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

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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.

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, 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

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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, ΔMRL_{BAD} might directly predict task performance, while ΔMRL_{GOOD} 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 [^{11}C]-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 ΔMRL_{BAD} 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