt, 1995) and the Barratt Impulsivity Scale (Patton et al., 1995).

All participants were recruited according to the principles of the Declaration of Helsinki and in accordance with the ethical guidelines of the University of Queensland.

Drug Administration

The study employed a randomized, double-blind, placebo-controlled, within-subject, crossover design. Participants were tested twice, on the same day and time, during

two consecutive weeks. At each testing session, the participant ingested with water a single identical blue gelatine capsule, receiving either 1.25-mg cabergoline or placebo (dextrose) in a randomized order. Cabergoline dosage was based on data from previous acute challenge studies that have demonstrated cognitive effects at the chosen dose (Frank & O'Reilly, 2006).

All participants were required to fast for at least 1 hr before drug administration. Caffeine was not to be consumed on test days. After drug administration, participants rested in a quiet waiting room for 90 min to await peak plasma levels (Persiani et al., 1996) before commencing the cognitive tasks that took a further 90 min. Participants then completed a battery of four cognitive tasks, with order of presentation counterbalanced using a balanced Latin square. Data from the SSRT task and the EAT are presented here. No participants withdrew because of drug-related side effects.

SST

Participants performed 512 trials of the stop-signal paradigm, in which the go stimuli were the letters O and X mapped to the left and right button press responses, respectively. The stop signal was a red box that surrounded the go stimulus on 25% of trials. The delay between the onset of the go stimulus and the onset of the stop signal (stop-signal delay [SSD]) was initially set to 250 msec and thereafter was adjusted dynamically in increments of 50 msec contingent on the performance of the participant. Successful inhibitions resulted in an increase of the SSD, whereas failed inhibitions resulted in a reduction of the SSD, thereby facilitating inhibitory success. This procedure ensured that, on average, each participant in each session had a probability of successful inhibition approaching 50%. Under these circumstances, SSRT—a measure of the latency of the inhibitory process—is derived as the mean RT to go stimuli minus the SSD for the 50% inhibition threshold (SSRT = MRT − SSD; Logan, Schachar, & Tannock, 1997).

EAT

The EAT was used to assess conscious detection of errors. It is a motor GNG response inhibition task that is used to assess whether participants are aware (aware errors) or unaware (unaware errors) of their errors of commission. The go trials consisted of a consecutive stream of single color words in incongruent font (e.g., the word "RED" written in blue font) presented to the participant for 800 msec followed by a 700-msec intertrial interval. Participants were trained to respond to each presentation of the go stimuli with a single button press and to withhold their response when either of two classes of no-go trial occurred (see Figure 1). The first type of no-go trial arose if the same colored word appeared on two sequential trials (repeat no-go trial), and the second arose if the word and the font were congruent (Stroop no-go trial; see Figure 1). Critically, in cases where the participants were aware of their commission error, they were trained to forego the regular go-trial response on the trial immediately subsequent to the error and to make an alternative nonspeeded "error awareness response." The dual requirement to monitor for two classes of no-go event was designed to lead to increased errors of commission, a percentage of which should escape conscious awareness (Hester et al., 2005).

Previous electrophysiological studies have shown that error awareness on the EAT is associated with the distinct ERP waveform known as the Pe (O'Connell et al., 2007). Specifically, O'Connell et al. showed that the Pe was maximal when participants indicated an explicit awareness of their error and was virtually absent when errors went unnoticed. The same modulation by error awareness was not seen for other error-related components such as the ERN and Pe, suggesting that the Pe may indeed index the awareness response (see also Steinhauser & Yeung, 2010). In support of this, Murphy,

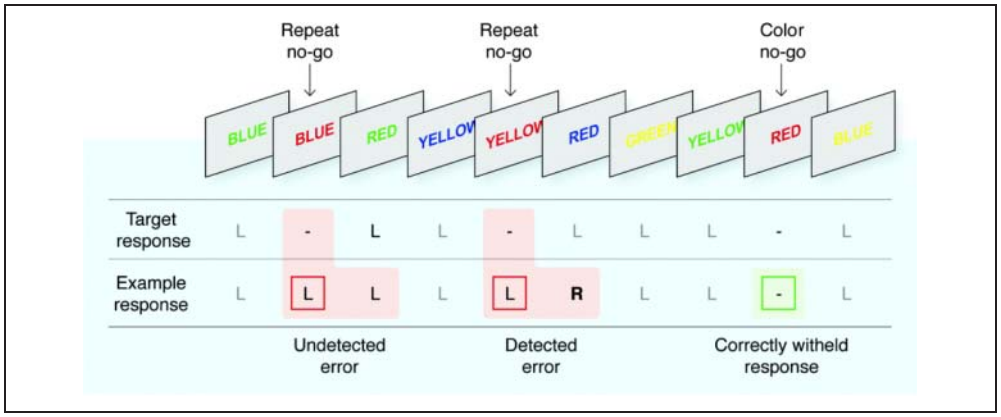

Figure 1. The EAT. The EAT presents a serial stream of single color words in incongruent fonts, with the word presented for 800 msec followed by a 700-msec ISI. Participants were trained to respond to each of the words with a single "go trial" (left) button press and to withhold this response when either of two different circumstances arose. The first was if the same word was presented on two consecutive trials (repeat no-go), and the second was if the word and font of the word matched (color no-go). To indicate "error awareness," participants were trained to forego the regular go-trial button response (left) and, instead, to respond with the alternative (right) button following any commission error.

Robertson, Allen, Hester, and O'Connell (2012) have recently shown that the latency and amplitude of the Pe during the EAT were significantly correlated with error awareness rates between individuals but not with the overall number of commission errors to the no-go trials.

In this study, participants performed 900 trials of the EAT across four blocks including 100 pseudorandomly placed no-go trials. Key dependent variables included the percentage of commission errors on no-go trials, the mean and standard deviation of correct go responses, and the percentage of errors for which awareness was indicated.

Other Assessments: Subjective and Physical Measurements

Subjective and physical ratings of participants' side effects to cabergoline and the placebo were taken. Subjective side effects were measured using the Visual Analogue Scale (VAS), a 16-item rating battery (Bond, James, & Lader, 1974). The VAS items are divided into three categories: alertness, contentedness, and calmness. Participants were required to mark an ungraduated 10-cm line to express the state of their feelings for each dimension, with the ends of each line indicating the extremes for that dimension. The ratings for each category were compared between testing time and drug condition to determine if participants were subjectively aware of any changes in their feelings because of drug condition.

Physical side effect ratings included measures of heart rate, systolic BP, and diastolic BP. These three objective measures were similarly compared between time point and drug condition to see if the drug condition, the testing time, or the interaction of the two was having significant effects on the participants' physical status. Subjective and physical ratings were recorded at baseline and at +90 and +180 min after drug administration.

RESULTS

Stop-signal Paradigm

Data from two participants for the stop-signal paradigm was incomplete because of computer malfunction. A further two participants had SSRTs that were 2 *SD* outside the mean and were excluded from analysis. The final analysis was therefore based on 21 participants. The mean percentage inhibition rate in both the cabergoline and placebo conditions was 49.5%, indicating that the tracking algorithm had successfully converge on the critical 50% inhibition threshold. Dependent variables from the stop-signal paradigm were submitted to a paired-samples *t* test comparing the effect of cabergoline versus placebo. There was a significant main effect of Drug Condition on SSRT [$t(20) = 2.41, p < .05$] such that cabergoline speeded SSRT ($M = 217$ msec, $SD = 31.7$ msec) compared with placebo ($M = 232$ msec, $SD = 37.9$ msec). The enhancement of action cancellation by cabergoline, compared with placebo, was associated with a medium Cohen's *d* effect size of 0.43. The enhancement of action cancellation by cabergoline occurred in the absence of any effect of the drug on mean go RT [$t(20) = 0.33, p > .05$] or go-trial RT variability [$t(20) = 0.505, p > .05$]. Full results can be found in Table 1.

EAT

The critical behavioral measure of error awareness was transformed to improve normality using an arcsine function before parametric analyses (see Hester et al., 2012). A paired-samples *t* test revealed that cabergoline was able to significantly increase awareness of the percentage of commission errors ($M = 73\%$, $SD = 16.5$), compared with placebo [$M = 65\%$, $SD = 17.9$; $t(24) = 2.2, p < .05$]. This enhancement of error awareness by cabergoline compared with placebo was associated with a medium Cohen's *d* effect size of 0.43. In contrast to enhancement of action cancellation in the SST by cabergoline, the drug had no effect on improving the number of commission errors for the GNG element of the EAT [$t(24) = 0.45, p > .05$]. In line with the results for the SST, no effect of Drug was found for go-trial RT [$t(24) = 0.24, p > .05$] or go-trial variability in RT [$t(20) = 0.18, p > .05$]. Full results can be found in Table 2.

Other Assessments: Subjective and Physical Measurements

There were no significant effects of cabergoline on subjective side effects as measured by the VAS. Critically, there were no significant Drug × Time interactions for any of the three VAS factors [calmness: $F(2, 48) = 1.05$, $p > .05$; alertness: $F(2, 48) = .14, p > .05$; contentedness: $F(2, 48) = 2.53, p > .05$]. Equally, the results for heart rate revealed no significant Drug × Time interaction, $F(2, 48) = 2.71, p > .05$. Neither where there Drug ×

Table 1. SSRT Task Performance Measures as a Function of Drug Condition (Cabergoline vs. Placebo)

	Cabergoline (1.25 mg)		*Placebo*	
	M	*SD*	*M*	*SD*
SSRT (msec)*	217	31.7	232	37.9
go RT (msec)	447	72.8	442	82.7
% Stop	49.5	1.1	49.5	0.75
SD of go RT	98.7	16.9	95.9	26.8

go RT = mean correct RT to go trials; % stop = mean percentage of successful inhibition on stop trials; *SD* of go RT = *SD* of correct RT to go trials.

*$p < .05$.

Table 2. Error Awareness Task Performance Measures as a Function of Drug Condition (Cabergoline vs. Placebo)

	Cabergoline (1.25 mg)		*Placebo*	
	M	*SD*	*M*	*SD*
no-go accuracy (% correct)	45	18.1	44	20.6
Error awareness* (% aware errors)	73	16.5	65	17.9
go RT (msec)	460	71.9	464	65.9
SD of go RT	143	37.8	144	37.2

no-go accuracy = % of successful inhibitions on no-go trials; error awareness = % of commission errors for which the participant indicated awareness of their error (statistics performed on arcsine transformed data); go RT = mean correct RT to go trials; *SD* of go RT = *SD* of correct RT to go trials.

*$p < .05$.

Time interactions for systolic BP, $F(2, 48) = .74$, $p > .05$, nor diastolic BP, $F(2, 48) = 1.59$, $p > .05$.

DISCUSSION

The results of the current study show that a D_2 agonist, cabergoline, was able to improve behavioral measures of action cancellation and error awareness, compared with placebo. Notably, the enhancement of these clinically relevant components of cognitive control occurred without concomitant changes in RT or RT variability.

During the SST, stop and go processes are in direct competition to produce the final behavioral outcome of either successful or unsuccessful action cancellation. Yet, the stop process begins at a competitive disadvantage, having to start after the onset of the prepotent go stimulus. Hence, for successful action cancellation, the stop process must "overtake" the prepotent go response. In existing models of the striatal control of action, postsynaptic D_2 activation promotes the rapid completion of action via suppression of inhibitory medium projection neurons within the indirect pathway of the BG (Surmeier, Ding, Day, Wang, & Shen, 2007). Accordingly, postsynaptic D_2 stimulation also promotes the rapid completion of action. Hence, during successful action cancellation in the SST, which, crucially, must be understood as an "active" process, striatal dopamine at postsynaptic D_2 receptors (within the indirect pathway of the BG) facilitates the salient "stop" process to rapidly complete before the prepotent go response (Eagle, Wong, et al., 2008). Cabergoline's potent postsynaptic D_2 agonist activity (0.4 nM) and lack of D_1 effects (32,000 nM; Sharif et al., 2009) would favor such a disinhibition of the indirect pathway and the rapid completion of the stop process to improve SSRT, as we observed. Our data compliment that from rodent striatal infusion studies in which D_2 antagonism worsened SSRT (Eagle, Wong, et al., 2008). The latter finding was interpreted as post D_2 antagonism retarding the completion of action cancellation. This is because postsynaptic D_2 blockade would prevent endogenous dopamine from suppressing indirect pathway inhibitory activity, thus preventing a salient stop process from efficiently completing before the prepotent response. Considering the transferability of the SST between species, these rodent findings make it plausible that the enhancement of human action cancellation with cabergoline was likely because of postsynaptic D_2 agonism in the striatum. Importantly, cabergoline did not reduce mean go RT compared with placebo, supporting the interpretation that cabergoline was differentially enhancing the salience of the stop process rather than simply speeding overall responding as had been seen with non-receptor-specific dopamine agonists (Overtoom et al., 2003).

One cannot however discount the possibility that the positive effect of cabergoline on action cancellation might be because of its moderate α_{2A} receptor binding (132 nM; Sharif et al., 2009). Antagonism of α_{2A} autoreceptors in the locus coeruleus is thought to increase noradrenaline levels throughout the forebrain, allowing increased responsiveness to salient stimuli such as the stop signal (Jocham & Ullsperger, 2009). However, considering that guanfacine, a significantly more potent α_{2A} receptor agonist (20 nM; Uhlen, Muceniece, Rangel, Tiger, & Wikberg, 1995), was unable to influence SST performance in humans (Muller et al., 2005), it seems unlikely that our SST results were because of an alpha adrenoceptor mediated effect. In addition, cabergoline was not able to influence go RT variability, arguably an objective measure of arousal/attention or subjective measures of attention on the VAS. Such attention processes are thought to be regulated by noradrenergic mechanisms (Smith & Nutt, 1996), and cabergoline's lack of effect on these markers also supports the contention that our SST results are unlikely to be noradrenergic in origin.

Cabergoline's inability to improve inhibition during the EAT, which is a modified GNG task, supports the accumulating experimental evidence that modulating D_1/D_2 does not affect action restraint (Eagle, Wong, et al., 2008; Inase et al., 1997). Considering that DNA variation in the D_4 receptor gene predicts poor action restraint in humans (Altink et al., 2011), cabergoline's lack of effect is consistent with its only moderate activity at D_4 (56 nM; Sharif et al., 2009). On the first inspection, our negative GNG findings may appear to contradict those of Frank and O'Reilly (2006), who reported modulation of performance on a GNG task by cabergoline in healthy volunteers. There are, however, significant differences between the GNG tasks in the two studies. During the EAT, GNG is denoted as a simple choice of go versus no-go depending on a set of fixed criteria, whereas in Frank and O'Reilly's study, go versus no-go was linked to reward modulated by probabilistic learning. Correspondingly, Frank and O'Reilly attributed a significant portion of their results to cabergoline being able to influence the learning of changing go versus no-go criteria to maximize reward. Indeed, the only other study

to find effects of nonstimulant dopamine agents on action restraint also required learning reinforcement during a GNG task (Leyton et al., 2007). Hence, our failure to modulate GNG inhibition on the EAT with cabergoline is consistent with the assertion that dopaminergic modulation has only a minimal influence on pure action restraint (Eagle, Bari, et al., 2008).

The result of cabergoline improving error awareness during the EAT might be understood by reference to earlier pharmacological studies that attempted to modulate physiological indices of both preconscious and conscious error processing, such as ERN and Pe, respectively. Although there is evidence that D_2 modulation can affect the amplitude of the ERN (Zirnheld et al., 2004), there is only indirect evidence that dopamine can modulate ERP markers of error awareness such as the Pe in healthy populations. Caffeine, an indirect dopamine agonist via adenosine, was shown to modulate the Pe, but ethanol and lorazepam, indirect dopamine antagonists via GABA, do not (Overbeek, 2005). Hence, it remains unknown whether specific dopamine receptor modulation can influence the Pe. Hester and colleagues showed that, during the EAT, the indirect dopamine agonist methylphenidate improved error awareness behavior and that this effect was underpinned by BOLD changes within the dorsal ACC and inferior parietal lobule (IPL) for errors made with, versus without, awareness (Hester et al., 2012). The relationship between error awareness and activity within the IPL accords well with electrophysiological evidence that P300-like components such as the Pe have neural generators in the IPL (Linden, 2005). Accordingly, one may hypothesize that error awareness is mediated, at least in part, by nigro-cortical dopamine (i.e., D2) inputs to parietal cortex. Indeed, strong dopamine projections to parietal cortex exist in addition to the well-documented dopamine inputs to striatum and frontal cortex (Haber & Knutson, 2010).

As is the case with action cancellation, we cannot rule out a contribution of the noradrenergic system in the error awareness result. For instance, the moderate α_{2A} receptor effects of cabergoline may alter the optimal balance between tonic and phasic modes of locus coeruleus activity, which may then influence the selection of appropriate behavioral responses (Aston-Jones & Cohen, 2005; Nieuwenhuis, Aston-Jones, & Cohen, 2005). As has been more broadly suggested for error processing (Jocham & Ullsperger, 2009), dopamine and noradrenaline may share overlapping and complimentary roles during error awareness (Hester et al., 2012). However, cabergoline has much less affinity for α_{2A} receptors than D_2 receptors (K_1 of 132 nM vs. 0.4 nM, respectively; Sharif et al., 2009), again favoring dopaminergic mechanisms in our results.

In summary, this study has shown that cabergoline is able to selectively enhance components of response inhibition and error processing in humans. Specifically, cabergoline improved SST performance without changing overall response times and had no effect on commission errors during a GNG task. These findings suggest a dissociable contribution of dopamine D_2 receptor mechanisms to action cancellation versus action restraint. The current study also provides critical evidence for the enhancement of human error awareness by dopamine D_2 receptor mechanisms. These data add to a growing body of evidence for a pivotal role of D_2 in error processing and help demonstrate the subtle yet specific neurobiology of executive processes. Considering the prevalence and burden of these cognitive impairments in neuropsychiatric populations, defining their precise neurochemical architecture must remain a priority for the future development of more specific and targeted pharmacotherapy.

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