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Age moderates the effect of acute dopamine depletion on passive avoidance learning

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ABSTRACT

Despite extensive links between reinforcement-based learning and dopamine (DA), studies to date have not found consistent effects of acute DA reduction on reinforcement learning in both men and women. Here, we tested the effects of reducing DA on reward- and punishment-based learning using the deterministic passive avoidance learning (PAL) task. We tested 16 (5 female) adults (ages 22–40) in a randomized, cross-over design to determine whether reducing global DA by administering an amino acid beverage deficient in the DA precursors, phenylalanine and tyrosine (P/T[-]), would affect PAL task performance. We found that P/T[-] beverage effects on PAL performance were modulated by age. Specifically, we found that P/T depletion significantly improved learning from punishment with increasing participant age. Participants committed 1.49 fewer passive avoidance errors per additional year of age (95% CI, −0.71 – −2.27, $r = -0.74$, $p = 0.001$). Moreover, P/T depletion improved learning from punishment in adults (ages 26–40) while it impaired learning from punishment in emerging adults (ages 22–25). We observed similar, but non-significant trends in learning from reward. While there was no overall effect of P/T-depletion on reaction time (RT), there was a relationship between the effect of P/T depletion on PAL performance and RT; those who responded more slowly on the P/T[-] beverage also made more errors on the P/T[-] beverage. When P/T-depletion slowed RT after a correct response, there was a worsening of PAL task performance; there was no similar relationship for the RT after an incorrect response and PAL task performance. Moreover, among emerging adults, changes in mood on the P/T[-] beverage negatively correlated with learning from reward on the P/T[-] beverage. Together, we found that both reward- and punishment-based learning are sensitive to central catecholamine levels, and that these effects of acute DA reduction vary with age.

1. Introduction

Data from animal models have long established that dopamine (DA) signaling modulates reinforcement learning (Bayer and Glimcher, 2005; Satoh et al., 2003; Schultz, 2002). Links between DA signaling and reinforcement learning have also been established in humans, where changes in striatal DA signaling differentially affect learning from positive and negative feedback (Cools et al., 2006, 2009; Frank, 2005; Frank et al., 2004; Moustafa et al., 2008; Pessiglione et al., 2006; Robinson et al., 2010; Shohamy et al., 2008); however this issue remains incompletely explored. Both reward-based and punishment-based learning are adaptive, and both may depend to some degree on DA signaling. To investigate DA's role in reinforcement learning, we used a passive avoidance learning (PAL) task, which quantifies learning from both positive and negative feedback (Newman and Kosson, 1986), in the context of acute DA precursor depletion in healthy human subjects.

Successful PAL task performance involves a learning period followed by a plateau phase. Neuroimaging data indicate that increased activation with successful PAL task learning, in response to rewarded or punished stimuli, occurs in the rostral anterior cingulate, insula, caudate, and amygdala, which are all DA terminal fields (Kosson et al., 2006). The role of DA in PAL task performance has been investigated using acute DA-depletion with alpha-methyl-paratyrosine (AMPT), a competitive inhibitor of the rate-limiting enzyme in DA synthesis, in females with major depressive order in full remission and healthy controls (Hasler et al., 2009). All participants were less likely to respond to rewarded stimuli later in the task than in earlier in the task, but there was no effect of AMPT on responding to punished stimuli (Hasler et al., 2009).

To date, no studies in medically healthy males and females have examined the effect of acute DA-depletion on PAL task performance.

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Therefore, we tested whether reducing DA levels with an amino acid beverage deficient in the amino acids required for DA synthesis, phenylalanine and tyrosine, would affect PAL task performance in both medically healthy males and females. We hypothesized that the phenylalanine/tyrosine-depleted (P/T[-]) beverage would decrease responding to rewarded stimuli and increase responding to punished stimuli compared to the controlled/balanced amino acid beverage. Moreover, the lower age bound for recruitment to this study was set at 22 years based on published data showing that functional brain maturation asymptotes at ~22 years of age (Dosenbach et al., 2010). However, abundant evidence indicates that the emerging adult period, most commonly defined as ages 18–25 (Arnett, 2000), is distinct from adulthood in numerous respects. Although emerging adulthood has been defined largely based on cultural factors, emerging adulthood is also characterized by ongoing neural development in brain regions associated with self-regulation and inhibitory control (Sowell et al., 1999), which play a role in passive avoidance learning. Furthermore, recent data show impaired inhibitory control within an affective information processing context among emerging adults relative to adults (Cohen-Gilbert et al., 2014). As such, we also separated participants into emerging adult (22–25 years old) and adult (26–40 years old) groups to determine whether the response to dopamine depletion differed among emerging adults.

2. Methods

2.1. Participants

Participants ($n = 16$, 5 females) were recruited from the University of North Carolina at Chapel Hill (UNC) and surrounding community. Participants were 22–40 yr old native English speakers with a high school education or more. Subjects were free from psychoactive medications or illicit drug use and had no current psychiatric or neurological diagnosis. Smokers were also excluded. Females were not breastfeeding or pregnant (confirmed via urine test), and were tested during the follicular phase (d 1–10) of the menstrual cycle. Participants with phenylketonuria were also excluded. Participants gave written, informed consent in accordance with the guidelines of the UNC Office for Human Research Ethics. Participants were paid for their participation; payment did not depend upon performance. Nine additional subjects were tested, but were excluded from all analyses due to a programming error that rendered their data unusable.

2.2. Procedure

In a double-blind, placebo-controlled, within-subjects, counterbalanced design, we used acute P/T depletion to temporarily reduce central DA levels, using a previously described protocol (Kelm and Boettiger, 2013). Subjects consumed a low protein diet (<20 g) for 24 h before each session and fasted from midnight until session onset, which occurred between 7 and 9 A.M. Following the consent procedure and urine screening, participants completed the Profile of Mood States (POMS) (McNair et al., 1971), and we collected a baseline blood sample via finger prick. Participants then consumed an amino acid beverage (balanced/control or P/T[-]). Participants waited 5 h in the lab to allow sufficient time for P/T depletion to occur (Sheehan et al., 1996). We then collected a second blood sample, and the participant completed computerized cognitive testing, followed by the POMS. Participants had access to low protein snacks from 1 h post-beverage consumption to 1 h before the second blood sample collection. Participants were offered a high protein snack at session end. Sessions were separated by ≥72 h.

2.3. Amino acid beverages

The amino acid mixes were prepared by SHS International (Liverpool, UK). The balanced/control beverage consisted of (in g): L-alanine, 4.1; L-arginine, 3.7; L-cysteine, 2.0; L-glycine, 2.4; L-histidine, 2.4; L-isoleucine, 6; L-leucine, 10.1; L-lysine, 6.7; L-methionine, 2.3; L-phenylalanine, 4.3; L-proline, 9.2; L-serine, 5.2; L-threonine, 4.9; L-tryptophan, 3.0; L-tyrosine, 5.2; and L-valine, 6.7. The P/T[-] beverage had the same composition except that phenylalanine and tyrosine were omitted. Because these amino acid beverages can cause nausea and emesis, individuals weighing <160 lb ($n = 6$) received a light version of each beverage that was reduced in composition by 20%. Beverages were mixed with cold water and a cherry-vanilla, grapefruit, or lemon-lime flavor packet from Nutricia (Gaithersburg, MD) in an 8 oz sterile cup.

2.4. Behavioral inventories

Participants completed questionnaires during the waiting period in session one. Demographic information was collected, including age, gender, ethnicity and socioeconomic status (SES). SES was quantified according to (Hollingshead, 1975) using the modification of (Barratt, 2006). Other standard questionnaires included: the Alcohol Use Disorders Identification Test (AUDIT) (Saunders et al., 1993), the Barratt Impulsiveness Scale (BIS) (Barratt, 1994), part I of the Drug Use Screening inventory (DUSI) (Tarter, 1990), the Family Tree Questionnaire (FTQ) (Mann et al., 1985), part I of the Future Time Perspective Inventory (FTPI) (Wallace, 1956), Rotter's Locus of Control Scale (LOC) (Rotter, 1966), the State-Trait Anxiety Inventory (STAI) (Spielberger, 1985), the Beck Depression Inventory (BDI) (Beck and Steer, 1987), and the Anti-social Practices Scale of the Minnesota Multiphasic Personality Inventory 2 (MMPI) (Butcher et al., 1990). Age groups did not differ on any of these measures, excepting age (Table 1).

2.5. Amino acid analysis

We analyzed the pre- and post-beverage blood samples to determine the total plasma P/T levels and the ratio of P/T to other large, neutral amino acids (LNAA; tryptophan, valine, isoleucine, and leucine) to confirm P/T depletion by the P/T[-] beverage. This ratio was calculated from the total serum concentrations of P and T divided by the sum of the concentrations of the other LNAA [$(P + T) / \sum$ LNAA]. We used this combined P/T ratio, as it correlates with DA availability within the brain

Table 1
A comparison of the emerging adult (22-25 years old) and adult groups (26-40 years old).

	Emerging adults ($n = 7$)	Adults ($n = 9$)	$t_{(14)}$	p Value
General				
Age	23.14 ± 0.46	29.44 ± 1.58	−3.83[a]	0.004
SES	52.25 ± 1.62	53.64 ± 2.46	−0.44	*ns*
Gender (% female)	28.6	33.3		*ns*[†]
Ethnicity (% non-white)	14.3	33.3		*ns*[†]
Personal and familial substance use				
AUDIT	4.29 ± 0.87	5.56 ± 1.24	−0.79	*ns*
DUSI	0.12 ± 0.04	0.11 ± 0.05	0.22	*ns*
FTQ	0.23 ± 0.06	0.13 ± 0.06	1.13[b]	*ns*
Psychometric measures				
BIS	59.00 ± 1.84	57.56 ± 1.59	0.60	*ns*
FTPI-mean extension	11.70 ± 3.31	8.78 ± 2.42	0.73	*ns*
FTP1-max extension	42.29 ± 9.46	35.44 ± 9.85	0.49	*ns*
MMPI	8.00 ± 1.23	6.78 ± 1.27	0.68	*ns*
BDI	3.86 ± 1.06	3.00 ± 0.82	0.65	*ns*
STAI-trait score	30.29 ± 1.39	34.78 ± 2.72	−1.35	*ns*
LOC	11.71 ± 0.68	10.11 ± 1.09	1.25[c]	*ns*

Values are reported as mean ± standard deviation. Reported p-values reflect the results of unpaired two-tailed comparison between groups. Exact p-values reported unless $p<0.001$. [†]p-value represents results of χ^2 test. Where variances between groups were not equal, df were adjusted; [a]$df = 9.3$ [b]$df = 13$, [c]$df = 12.9$; *ns*, non -significant.