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Impairments of Probabilistic Response Reversal and Passive Avoidance Following Catecholamine Depletion

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Abstract

Catecholamines, particularly dopamine, have been implicated in various aspects of the reward function including the ability to learn through reinforcement and to modify flexibly responses to changing reinforcement contingencies. We examined the impact of catecholamine depletion (CD) achieved by oral administration of alpha-methyl-paratyrosine (AMPT) on probabilistic reversal learning and passive avoidance in 15 female subjects with major depressive disorder in full remission (RMDD) and 12 healthy female controls. The CD did not affect significantly the acquisition phase of the reversal learning task. However, CD selectively impaired reversal of the 80-20 contingency pair. In the passive avoidance learning task, CD was associated with reduced responding towards rewarding stimuli, although the RMDD and control subjects did not differ regarding these CD-induced changes in reward processing. Interestingly, the performance decrement produced by AMPT on both of these tasks was associated with the level of decreased metabolism in the perigenual anterior cingulate cortex. In an additional examination using the affective Stroop task we found evidence for impaired executive attention as a trait abnormality in MDD. In conclusion, this study showed specific effects of catecholamine depletion on the processing of reward-related stimuli in humans and confirms previous investigations that demonstrate impairments of executive attention as a neuropsychological trait in affective illness.

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Disclosure/Conflict of Interest

Dr. Hasler has no conflict of interest.
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Introduction

Abnormalities of catecholaminergic neurotransmitter systems have been implicated in various neuropsychiatric conditions including depression and addiction (Volkow *et al*, 2004; Dunlop and Nemeroff, 2007; Hasler *et al*, 2008). While catecholaminergic neurotransmission is thought to be reduced in these disorders, the specific contributions of catecholamines to attention, cognition and affect remain unclear. An instructive paradigm for investigating the relationship between catecholaminergic function and behavior has involved the behavioral response to catecholamine depletion (CD), achieved by oral administration of alpha-methyl-paratyrosine (AMPT) (Berman *et al*, 1999; Hasler *et al*, 2004). AMPT is a competitive inhibitor of tyrosine hydroxylase, the rate-limiting enzyme involved in catecholamine synthesis (Nagatsu *et al*, 1964). Catecholamines, particularly dopamine, have been implicated in various aspects of reward processing including the ability to learn through reinforcement and to flexibly modify responses on the basis of changing reinforcement expectancies.

Impaired processing of reward-related stimuli and attentional bias toward negative information have been hypothesized to constitute behavioral endophenotypes in major depressive disorder (MDD) (Hasler *et al*, 2004). These behavioral deficits may reflect the biological endophenotype of reduced dopaminergic and noradrenergic function in depression (Hasler *et al*, 2008). To identify relationships between catecholamine function and potential deficits in reward learning as trait characteristics in MDD, we included subjects with MDD in full remission (RMDD) and healthy volunteers without increased risk for depression. We selected three tasks. The first two, the Probabilistic Response Reversal task (Budhani and Blair, 2005) and the Passive Avoidance Learning task (Newman and Kosson, 1986) rely on positive outcome reinforcement signaling. Previous work has shown that successful performance on both these tasks relies on the representation of reinforcement expectancy information by orbital frontal cortex (see (Hampton *et al*, 2006; Kosson *et al*, 2006; Budhani *et al*, 2007)). If CD disrupts the representation of reward expectancy information, it can be predicted that CD will disrupt performance on both tasks perhaps particularly in RMDD. The third task, the affective Stroop task (aSt) (Blair *et al*, 2007), assesses the degree to which emotional information interferes with the representation of task-relevant material. If CD interferes with top down attentional control (Coull, 1998), it can be predicted that CD will increase interference in the aSt, perhaps particularly in RMDD.

Methods

Participants

Female right-handed individuals ages 18 to 56 years either met DSM-IV criteria for MDD in full remission (RMDD) or had no history of any psychiatric disorder and no major psychiatric condition in first-degree relatives. Diagnosis was established using the Structured Clinical Interview for DSM-IV (First *et al*, 2001) and confirmed by an unstructured interview with a psychiatrist. The educational level was scored as follows: 1=grade 6 or less; 2=grade 7 to 12; 3=graduating high school; 4=part college; 5=graduated 2 year college; 6=graduated 4 year college; 7=part graduate/professional school; 8=completed

graduate/professional school. The subjects were recruited through the outpatient clinical services of the NIMH and by advertisements in local newspapers and posters on the NIH campus. Exclusion criteria included major medical illnesses, pregnancy, psychotropic drug exposure (including nicotine) within 3 months, substance abuse within one year, lifetime history of substance dependence, psychiatric disorders other than MDD, or structural brain abnormalities on MRI. Inclusion criteria required that RMDD subjects had remained in remission while off medications ≥3 months, and manifested depression-onset prior to age 40 years. Written informed consent was obtained as approved by the NIMH IRB, and the study has been carried out in accordance with the Declaration of Helsinki.

Experimental Design

Using a randomized, double-blind, placebo-controlled, crossover-design, subjects underwent two identical sessions separated by at least one week, in which they received either AMPT or placebo. To reduce risk for adverse reactions we used a body weight-adjusted AMPT dose of 40 mg/kg body weight p.o., to a maximum of 4g, over 22 hours. Each session involved 3 days, performed on an inpatient basis at the NIH Clinical Center. To reduce the risk of crystalluria during AMPT administration, subjects received sodium bicarbonate, drank ≥2L of water daily, and underwent urine analysis twice daily.

Brain Imaging

Two hours before neuropsychological testing, resting cerebral glucose metabolism was assessed by means of positron emission tomography (PET) and [F-18]fluorodeoxyglucose. The methods of image acquisition and analysis including the selection and boundaries of the brain regions-of-interest are detailed in (Hasler *et al*, 2008). *Exploratory* correlational analysis examined the relationship between behavioral performance and metabolic activity changes following AMPT administration. In previous work, we have shown that CD influenced metabolic activity in several neural regions (Hasler *et al*, 2008). These regions include those implicated previously in successful reversal learning and/or passive avoidance; in particular, the perigenual anterior cingulate cortex, ventrolateral prefrontal cortex, amygdala and ventral striatum (Budhani et al., 2007; Kosson et al., 2006). We thus examined whether the neurophysiological effect of CD, as measured by the change in regional metabolic activity (averaged across hemispheres) under AMPT versus placebo, related to behavioral performance.

Neuropsychological Testing

The neuropsychological assessments were initiated 34 hours after the first AMPT intake and included the Probabilistic Response Reversal Task (PRR), the Passive Avoidance Learning Task (PA), and the Affective Stroop Task (aST). The order of the tasks was randomized across participants.

The PRR task was previously described in (Budhani and Blair, 2005). The stimuli were 12 line drawings of animals (Snodgrass and Vanderwart, 1980) each shaded a different color. These stimuli were randomly assigned to pairs at the beginning of the task. Stimuli measured 4×4 cm and were presented on a gray background.

On each trial, one of the stimulus pairs was presented on a computer screen. The location of individual stimuli was randomly assigned to one of 16 locations on each trial. Participants chose one of the stimuli by clicking on it with the mouse, after which they received either positive ('you win 100 points') or negative ('you lose 100 points') feedback on the basis of the reinforcement contingency of that pair. A running total of points was presented at the bottom of the screen after each trial. Trials were self-paced. The reinforcement contingencies were probabilistic such that the 'correct' pair was not always rewarded and the 'incorrect' pair was not always punished. The 'correct' stimulus in a pair with an 80-20 reward-punishment contingency was rewarded on 8 out of every 10 trials and punished on 2 out of every 10 trials. Conversely, the 'incorrect' stimulus was punished on 8 out of every 10 trials and rewarded on 2 out of every 10 trials. The order of probabilistic feedback was randomized within the program. There were six different pairs of stimuli: two test pairs which changed contingency (reversing pairs) and four 'dummy' pairs which did not (non-reversing pairs). The two reversing pairs had contingencies 100-0 and 80-20. The reinforcement contingency of the reversing pairs remained constant for 40 trials (phase 1: acquisition of the discrimination). Upon completing 40 trials the reinforcement contingency of the reversing pairs reversed (phase 2: reversal of the discrimination), so that the previously correct stimulus became the incorrect stimulus and the previously incorrect stimulus now became the correct stimulus. This reversed pattern continued for a total of 80 trials per stimulus pair. Three of the nonreversing dummy pairs had a contingency of 100-0 and the fourth had a contingency of 80-20.

The PA task was a modified version of Newman and Kosson's task (Newman and Kosson, 1986; Blair *et al*, 2004). Stimuli were 16 white 2-digit numbers presented for 3000 ms sequentially on a black background. Six of the stimuli, the S+ s, were 'good' stimuli; an approach (bar press) response to these stimuli led to the participant gaining 100 points. Six of the stimuli, the S− s, were 'bad' stimuli; the participant learned to avoid these stimuli as an approach (bar press) response to them led to the participant losing 100 points. Participants learned by trial-and-error to click on the mouse button to the S+ and to refrain from responding to the S−. After each response, participants received feedback on points they had won or lost. If no response was made, a blank screen appeared in place of feedback. Stimuli were presented once per block for 10 blocks per session. Performance was assessed by analysis of omission errors (failure to respond to a rewarded stimulus) or commission errors (response to a punished stimulus). The omission error rate was equal to the number of times a participant failed to respond to an S+ (and thus failed to obtain a reward). The passive avoidance error rate was defined as the number of times a participant responded to an S− (and was thus punished). Following previous work (Newman and Kosson, 1986; Finger *et al*, 2007), the omission and passive avoidance data were analyzed with separate 2 (group: patients vs. healthy comparison) × 2 (drug: AMPT vs. placebo) × 10 (Block) ANOVAs.

The aST (Blair *et al*, 2007) was adapted from a Number Stroop task developed by Pansky & Algom (Pansky and Algom, 2002). In the original Number Stroop task, participants are presented sequentially with two numerical displays presented within a nine-point grid (see Fig. 1). The subject must determine which numerical display contains the greater

numerosity. If there were more numbers in the first numerical display (50% of task trials), they responded by pressing a button with their left hand (more numbers in the second numerical display was instead indicated using a right-hand response). Participants did not receive feedback on their performance. The Stroop element of the task is based on the competition between the numerosity and number-reading information. On congruent trials, the Arabic numeral distracter information was consistent with the numerosity information; that is, the second (greater numerosity) display also contained Arabic numerals of larger value than the first display (e.g. two 2s and four 4s) (see Fig. 1a). On incongruent trials, the Arabic numeral distracter information was inconsistent with the numerosity information; that is, the second (greater numerosity) display contained numerals of smaller value than the first display (e.g. four 5s and five 4s) (see Fig. 1b). There were three different levels of incongruent trials according to the numerical distance between the numerosity and Arabic numeral information. Incongruent trials with a distance of 1 (two 3s and three 2s) are significantly more difficult than incongruent trials with a distance of 3 (two 5s and five 2s). The aST modifies this Number Stroop task by having positive, negative or neutral images temporally bracket the numerical displays such that the trial consists of four, very rapid (400 ms each) consecutive displays (e.g. four 5s, picture of snake, five 4s, picture of snake). The emotional stimuli consisted of 40 positive, 40 negative (primarily threat-related), and 40 neutral pictures selected from the International Affective Picture System (IAPS (Lang and Greenwald, 1988)). The normative mean [±standard error (S.E.)] valence and arousal values on a nine-point scale were respectively 2.71±0.11 and 5.85±0.11 for negative pictures, 7.30±0.11 and 5.01±0.10 for positive pictures and 4.96±0.07 and 2.78±0.08 for neutral pictures. Overall, each participant was presented with 480 trials (160 positive, 160 negative and 160 neutral). Within each of the 160 trials, for each valence, 40 were congruent, 40 were incongruent distance 1, 40 were incongruent distance 2 and 40 were incongruent distance 3. Trials were randomized across participants.

Results

Of the 15 female RMDD subjects (mean age=39±11 years; HDRS<8 (mean=1.9±1.9), 4 had one previous major depressive episode, 7 had two previous episodes, and 5 had three or more previous episodes. The 12 healthy female controls did not differ significantly from the RMDD subjects regarding mean age (mean age=39±12 years; mean HDRS=0.7±1.2). There was no difference in educational level between groups (mean educational level in RMDD subjects: 6.1±1.0; in controls: 6.3±0.62; p=0.70). The behavioral, neural and endocrine responses to AMPT in the same study samples are described in (Hasler *et al*, 2008).

Probabilistic reversal learning task

A 2 (group: patients versus healthy comparison) × 2 (drug: AMPT versus placebo) × 2 (pair: 100-0 versus 80-20) × 2 (phase: acquisition versus reversal) ANOVA was conducted on errors to criterion. This revealed main effects for pair [$F(1, 24) = 24.35$; $p < 0.001$; mean errors 100-0 pair = 1.59 (s.e. = 0.16); mean errors 80-20 = 3.69 (s.e. = 0.36)] and phase [($F(1, 25) = 31.86$; $p < 0.001$; mean errors acquisition = 1.49 (s.e. = 0.25); mean errors reversal = 3.80 (s.e. = 0.36)]. There were significant interactions for drug by pair [$F(1, 25) = 4.99$; $p < 0.05$], pair by phase ($F(1, 25) = 6.23$; $p < 0.05$) and, critically, drug by pair by

phase [F(1, 25) = 5.35; p < 0.05; see Figure 1]. As shown in Figure 1, AMPT selectively and significantly increased errors for the reversal of the 80-20 contingency pair [F(1, 27) = 4.94; p < 0.05]. There was no significant main effect of, or interaction with, diagnosis (p > 0.20 in all cases).

Passive avoidance learning

The ANOVA conducted on the omission error data revealed both a main effect for block [F(9, 207) = 4.04; p < 0.005)] and a drug by block interaction [F(1, 23) = 5.31; p < 0.05; linear contrast]; see Figure 2. This interaction was driven by the fact that under CD participants were less likely to respond to the S+ stimuli in the later blocks (7–10) relative to the earlier blocks (1–4) [F(1, 23) = 10.29; p < 0.01] while participants administered placebo were not [F(1, 23) < 1; n.s.]. There was no significant main effect of, or interactions with, diagnosis (p > 0.15 in all cases). A second 2 (group: patients versus healthy comparison) × 2 (drug: AMPT versus placebo) × 10 (Block) ANOVA was conducted on the passive avoidance error data. This revealed no significant main effect of, or interaction with, drug (p > 0.45 in all cases). However, there was a highly significant main effect for block [F(1, 23) = 88.93; p < 0.001]; participants made fewer commission errors as the blocks progressed.

Affective Stroop task

Two 2 (group: patients versus healthy controls) × 2 (drug: AMPT versus placebo) × 3 (emotion: positive, negative, neutral) × 4 (Distance: Congruent, Distance 3, Distance 2, Distance 1) ANOVAs were conducted on the RT and error data, respectively. The RT ANOVA revealed main effects for emotion [F(2, 48) = 16.73; p < 0.001] and distance [F(3, 72) = 16.69; p < 0.001]. The participants were slower to respond in the context of positive and negative distracters relative to neutral distracters [mean positive = 889.8 msec (s.e. = 30.65); mean negative = 895.43 msec (s.e. = 31.44); mean neutral = 872.55 msec (s.e. = 31.49)]. The participants were slower to respond to the different distance incongruent trials relative to the congruent trials [mean RT for distance 1 = 893.73 msec (s.e. = 30.63); mean for distance 2 = 901.61 msec (s.e. = 30.38); mean for distance 3 = 895.01 msec (s.e. = 31.70); mean congruent = 852.21 msec (s.e. = 33.11)]. There was also a trend of drug [F(1, 24) = 3.74; p < 0.1], as participants were slower to respond under CD than under placebo [mean RT under CD = 904.96 msec (s.e. = 30.65); mean placebo = 866.33 (s.e. = 32.85). There was no significant main effect of, or interaction with, diagnosis (p > 0.10 in all cases).

The error rate ANOVA revealed no significant main effect of drug or emotion (p = 0.472 and 0.12 respectively). However, there was a main effect of distance [F(3, 72) = 3.84; p < 0.05]. The participants made greater numbers of errors as numerical distance between the target and distracter information decreased [mean distance 1 = 0.68 (s.e. = 0.13); mean distance 2 = 0.60 (s.e. = 0.12); mean distance 3 = 0.55 (s.e. = 0.10); mean congruent = 0.39 (s.e. = 0.08)]. There was also a significant group by distance interaction [F(3, 72) = 3.77; p < 0.05]. The RMDD individuals made significantly greater errors for distance 2 [F(1, 24) = 5.08; p < 0.05; see Figure 3).

Correlations with brain metabolism

Two measures were generated from the two reward learning tasks: (1) As CD selectively and significantly increased errors for the reversal of the 80-20 contingency pair, the first behavioral performance difference score was AMPT 80-20 reversal errors – Placebo 80-20 reversal errors; (2) As participants under CD significantly increased missed responses to the S+ "good" stimuli in the later blocks relative to the earlier blocks, we generated the behavioral performance difference score: AMPT misses of good stimuli for blocks 7 to 10 – AMPT misses of good stimuli for blocks 1 to 4. Thus, ten correlations were conducted. These resulted in two clear results: the greater the extent to which metabolism in perigenual ACC decreased under CD (Figure 4), the greater the number of 80:20 reversal errors occurred under CD relative to placebo ($r = -0.52$; $p < 0.01$) and the more often good stimuli were missed in blocks 7 to 10 relative to blocks 1 to 4 under CD versus placebo ($r = -0.46$; $p < 0.05$).

Discussion

This is the first study examining the effects of catecholamine depletion on reversal learning and passive avoidance in humans. Although AMPT did not affect the acquisition phase of the reversal learning task, it selectively impaired reversal of the 80-20 contingency pair and reduced responding towards rewarding stimuli. Moreover, the performance decrement produced by AMPT on both tasks was associated with the level of decreased metabolism in the perigenual ACC. Lastly, using the affective Stroop task, we found evidence for impaired executive attention, reflected by a greater error rate in an executive attention task in RMDD than in controls, as a trait abnormality in MDD.

Dopamine and to a lesser extent norephinephrine have been implicated in various aspects of reinforcement-based learning (Crow and Wendlandt, 1976; Wilkinson *et al*, 1998; Kabai *et al*, 2004). Moreover, previous studies have provided evidence for a prominent role of dopamine in reversal learning. For example, in mice administration of the selective D1-like agonist SKF81297 produced an impairment in the early phase of reversal learning (Izquierdo *et al*, 2006), administration of the D2/D3 receptor antagonist raclopride impaired performance in the reversal of a learned visual discrimination in monkeys (Lee *et al*, 2007); and administration of amphetamine or cocaine, which increase intrasynaptic dopamine concentrations, impaired reversal learning and induced response perseveration (Ridley *et al*, 1981; Stalnaker *et al*, 2007). The literature is, however, in disagreement regarding the effects of reduced dopaminergic neurotransmission on reversal learning. While dopaminergic lesions of the nucleus accumbens impaired reversal learning in rodents (Taghzouti *et al*, 1985), depletion of dopamine in the orbitofrontal cortex did not impair serial discrimination reversal learning in mice (Clarke *et al*, 2007), and dopaminergic antagonists such as haloperidol caused only a mild, non-perseverative impairment on reversal learning in marmosets (Ridley *et al*, 1981). The current data confirm the role of dopamine in reinforcement-based decision making and suggest that, in humans, dopamine depletion impairs reversal learning. Interestingly, enhanced dompaminergic activity has also been associated with impaired reversal learning: in Parkinson's patients, dopaminergic medication impaired probabilistic reversal learning, possibly due to 'over-dosing' of the

ventral striatum, which is relatively spared of dopamine loss in early stage Parkinson's disease (Cools *et al*, 2001; Cools *et al*, 2007). Interactions between the dopaminergic and the serotonergic systems during reversal learning have been proposed since tryptophan depletion also affected reversal learning, particularly during the processing of aversive signals by modulation of the dorsomedial PFC (Evers *et al*, 2005)

Studies of experimental animals indicate that performance on a task homologous to the current passive avoidance learning task relies on the amygdala, striatum and orbitofrontal cortex (Schoenbaum *et al*, 2006). FMRI data confirm the role of these structures in humans examined during passive avoidance learning (Kosson *et al*, 2006). Studies in non-human primates have shown that a neural network that includes the orbitofrontal cortex, striatum and ascending monoaminergic systems plays a critical role in the ability to adjust responses during reversal learning (Iversen and Mishkin, 1970; Rolls *et al*, 1996; Clarke *et al*, 2004; Izquierdo *et al*, 2004; Clarke *et al*, 2007; Bellebaum *et al*, 2008). These results have been extended to humans through fMRI studies (Hampton *et al*, 2006; Budhani *et al*, 2007). Thus, studies in humans and experimental animals implicate both orbitofrontal cortex and striatum in successful performance on both the passive avoidance and reversal learning tasks. While metabolic activity changes within ventral striatum following AMPT were not related to performance decrements on these two tasks, metabolic changes within the perigenual ACC following AMPT were related to them. The perigenual ACC contains abundant concentrations of dopamine receptors, and its projections to the ventral tegmental area play major roles in organizing the release of dopamine in the striatum and prefrontal cortex (reviewed in (Drevets *et al*, 1998)). As such, the degree to which AMPT has an impact on metabolic activity within ACC may influence function in the orbitofrontal cortex and striatum, potentially accounting for the relationship between the change in ACC metabolism and the change in behavioral performance on two tasks that putatively rely on the function of the orbitofrontal cortex and striatum.

Both passive avoidance and reversal learning rely on positive outcome reinforcement signaling. Within the passive avoidance learning task, the subject must associate specific stimuli with reward and respond when they are present, while also associating other stimuli with punishment and avoid responding when they are present (Schoenbaum *et al*, 2006). Impaired representation of reinforcement outcome information thus will disrupt task performance. Within the reversal learning task, the subject must update reinforcement values associated with specific responses when the reinforcement contingencies change during the reversal phase (Hampton *et al*, 2006). The orbitofrontal cortex is critically involved in the representation of reinforcement outcomes (Hampton *et al*, 2006). Importantly, the current data add to evidence of an associations between dopamine (and possibly norepinephrine) neurotransmission and the representation of reinforcement outcome information. Brain signals related to reward-related learning have been located in the midbrain dopamine neurons, select neurons of the orbitofrontal and ventromedial prefrontal cortex, ventral and dorsal striatum and amygdala (Everitt *et al*, 2003; O'Doherty, 2004; Schultz, 2007). In monkeys, a prominent relationship between oribtofrontal neuronal activity and outcome reinforcement signaling has been demonstrated (Tremblay and Schultz, 2000). Taken together, the mechanisms by which CD resulted in impairments of reversal learning and

passive avoidance may involve effects on rapid dopamine phasic responses to reward-predicting stimuli within orbitofrontal and medial prefrontal cortex (Schultz, 1997). While there has been little examination how coeruleo-cortical noradrenergic projections influence the processing of rewarding stimuli, it is possible that norephinephrine depletion may also have contributed to impaired reinforcement signaling. Alternatively, or additionally, there may have been an interaction effect of the dopamine and norepinephrine depletion by AMPT (Devoto *et al*, 2004).

Attentional bias toward processing of mood congruent information including sad, unpleasant and negative words, and fearful and sad facial expression have previously been reported in patients with MDD (Watkins *et al*, 1996; Murphy *et al*, 1999). Moreover, they have also been found in subjects with remitted MDD suggesting a trait-like abnormality (Hammen *et al*, 1985; Koschack *et al*, 2003). While depletion of central serotonin led to the emergence of mood-congruent memory bias (Klaassen *et al*, 2002), the effects of catecholamine depletion on attentional and mnemonic biases toward negative information have not been examined. We found that both RMDD subjects and controls were slower to respond in the context of positive and negative distracters relative to neutral distracters, and they were slower to respond to the different distance incongruent trials relative to the congruent trials. AMPT led to a slight general increase in reaction time, but there was no interaction with diagnosis. The participants made greater numbers of errors as numerical distance between the target and distracter information decreased, and this effect was significantly more pronounced in RMDD subjects than controls. In summary, these findings suggest no important influence of catecholamines on attentional bias induced by emotional distractors and provide no evidence for attentional bias as a trait marker in MDD with respect to emotional distractors. However, this study confirms previous reports of impairments of executive attention as assessed by the Stroop test as a neuropsychological trait in affective illness (Zubieta *et al*, 2001; Blumberg *et al*, 2003; Hasler *et al*, 2006).

Several limitations of our methods merit comment. We did not include an active placebo because of the pharmacological actions of sedatives (e.g., anticholinergic or benzodiazepine agents) that have previously been used as active controls in AMPT studies might have had affected task performance in the control condition and thus confounded the results of this study. Moreover, there was no difference between RMDD subjects and controls regarding the sedative effects of AMPT. The subject samples were small and included only female subjects, precluding generalization of the results to males. The generalizability of our results also was affected by selection biases introduced by the requirement that RMDD subjects had maintained remission while off medications for ≥3 months, which yielded a sample with a relatively small number of past depressive episodes (2.5±1.5), which may have contributed to the lack of associations between AMPT-induced impairments of reward processing and risk of MDD. Finally, the sample size was relatively small for a behavioral study, which reduces the reliability of our results and calls for studies that evaluate their replicability.

In conclusion, this study showed specific effects of catecholamine depletion on the processing of reward-related stimuli in humans: CD impaired both the reversal of probabilistic contingency pairs and the retention of stimulus-reward learning in a passive avoidance task. These CD-induced impairments of reward processing were found both in

healthy controls and in subjects with fully-remitted MDD. In addition, this study confirms previous investigations that demonstrate impairments of executive attention as a neuropsychological trait in affective illness (Hasler *et al*, 2006).

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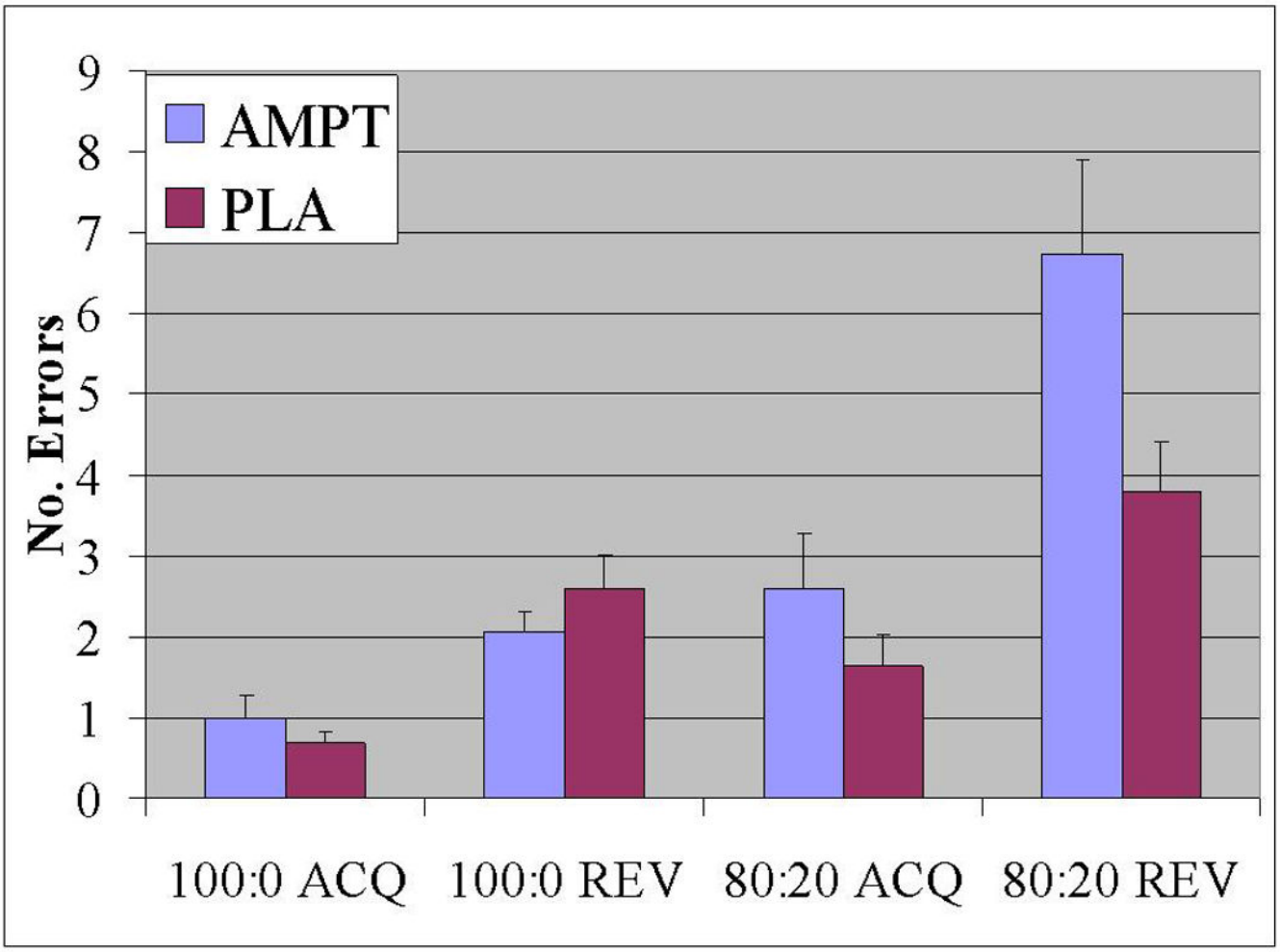

Figure 1.
Probabilistic Response Reversal Task: Number of errors by treatment and pair and learning phase. As expected, the numbers of errors were higher in the 100:0 pair trials than in the probabilistic 80:20 pair trials ($p<0.001$); and there were more errors in the reversal phase than in the acquisition phase ($p<0.001$). In the reversal phase of the 80:20 pair trials, errors were more frequent following catecholamine depletion than under placebo (drug by pair by phase interaction, $p<0.05$).

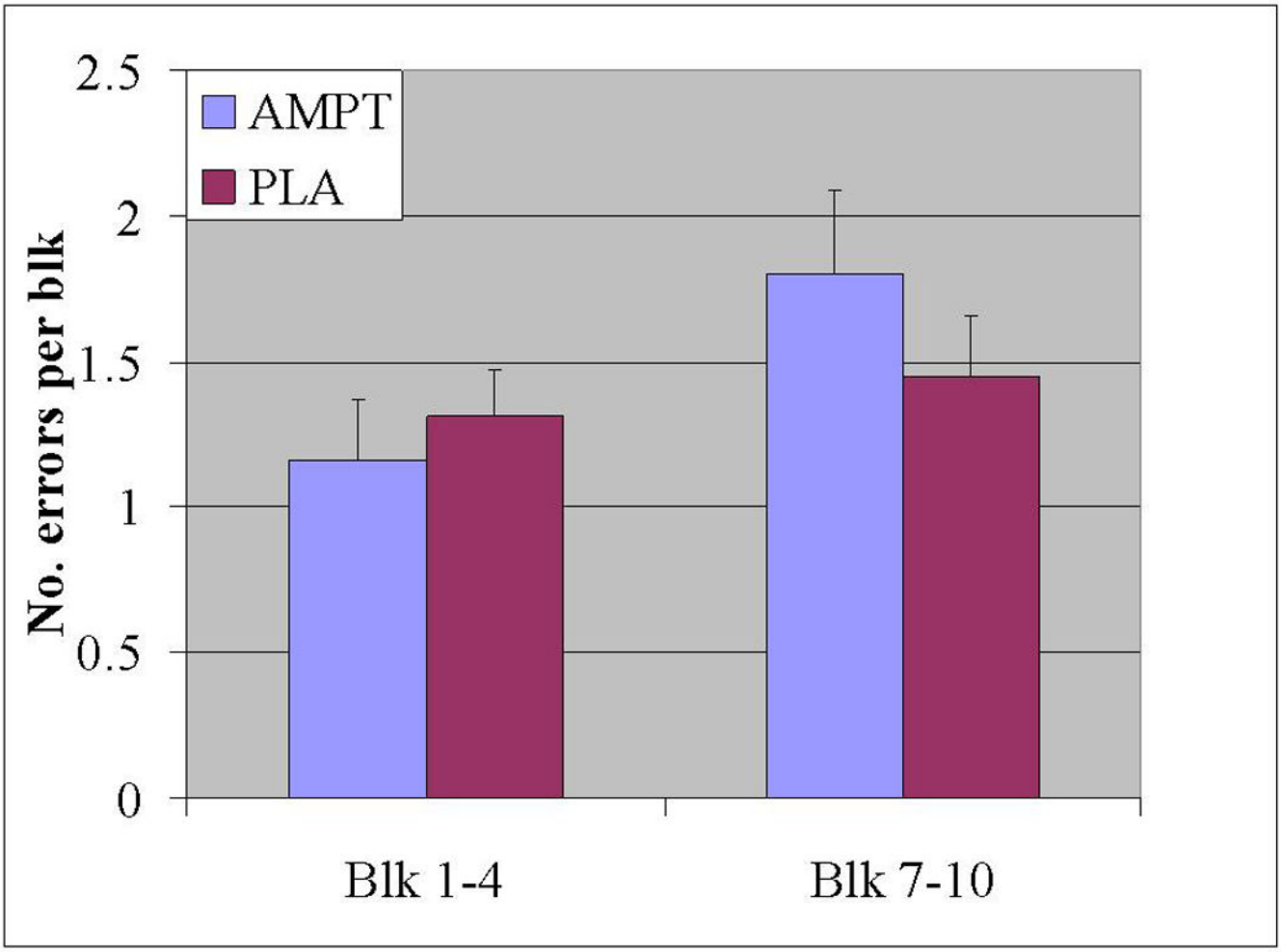

Figure 2.

Passive Avoidance learning task: Number of omission of responses to rewarded stimuli by treatment and block. Following catecholamine depletion, subjects were less likely to respond to S+ stimuli in the later blocks (7–10) relative to the earlier blocks (1–4, $p<0.01$), while under placebo subject did not show such an influence of the blocks on the number of omission errors (drug by block interaction, $p<0.05$).

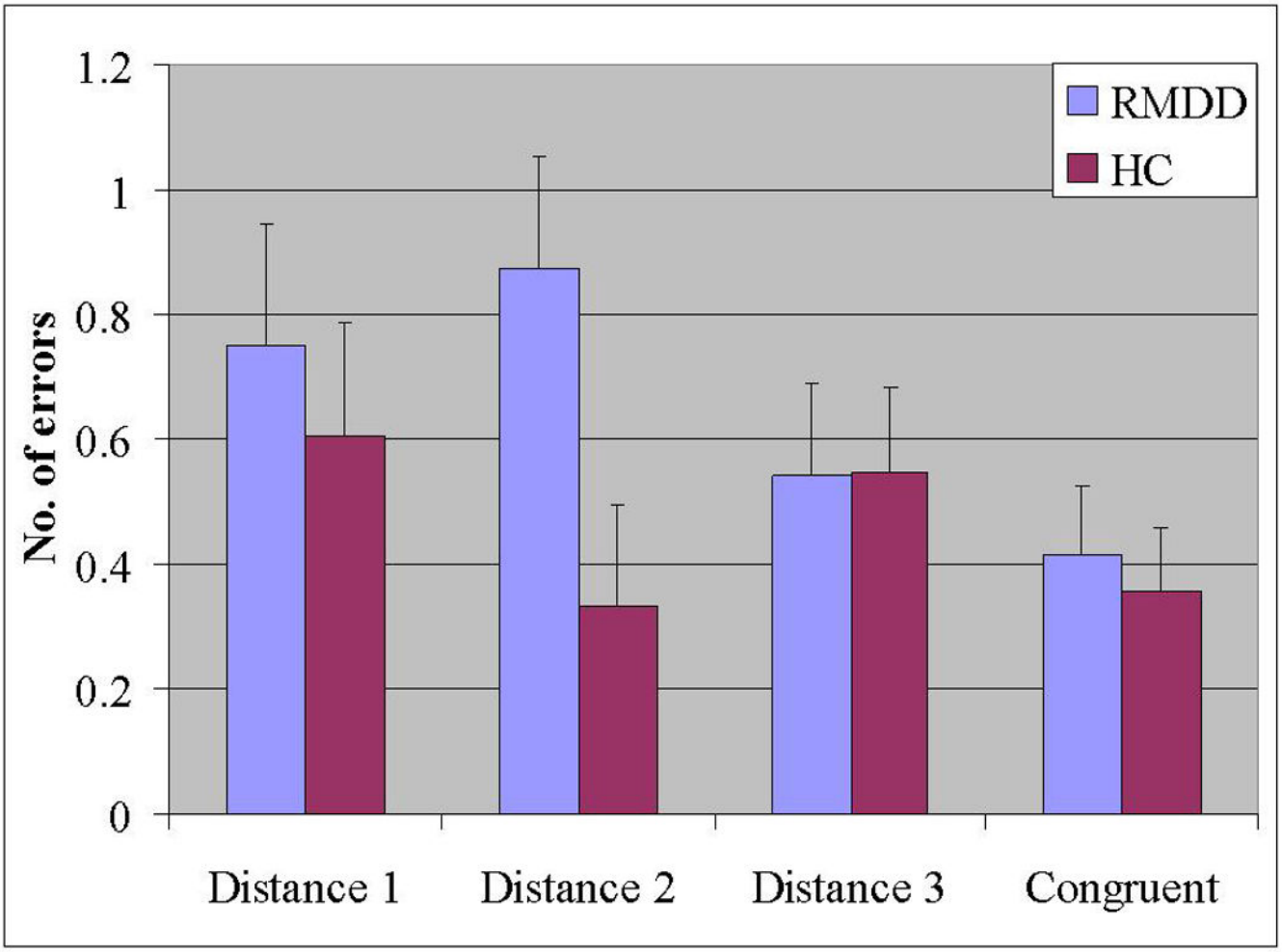

Figure 3.

Affective Stroop Task: Error rates by group and condition. As expected, subjects made a greater number of errors as numerical distance between the target and distracter information decreased ($p<0.05$). In addition, the fully remitted subjects with MDD made significantly more errors for distance 2 ($p <0.05$; group by distance interaction, $p<0.05$)

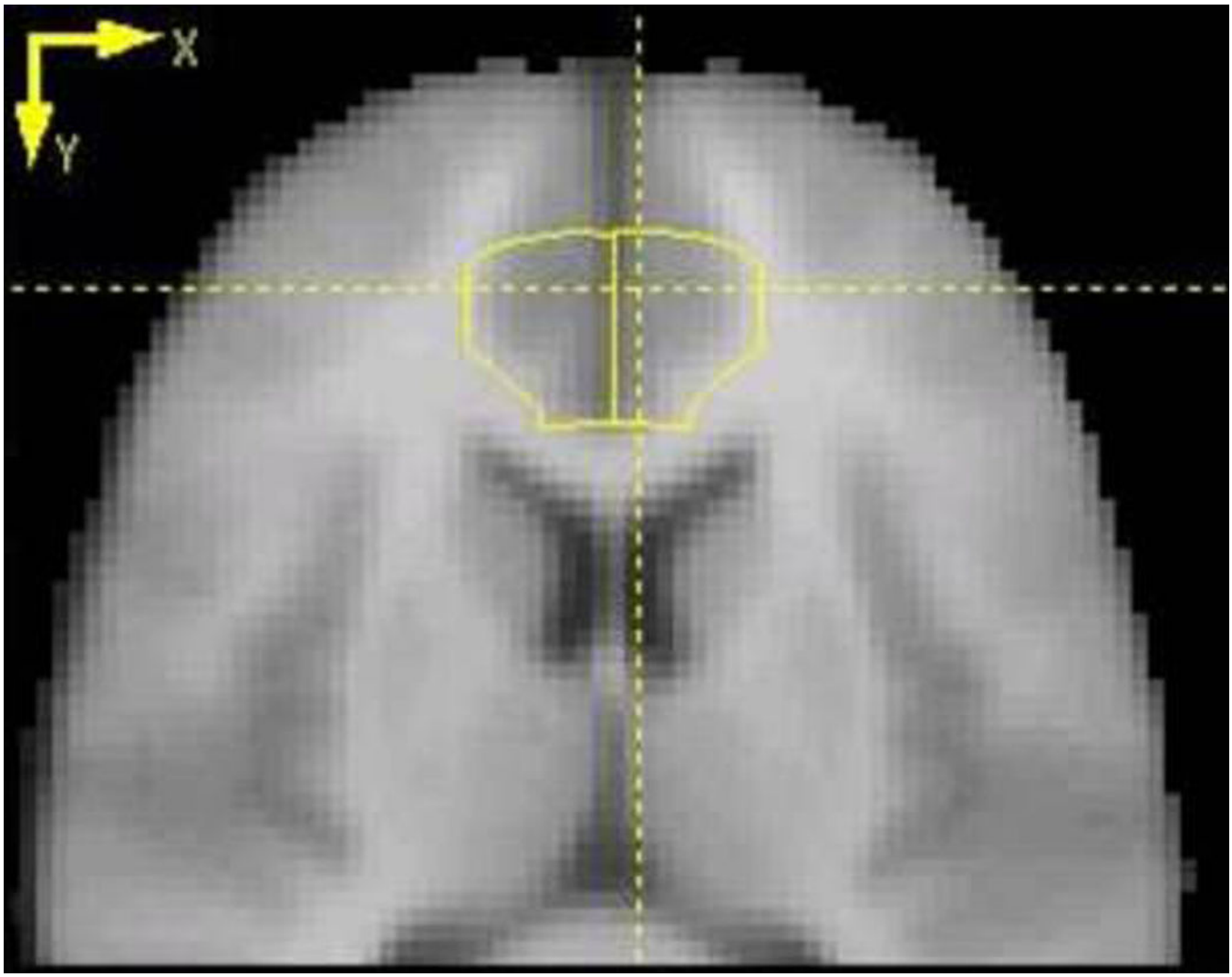

Figure 4.

Placement of the perigenual anterior cingulate cortex (ACC) region-of-interest (ROI) in the horizontal plane. The crosshair is placed over the pregenual ACC within the left perigenual ACC ROI. In this voxel, CD-induced change in brain metabolism correlated with CD-induced errors in the reward learning tasks: the greater the extent to which metabolism in perigenual ACC decreased under CD, the greater the number of 80:20 reversal errors occurred under CD relative to placebo ($r = -0.52$; $p < 0.01$) and the more often good stimuli were missed in blocks 7 to 10 relative to blocks 1 to 4 under CD versus placebo ($r = -0.46$; $p < 0.05$).