The effect of acute tyrosine phenylalanine depletion on emotion-based decision-making in healthy adults

By: Suzanne Vrshek-Schallhorn, Dustin Wahlstrom, Tonya White, Monica Luciana

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Abstract:

Despite interest in dopamine's role in emotion-based decision-making, few reports of the effects of dopamine manipulations are available in this area in humans. This study investigates dopamine's role in emotion-based decision-making through a common measure of this construct, the Iowa Gambling Task (IGT), using Acute Tyrosine Phenylalanine Depletion (ATPD). In a between-subjects design, 40 healthy adults were randomized to receive either an ATPD beverage or a balanced amino acid beverage (a control) prior to completing the IGT, as well as pre- and post-manipulation blood draws for the neurohormone prolactin. Together with conventional IGT performance metrics, choice selections and response latencies were examined separately for good and bad choices before and after several key punishment events. Changes in response latencies were also used to predict total task performance. Prolactin levels increased significantly in the ATPD group but not in the control group. However, no significant group differences in performance metrics were detected, nor were there sex differences in outcome measures. However, the balanced group's bad deck latencies speeded up across the task, while the ATPD group's latencies remained adaptively hesitant. Additionally, modulation of latencies to the bad decks predicted total score for the ATPD group only. One interpretation is that ATPD subtly attenuated reward salience and altered the approach by which individuals achieved successful performance, without resulting in frank group differences in task performance.

Keywords: dopamine | acute tyrosine phenylalanine depletion | Iowa Gambling Task | healthy adults | decision making

Article:

1. Introduction

The dopamine (DA) system is widely implicated in psychopathology, including schizophrenia, bipolar disorder, substance use disorders, and unipolar depression. These conditions are thought to disrupt the modulation of motivated behavior, a function that is controlled by DA in frontostriatal regions (Schultz, 1998, Wise, 2004). Specific abnormalities can include anhedonia or the converse, a reduced ability to predict or benefit from predicting the destructive consequences of certain goal-directed or pleasure-seeking behaviors.

In controlled human studies, motivated behavior is often assessed through emotion-based decision making tasks where participants must decide between alternatives that vary in their risk for negative consequences and rewards. A commonly employed measure of emotion-based decision-making is the Iowa Gambling Task (IGT; Bechara et al., 1994). Despite interest in DA's role in motivated behavior, there have been few experimental investigations of DA manipulations' effects on incentive learning on emotion-based decision-making tasks similar to the IGT, although several more papers examine IGT performance and basal DA functioning (Linnet et al., 2010a, Linnet et al., 2010b). More specifically, a safe, transient DA depletion paradigm (acute tyrosine phenylalanine depletion; ATPD) reduced the size of wagers placed during the Cambridge Gambling Task in two studies, suggestive of reductions in reward salience or increases in punishment salience (McLean et al., 2004, Roiser et al., 2005). ATPD was also associated with reduced accuracy for reward conditions on a trial and error learning task that included reward incentives (Leyton et al., 2007). In a related type of task, a reversal learning paradigm, ATPD appeared to shift learning from reward-focused to punishment-focused (Robinson et al., 2010). Finally, one study used a different type of DA depletion paradigm, a branched chain amino acid beverage (BCAA, known to also reduce tryptophan, the precursor to serotonin) in 11 men, demonstrating that those in the depleted condition lost more money on the IGT, but did not differ significantly in the conventional performance metric, good minus bad deck choices (Sevy et al., 2006).

Taken together, these findings suggest that ATPD may impact the relative salience of reward versus punishment contingencies. The present investigation aimed to examine DA's influence on emotion-based decision-making on the IGT in healthy humans. ATPD was employed to lower central DA levels in healthy adult humans and to compare their performance with that of controls on the IGT. To our knowledge, this is the first report of ATPD's effects on emotion-based decision-making using the IGT.

1.1. The Iowa Gambling Task (IGT)

The IGT (Bechara et al., 1994) is composed of four “decks” of cards, from which participants are instructed to choose. Each of the task's 100 trials is followed by feedback about winnings on every trial, and losses, which occur only intermittently. In two disadvantageous decks, winnings are larger compared with the remaining two (advantageous) decks, making them deceptively attractive; however, losses in these “bad” decks are commensurately larger, ultimately netting a negative score. Given that winnings are predictable, while variable magnitude punishments occur periodically, participants' abilities to appreciate and respond to punishment contingencies is important for performance (Dunn et al., 2006). Importantly, participants are told only that some decks are worse than others in terms of their ultimate payouts. They must infer deck contingencies

from feedback provided after each selection. Thus, it is necessary to examine the quality of performance over time as inferences about feedback contingencies impact later performance.

One challenge to examining DA's influence on reward learning in healthy adults is that they may lack frank deficits in instrumental (operant) learning, the type of learning necessary for successful IGT performance (d'Acremont et al., 2009). Previous research supports that a potentially complementary approach to traditional IGT learning assessments is examining changes in response latencies throughout the task. Using the IGT, longer response latencies have been positively correlated with impairment (Tucker et al., 2004), advantageous alternatives are selected more rapidly (Crone and van der Molen, 2004), and responding becomes more rapid following non-punishment trials (Goudriaan et al., 2005). This learning-based increase in reaction time would seem to reflect heightened confidence in choice selection. We used this measure of participants' confidence or hesitancy in selection by examining changes in median response latencies ("MRLs") separately for good and bad deck choices earlier versus later in the task. Adaptive integration of task contingencies later versus earlier in the task could be signified by either more rapid selection (i.e., decreasing MRLs) of good decks or slower, more hesitant selection (i.e., increasing MRLs) of bad decks.

Such an analytic approach requires segmentation of the task's trials. Participants vary considerably in the information they receive about the task in any one of the five traditional task blocks. One block typically consists of 20 trials (Bechara et al., 1994). Alternatively, performance can be examined in relation to events during the task that reflect when participants have been exposed to important outcome contingencies. These events are (1) the point when a participant has experienced one punishment from each of the four choices, allowing him/her to correctly infer punishment magnitudes for each choice, and (2) the point at which participants have been exposed to two punishments from each of the four choices, allowing correct inferences about each deck's punishment magnitude as well as frequency. Punishment events represent the task's most salient outcome markers, because rewards are provided on every trial. Punishments occur in a pseudorandom sequence based on how many times a person has selected a given choice. We refer to these points as the "one punishment event" and the "two punishment event." When they occur varies considerably across individuals based on the individuals' patterns of choices. We also calculated the change in MRL before versus after each event (ΔMRL = post-event MRL − pre-event MRL) to examine relationships between ΔMRLs and total good minus bad choices, which represents the conventional metric used to evaluate IGT performance. Larger/positive values of ΔMRL characterize increasing hesitation to make selections from a deck type over the course of the task, while smaller/negative ΔMRL values characterize increasing confidence in selecting from a deck type. Thus, ΔMRLBAD might directly predict task performance, while ΔMRLGOOD might inversely predict task performance.

1.2. Acute tyrosine-phenylalanine depletion (ATPD) in adult humans

The ATPD protocol involves administering an amino acid rich beverage that lacks DA's amino acid precursors (tyrosine, TYR, and phenylalanine, PHE). This manipulation decreases rates at which naturally present TYR and PHE compete for access to amino acid transporters in the blood–brain barrier, impacting dopamine synthesis. A balanced beverage containing TYR and PHE serves as a control. Human studies show significant decreases in peripheral blood TYR and PHE following ATPD (Le Masurier et al., 2004), as well as decreases in their ratio to the LNAAs (Moja et al., 1996). An expected increase in serum prolactin resulting from decreased hypothalamic DA

inhibition (Luciana and Collins, 1997) has been observed following ATPD relative to placebo (e.g., Harmer et al., 2001, Lythe et al., 2005). Two PET studies found that striatal binding of the competitive DA agonist [11C]-Raclopride increased by approximately 6% following ATPD, supporting a comparable decrease in DA (Leyton et al., 2004, Montgomery et al., 2003). Thus, human physiological evidence supports that ATPD depletes striatal DA. ATPD has been reported to impact mood regulation and motivation (Roiser et al., 2005), affective stimulus processing (Barrett et al., 2008, Leyton et al., 2005, McLean et al., 2004, McTavish et al., 2001, Vrshek-Schallhorn et al., 2006), and response modulation (Vrshek-Schallhorn et al., 2006), all processes mediated by mesolimbic DA activity. Despite evidence that ATPD alters affective processing, there are few reports of ATPD's or other DA manipulations' effects on emotion-based decision-making. As reviewed earlier, several related studies suggest that ATPD may impact the relative salience of reward versus punishment contingencies (e.g., Leyton et al., 2007, McLean et al., 2004, Robinson et al., 2010, Roiser et al., 2005).

We hypothesized that the large punishments associated with the bad decks may be relatively more salient to the APTD group. We reasoned that brain DA depletion using ATPD would reduce appreciation of reward, which ought to decrease the attractiveness of the deceptively large rewards contained in the bad decks, making large punishments more salient by comparison given their effects on overall net gains and losses. Because IGT performance is thought to depend upon appreciation of punishment events (Dunn et al., 2006), we hypothesized that ATPD would be associated with enhanced IGT performance or more adaptive response styles compared with the balanced group. Enhanced performance could be indexed by greater good minus bad choices or a greater rate of change in good minus bad choices, while more adaptive response styles could be indexed by greater hesitancy in MRLs for bad choices after each punishment event than before each event, and faster MRLs for good choices after each punishment event than before each event. Further, if punishment information becomes more salient following ATPD, the predicted direct relationship of ΔMRLBAD to total good minus bad choices may be strengthened in the ATPD group relative to a control group. Similarly, we also expected that MRLs for good choices would accelerate across the task—but more strongly for the ATPD group. Finally, we hypothesized that serum prolactin levels would increase following ATPD but not a control manipulation.

2. Methods and materials

2.1. Participants

Undergraduate students (n = 44, including 26 males and 18 females) were recruited from psychology courses and were compensated in the form of extra credit in their courses. A previous study reports the performance of the same participants on other tasks (Vrshek-Schallhorn et al., 2006). Participants provided written informed consent at an eligibility screening session, and all procedures were approved by the University of Minnesota's Institutional Review Board. Participants were determined to be psychologically healthy using the Structured Clinical Interview for DSM-IV, Patient Version (First et al., 1997). Exclusions were made for histories of significant head trauma, neurological disease, current use of contraindicated prescription medication (any medication with psychoactive or hormonal effects), daily nicotine use, recreational drug use (> 1 use per week), heavy alcohol use (> 15 drinks per week), pregnancy, menstrual irregularities, and/or lifetime history of any DSM-IV Axis I disorder. Eligible participants were scheduled for a

full testing day and were randomized in a double-blind fashion to ATPD or to a balanced condition (Table 1).

Table 1. Demographic and IGT response characteristics by drug condition.

Drug condition	ATPD	Balanced
Demographics		
N	19	21
Males:females	11:8	14:7
Minority status	1	2
Age (months)	240.22 (17.30)	233.98 (12.96)
Height (m)	1.74 (.13)	1.77 (.09)
Weight (kg)	71.93 (12.00)	71.05 (12.30)
BMI	23.87 (3.55)	22.53 (3.05)
Years education completed	13.16 (.96)	12.86 (.96)
1 punishment at each of four decks	(N = 17)	(N = 19)
Mean trial number	44.00 (9.66)	41.68 (11.19)
Pre-event good deck MRL	584.09 (345.67)	563.34 (256.78)
Post-event good deck MRL	433.29 (181.19)	446.92 (166.88)
Pre-event bad deck MRL	575.03 (245.64)	597.39 (215.13)
Post-event bad deck MRL	666.41 (502.30)	484.76 (166.90)
2 punishments at each of four decks	(N = 13)	(N = 17)
Mean trial number	74.31 (11.49)	70.18 (11.77)
Pre-event good deck MRL	489.08 (163.71)	574.89 (250.13)
Post-event good deck MRL	392.58 (136.46)	525.75 (268.74)
Pre-event bad deck MRL[a]	491.38 (201.53), N = 12	569.86 (227.51), N = 14
Post-event bad deck MRL[a]	635.50 (356.54), N = 12	547.64 (172.71), N = 14

Groups did not differ significantly on demographics (see Results). Conventional good minus bad deck means and SDs are presented in Fig. 1b. Median response latencies are presented in ms.

a For the two punishment event, bad deck choice median response latencies have slightly different N's noted; this difference arises from individuals who made zero bad deck selections following the two punishment event as described in Table 2.

The most common adverse reaction to the beverage was nausea and/or vomiting. Participants who vomited were excluded from analyses (1 ATPD male, 1 balanced female). In addition, there were two participants whose IGT testing was invalidated (1 ATPD female due to technical problems, 1 balanced female due to prior knowledge of the test). The final ATPD group had n = 11 males and n = 8 females; the balanced group had n = 14 males and n = 7 females (Table 1). Due to the analytic strategies, sample sizes vary across analyses (Table 2).

2.2. Testing protocol

The testing session was conducted at the University of Minnesota's Clinical and Translational Science Institute. Participants arrived at 0815 h after following a 24-hour low monoamine diet (NIH guidelines were provided to participants by the investigators) and fasting from midnight the

previous evening. Females completed the testing day during the follicular menstrual phase. At 0830 h, an indwelling cannula was inserted in the participant's non-dominant arm for blood draws at 0900 h and 1400 h to obtain pre- and post-manipulation samples of serum prolactin. Following the 0900 h blood draw, the amino acid beverage (for preparations see McTavish et al., 2001, Vrshek-Schallhorn et al., 2006) was consumed. Due to lower average body weights, females received 20% less of each amino acid to prevent nausea and vomiting (e.g., Harmer et al., 2001). The cannula was removed after the second blood draw at 1400 h; cognitive testing then began.

Table 2. Summary of changes in sample size across analyses.

Analysis	ATPD	Balanced	Number excluded	Reason
Conventional IGT Performance	19	21	0	–
Prolactin	16	20	3 ATPD, 1 balanced	Out of range pre-test prolactin values
One punishment event	17	19	2 ATPD, 2 balanced	Did not reach event by task end, or had 5or fewer trials left
Two punishment event	13	17	6 ATPD, 4 balanced	Did not reach event by task end, or had 5 or fewer trials left
Bad deck MRL after the two punishment event	12	14	1 additional ATPD, 3 additional balanced	Made no selections from bad decks after the two punishment event

2.3. The Iowa Gambling Task

Participants completed a computerized version of the IGT, delivered using the E-prime 1.1 (SP3) software and task presentation program (Psychological Software Tools, Pittsburg, PA) on a Dell Optiplex GX150 with Pentium III processor and 14-inch Dell monitor. The IGT was identical to the original version with one exception: instead of representing gains and losses with "play" money, participants earned real money based upon their performance, to increase their motivation to do well (e.g., Evans et al., 2004, Hooper et al., 2004). Rewards and punishments were proportionately reduced from magnitudes reported by Bechara and colleagues, with maximal net winnings of $5.00. Participants were "loaned" $5.00 at the beginning of the task; this loan was deducted from their total score before a research assistant paid net winnings in cash at the end of the session.

Contingencies for each of the four decks can be found in Hooper et al. (2004). The task is administered without interruption. Immediately after each selection, the screen displayed, "You won: < amount>" for two seconds. Losses were displayed next for one second with the statement, "But you also lost:<amount >." In Bechara's original paradigm (Bechara et al., 1994), up to 40 selections could be made from each deck; participants sometimes exhaust the cards in a deck. When this occurs, a red "X" appears on the deck, and participants may select from the remaining decks. No participant exhausted Deck A. The groups did not significantly differ in the number of individuals who exhausted their choices from Deck B ($\chi 2(1) = .02$, NS) or Deck D ($\chi 2(1) = .63$, NS). Five ATPD participants and one balanced group participant exhausted Deck C, a significant group difference (Fisher's $\chi 2(1) = 3.86$, $p < .05$). Though intriguing, it does not appear to have impeded the performance of either group: closer inspection revealed that (adding across these participants within groups) both groups experienced a similar total number of task trials after exhausting Deck C (ATPD: 51 trials; Balanced: 53 trials).

Trials were coded as occurring before or after each of the one- and two-punishment events in order to calculate MRL and ΔMRL variables. Median values were used because they are less influenced by extreme values than are mean values. Trials 1–4 were excluded due to unrepresentatively long latencies. Individuals who did not reach the two events, or reached the events very late, leaving too few trials (five or fewer) to obtain useful MRLs post-event, were removed from those analyses (Table 2). It was common for participants to make either all good or all bad choices during at least one of the five traditional task blocks, thus producing no response latencies to evaluate for that deck type in that task block and leading to the participant's exclusion by repeated measures (RM) ANOVA; thus, no RM ANOVA analyses are reported for response latencies across the five blocks.

RM and one-way ANOVAs and linear regressions were performed using SPSS 13.0 for Windows. P-values ≤ .05 were considered statistically significant, while those ≤ .10 but > .05 are reported as approaching significance. Effect sizes are given as partial eta squared (ηp2) or r2.

3. Results

Individuals in each drug condition did not differ in height, weight, body mass index, age, or years of education (all F values < 2.0, NS), nor in sex ($\chi 2(1) = .33$, NS) or minority status ($\chi 2(1) = .26$, NS) (Table 1).

3.1. Effects of ATPD on serum prolactin levels

Prolactin results suggested that central nervous system DA depletion by ATPD was successful (Fig. 1a). An RM ANOVA with drug condition as the between subjects variable and time (pre- or post-ATPD administration) as the within subjects variable revealed the hypothesized Drug × Time interaction on prolactin levels ($F(1,34) = 10.15$, $p < .05$, $\eta p2 = .23$). There was no group difference prior to ATPD ($F(1,35) = 1.10$, NS, $\eta p2 = .03$). The ATPD group had significantly higher post-manipulation values ($F(1,35) = 30.35$, $p < .001$, $\eta p2 = .47$). The ATPD group showed a significant increase in prolactin level over time relative to baseline ($F(1,15) = 6.71$, $p < .05$, $\eta p2 = .31$). The balanced group showed a marginally significant decrease in serum prolactin level ($F(1,19) = 3.95$, $p = .06$, $\eta p2 = .17$), consistent with prolactin's diurnal rhythm (Sassin et al., 1972).

3.2. Effects of ATPD on IGT performance

There were no main effects or interactions of drug condition on the conventionally-used global metric of good minus bad deck choices (Fig. 1b). In an RM ANOVA that included five task blocks of 20 trials each, a main effect of task block showed the expected pattern of increasing good minus bad choices across the task ($F(4,152) = 12.16$, $p < .001$, $\eta p2 = .24$). There was no main effect of drug condition ($F(1,38) = 0.69$, NS, $\eta p2 = .02$), nor was there a task block by drug condition interaction ($F(1,37) = 1.38$, NS, $\eta p2 = .04$). The quality of performance was also examined before versus after the one-punishment and two-punishment events by drug condition. Although there were greater proportions of advantageous choices made after the experience of these events (one punishment event, $F(1,34) = 23.16$, $p < .001$, $\eta p2 = .41$; two punishment event, $F(1,24) = 13.06$, $p = .001$, $\eta p2 = .35$), drug condition did not contribute to these effects.

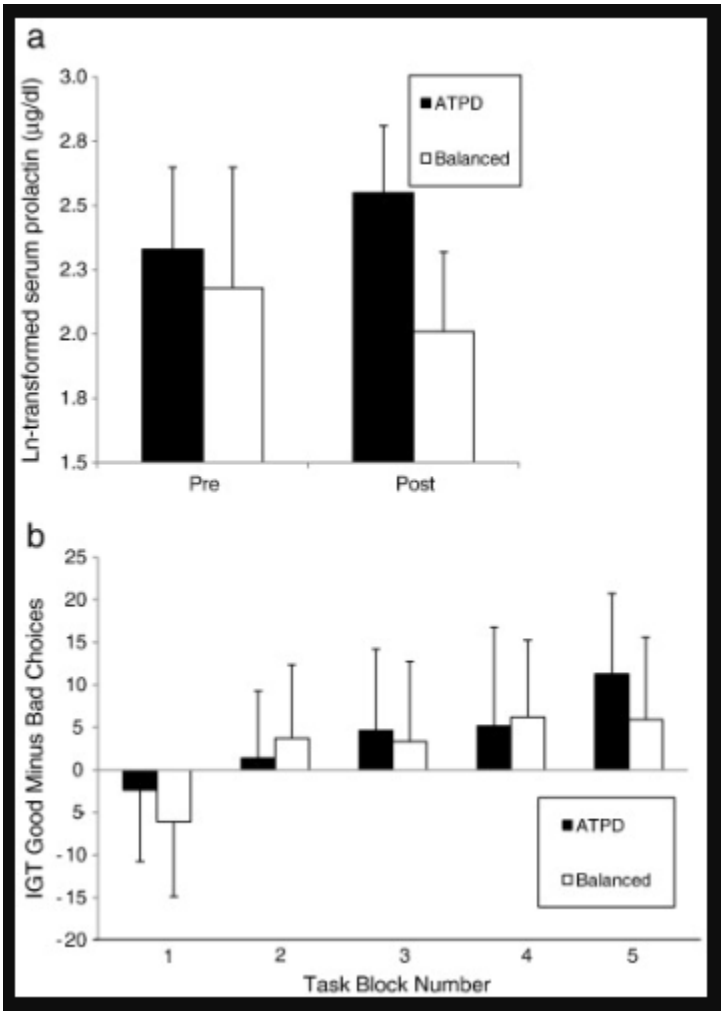

Fig. 1. Basic results. (a) Pre- and post-ATPD ln-transformed serum prolactin level means and standard deviations by drug condition: ATPD (N = 16) pre-manipulation M = 2.33 (SD = .32) and post-manipulation, M = 2.55 (SD = .26), Balanced (N = 20), pre-manipulation M = 2.18 (SD = .47) and post-manipulation, M = 2.01 (SD = .31). (b) Mean IGT good minus bad choices by task block (20 trials) and drug condition. Error bars represent group standard deviations.

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3.4. Relationship of median response latencies to task performance

There was no difference between groups in the trial number at which individuals encountered the one punishment event (combined M = 42.78, SD = 10.41) ($F(1,34) = .44$, NS, $\eta p2 = .01$) or the two punishment event (combined M = 71.97, SD = 11.64) ($F(1,28) = .93$, NS, $\eta p2 = .03$) (Table

1). To examine the relationship of drug condition to performance characteristics at the one and two punishment events, first, the effect of drug condition on MRLs for good and bad decks was examined using RM ANOVA. Second, the relationship of ΔMRLs to total task performance was examined by drug condition using hierarchical linear regression.

3.3.1. Bad deck response latencies

RM ANOVAs were conducted with drug condition as the between-subjects variable and time (pre- vs. post-event) as the within-subjects variable. At the one punishment event, there was no main effect of drug ($F(1,34) = .82$, NS, $\eta p2 = .02$) or time ($F(1,34) = .04$, NS, $\eta p2 = .00$), but the Drug × Time interaction was marginally significant with a moderate effect size ($F(1,34) = 3.95$, $p = .055$, $\eta p2 = .10$) (Fig. 2a). Accounting for sex in models did not alter this pattern of results. The balanced group's response latencies significantly decreased ($F(1,18) = 7.50$, $p < .05$, $\eta p2 = .29$). The ATPD group's latencies did not change significantly ($F(1,16) = 0.86$, NS, $\eta p2 = .05$). At the two punishment event, there were no main effects of drug ($F(1,24) = .003$, NS, $\eta p2 = .00$) or time ($F(1,24) = 2.08$, NS, $\eta p2 = .08$), but the Drug × Time interaction was again marginally significant ($F(1,24) = 3.87$, $p = .061$, $\eta p2 = .14$). The balanced group's response latencies did not significantly change ($F(1,13) = 0.26$, NS, $\eta p2 = .02$) while the ATPD group's latencies marginally increased ($F(1,11) = 3.61$, $p = .084$, $\eta p2 = .24$).

3.3.2. Good deck response latencies

At the one punishment event, there was a main effect of time ($F(1,34) = 8.96$, $p < .05$, $\eta p2 = .21$) but no main effect of drug condition or Drug × Time interaction (both F's$(1,34) \leq 0.15$, NS, $\eta p2 \leq .004$). Both groups selected good decks more quickly (smaller latencies) after the one punishment event compared with before it, consistent with adaptive task performance. For the two punishment event, no main effects or interactions were significant (all F's$(1,28) \leq 2.58$, NS, all $\eta p2 \leq .08$).

3.5. Relation of ΔMRL to total task performance by drug condition

For hierarchical linear regressions, ΔMRL values were standardized. For each regression predicting total good minus bad IGT score, drug condition (coded as ATPD = 0, Balanced = 1) and either good or bad ΔMRL were entered into the first step, while a Drug × ΔMRL interaction effect was added to this model in a second step. Among these regressions, one drug condition interaction was significant (Table 3): at the one punishment event, the Drug × ΔMRLBAD interaction predicted total good minus bad score (Fig. 2b), indicating that the relation between ΔMRLBAD and total performance differs significantly by group. The simple main effect of drug condition was not significant, while the simple main effect of ΔMRLBAD indicated a significant relationship between ΔMRLBAD and total performance for the ATPD group.

Follow-up analyses showed that in the ATPD group, ΔMRLBAD significantly predicted overall task performance (total good minus bad score; $R2 = .56$, $b = 26.45$, $SE(b) = 6.11$, $\beta = .75$, $p < .001$). Greater adaptation to the bad decks (increasingly slow or hesitant responding across the task) was highly and positively correlated with overall task performance. Within the balanced group, this relationship was not significant ($R2 = .06$, $b = -18.13$, $SE(b) = 16.90$, $\beta = -.25$, NS). At the two punishment event, there was no main effect of drug or ΔMRLBAD, but the Drug × ΔMRLBAD interaction approached significance. Post-hoc tests for this interaction mirrored the

pattern of those described above for the one punishment event. For ΔMRLGOOD, neither the one- nor the two-punishment event model significantly predicted total good minus bad score (Table 3).

Magnitude of prolactin change was not associated with IGT selections or reaction times (results not presented). No significant main effects or interactions involving sex were identified in any of the above analyses.

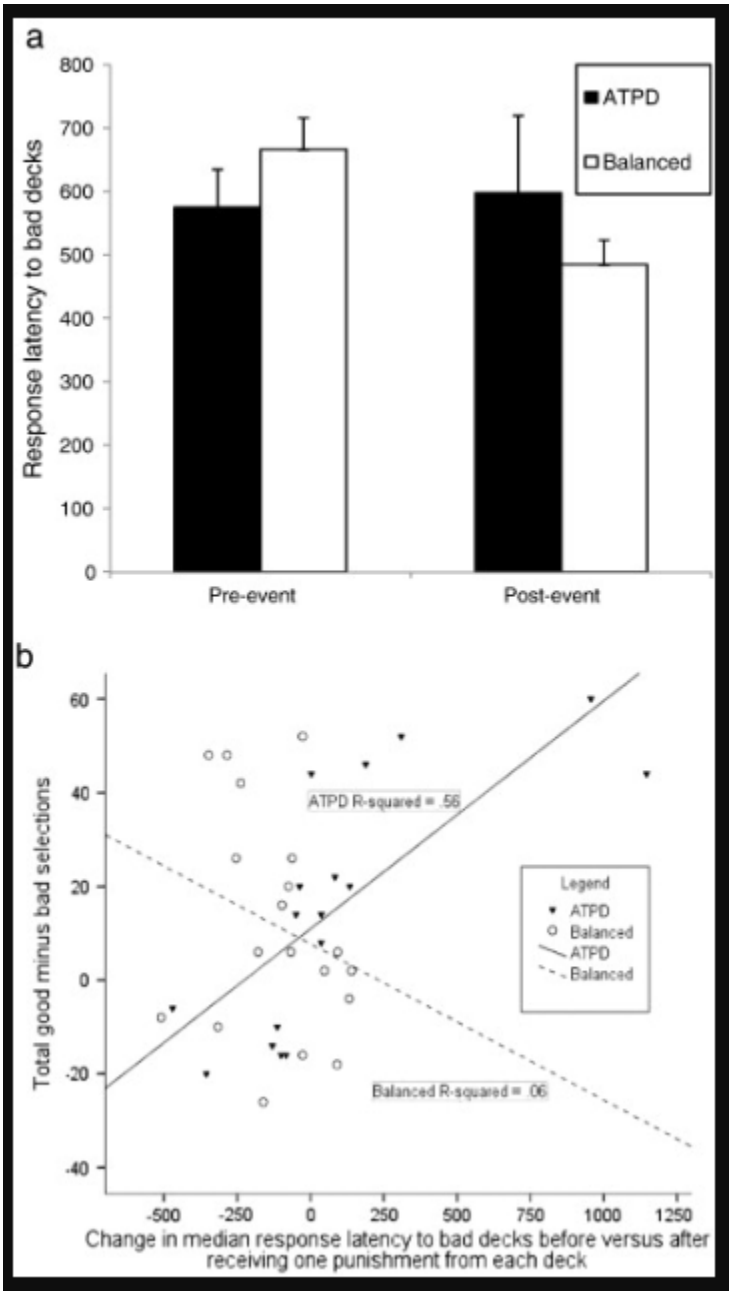

Fig. 2. Median response latency results. (a) Means and standard errors of median response latencies before and after receiving at least one punishment from each deck, by drug condition. The Drug Condition × Time interaction was marginally significant, $p = .055$. (b) Relationship of change in median response latency for bad deck selections before versus after the one punishment event to IGT performance, given by total good minus bad deck selections.

Table 3. Hierarchical linear regressions of Drug Condition, ΔMRL and Drug × ΔMRL interaction on total good minus bad score.

a. One punishment event

Deck type	Variable	Step					Step				
		R^2	*b*	SE(*b*)	*β*	*p*-Value	R^2	*b*	SE(*b*)	*β*	*p*-Value
Bad	Model	.18				.04	.15				.01
	Drug							− 7.89	8.55	− .16	.36
	ΔMRLBAD							26.46	7.13	.63	< .01
	Drug × ΔMRLBAD							− 44.59	16.81	− .51	.01
Good	Model	.05				.45		.04			.23
	Drug	− 3.29	8.34	− .07	.70			− 3.37	8.28	− .07	.68
	ΔMRLGOOD	− 4.93	4.17	− .20	.25			− 0.46	5.56	− .02	.93
	Drug × ΔMRLGOOD							− 10.19	8.36	− .28	.23

b. Two punishment event

Deck type	Variable	Step					Step				
		R^2	*b*	SE(*b*)	*β*	*p*-Value	R^2	*b*	SE(*b*)	*β*	*p*-Value
Bad	Model	.01				.87	.13				.09
	Drug		− 4.94	9.96	− .11	.63		− 6.94	9.57	− .16	.47
	ΔMRLBAD		− .01	5.07	.00	.99		5.90	5.84	.26	.32
	Drug × ΔMRLBAD							− 18.74	10.40	− .45	.09
Good	Model	.10				.24	.01				.58
	Drug		.46	8.43	.01	.95		− .33	8.65	− .01	.97
	ΔMRLGOOD		− 7.32	4.25	− .32	.097		− 1.55	11.05	− .07	.89
	Drug × ΔMRLGOOD							− 6.80	12.00	− .27	.58

4. Discussion

In this study, we examined the influence of ATPD, a brain DA depletion paradigm, on emotion-based decision-making on the IGT in healthy adults.

Increases in serum levels of the neurohormone prolactin were consistent with brain DA depletion in the ATPD group, indicating that the manipulation was successful in impacting the central nervous system. Pharmacological manipulations of the DA system that use antagonist compounds rather than amino acid manipulations have consistently revealed similar prolactin increases (e.g., Luciana and Collins, 1997). Prolactin levels are regulated by D2 DA receptors in the hypothalamus (for a review, see Fitzgerald and Dinan, 2008), so the increase following ATPD implies a central nervous system mechanism.

Conventional IGT analyses of good minus bad choices across five task blocks revealed no significant group differences in task performance. However, several significant findings were consistent with one another and with the study's hypotheses. We speculate that the significant results indicate that the ATPD manipulation subtly attenuated reward salience, yielding several group differences in the approach by which individuals achieved successful task performance. First, the balance group increased in speed of selecting bad decks early compared with later in the task (just as both groups come to select good decks more rapidly), an effect that was absent in the ATPD group. Further, in the ATPD group only, the ability to modulate response latencies to bad decks (i.e., to slow down) predicted total task performance, and this relationship was significantly stronger than in the balanced group, who did not show this effect at all. This difference in approaches to the task is also exemplified by the ATPD group's significantly greater rate of exhausting Deck C, which has the lowest magnitude punishments of any deck and often is neglected by healthy individuals in other research, perhaps because the small punishments occur relatively frequently, which the ATPD group appears to tolerate (i.e., the "sunken Deck C" phenomenon, for description and examples see Chiu and Lin, 2007, Crone et al., 2004, Hooper et al., 2004). Although disambiguation of reward and punishment sensitivity using the IGT is not fully possible because both rewards and punishments can occur simultaneously, it might be that ATPD reduced reward salience for the deceptively attractive large incentives found in the bad decks, clearing the way for individuals to appreciate the commensurately large punishments in these bad decks. This appreciation for the bad decks' large punishments may explain why the ATPD group remained hesitant in selecting these decks (compared with speeding up by the balanced group, as if for a good deck) and why their ability to do so predicted total performance among ATPDs. Similarly, the ATPD group's greater likelihood of exhausting Deck C (with the smallest punishments of any deck, if frequent) may arise from a relatively favorable evaluation in comparison to decks with large punishments.

What might thus be construed as a trade-off between reward salience and punishment salience is consistent with the apparent shift of primary salience from reward to punishment in a reversal learning task (Robinson et al., 2010), with reduced risk-taking behavior on the Cambridge Gambling Task (McLean et al., 2004, Roiser et al., 2005), and with the apparent "shift" we observed in processing efficiency from a positive bias to a negative bias on an affective Go/No-Go task following ATPD (Vrshek-Schallhorn et al., 2006). Under blunted reward salience, not only does punishment salience appear to increase on average, it may also be that individual differences in punishment sensitivity or salience take on heightened importance. In some ways, these findings are puzzling because they suggest an aspect of affective processing that conforms to a single, bipolar dimension, in contrast to our (and others') conceptualization of affect as two unipolar,

approximately orthogonal dimensions (e.g., Tellegen, 1985). However, these findings are consistent with an emerging literature implicating striatal DA levels in a trade-off between reward and punishment-based learning, in Parkinson's Disease patients on and off medication (Frank et al., 2004), in healthy individuals studied after administration of the D2 receptor agonist bromocriptine (Cools et al., 2009), and fMRI of healthy individuals performing a visual conditioning task for wins and losses (Seymour et al., 2007).

The observed effects were most prominent when response latencies were examined relative to the one punishment event, occurring on average at trial 43 of 100. Most effects were lost or weakened when examined relative to the two punishment event, on average at trial 72 out of 100. At the one punishment event, individuals have examples of punishment magnitude, but can only infer information about punishment frequency based on the number of trials required to reach a first punishment. Full information is available by the two punishment event. The ambiguity inherent at the one punishment event may permit greater influence by individual or group differences, such as a drug manipulation. Finally, the lack of significant effects on the quality of actual choices made may be due in part to the subtle nature of the ATPD manipulation, particularly in the context of assessing performance in healthy individuals.

4.1. Limitations

This study has several limitations. First, though comparable with other studies of this nature, the present sample is a relatively small one. Efforts to prevent type II errors are evident throughout this report, including noting marginal effects reaching only the $p < .10$ level. Second, no direct measurements of brain DA such as PET imaging are available in the present investigation (prolactin represents an indirect measure), which means that findings cannot be ascribed to specific brain regions thought to be involved in punishment and reward learning, such as the orbitofrontal cortex and the ventral striatum, implicated by several functional imaging studies (Li et al., 2010, Remijnse et al., 2005). Similarly, due to the expense associated with assaying peripheral plasma amino acid levels in the context of this internally funded study, we elected to assay serum prolactin, as this neurohormone provides indirect information about central DA activity. Prolactin changed in the predicted direction for each group and supports the success of the manipulation at the central nervous system level. Third, although we speculated about the interplay between reward and punishment salience in directing responses on the IGT, the task is limited in the extent to which it is possible to disambiguate the two, and as noted above, ATPD did not impact actual choice selection.

Finally, the study is underpowered to detect significant effects of sex, which could have taken the form of interactions including Sex × Drug or Sex × Drug × Block. This is due in part to small cell sizes of females per group. Given that females were required to be free of oral contraceptive use and to enter the study during the follicular phase of the menstrual cycle, they tended to participate in smaller numbers than did males. Others have reported that males perform the IGT significantly better than females (Bolla et al., 2004), although this pattern is not always observed. Moreover, males are reported to have greater amphetamine-stimulated striatal dopamine release than females (Munro et al., 2006), and in one study, ATPD enhanced punishment prediction during a reversal learning task in females but not significantly so in males (Robinson et al., 2010). Thus, examining the influence of ATPD on males' versus females' emotion-based decision-making may be of interest for future studies.

5. Conclusions

Acute tyrosine-phenylalanine depletion did not significantly alter Iowa Gambling Task choice selections compared with controls. However, examination of changes in response latencies for good and bad decks throughout the task provided preliminary evidence of what could be interpreted as diminished reward salience under dopamine depletion. In this interpretation of diminished reward salience, it appeared that individual differences in punishment sensitivity increased in importance in predicting total performance.

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Conflicting interest statement: Dr. Wahlstrom is now employed by a competitor of the company that distributes the commercial version of the Iowa Gambling Task; however, at the time of data collection and analysis, he was a graduate student at the University of Minnesota. The authors report no further disclosures.

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