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Research report

Urinary dopamine and turn bias in traumatized women with and without PTSD symptoms

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Abstract

Turning biases are known to occur in the direction of the brain hemisphere with decreased dopamine (DA). Although elevations in urinary DA have been shown in posttraumatic stress disorder (PTSD), evidence for dysregulation of dopaminergic activity in the brain is lacking. Turn bias and urinary DA levels were examined in mothers of childhood cancer survivors. As expected, cancer trauma mothers with PTSD symptoms ($n = 14$) had higher urinary DA levels than trauma mothers without PTSD symptoms ($n = 7$) and controls ($n = 8$) ($P = 0.01$). Groups were also significantly different in prevalence of left turn bias ($P = 0.03$). All controls (100%) showed a left turn bias compared to 75 and 37.5% prevalence among trauma mothers with and without PTSD, respectively. Urinary DA levels and turn bias rates were not correlated. Results lend support for further exploration of DA in traumatized groups with and without PTSD.

Keywords: Posttraumatic stress disorder; Trauma; Dopamine; Lateralization; Turn bias

1. Introduction

Among rodents, a preference for turning left or right has been associated with higher dopamine (DA) concentrations contralateral to the preferred side [27]. Turn biases have also been reported in normal humans [4,15,20,21,25] and in patients with dopaminergic abnormalities such as schizophrenia [3,6] and Parkinson's disease [5]. Results typically show a left turn bias for right-handed normal individuals and a bias being moderated toward the hemisphere with decreased DA in abnormal populations [3,4,20].

It has been proposed that cortical DA is dysregulated in traumatized individuals [11,14,24]. Recent studies among rodents indicate pre-existing (prior to stressor exposure) turn biases are associated with differential vulnerability to stressors and asymmetry in subcortical DA metabolism [7,8,12,17]. Thus, turn bias may be a marker for pre-existing stressor vulnerability, as well as for relative asymmetry in dopaminergic activity. In addition, animal data indicate changes in dopaminergic activity after stress differ as a function of the intensity and duration of the stressor [10,19,22,23]. Thus, it may be useful to explore turn bias and DA among individuals with varied levels of stressor exposure.

A search of the literature revealed no published studies of turn bias or cortical DA in a chronic stress or traumatized human population. However, several studies have demonstrated peripheral DA perturbations in posttraumatic stress disorder (PTSD). For example, studies have found increased plasma DA (male combat veterans [15]) and urinary DA (male combat veterans [26], adult female victims of childhood sexual abuse [18], abused and neglected boys and girls [9]). Whereas peripheral DA levels do not directly elucidate cortical DA functioning, further exploration of the role of DA in trauma populations at all levels appears warranted.

The present study had three aims. First, we sought to replicate and extend urinary DA elevations found in previous PTSD studies by use of a sample of females traumatized as adults. No previous study of DA among women traumatized as adults was found. Furthermore, only one DA study in a PTSD sample included a comparison group of traumatized individuals without PTSD symptoms [18]. Although

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urinary DA elevations were specific to the PTSD group in that study, further investigation is warranted to verify that DA dysregulation is associated with PTSD and not trauma exposure per se. We expected higher levels of urinary DA in those with PTSD symptoms compared to nontraumatized controls. Following the results of Lemieux and Coe [18], we further expected DA elevations to be found only in traumatized mothers with (not those without) PTSD symptoms.

Second, we examined evidence for a turn bias suggestive of a hemispheric imbalance in dopaminergic activity. Based on the methods and findings of Yazgan et al. [25] with humans and animal studies of DA, turn bias and stress [7,8,12,17], we hypothesized a left turn bias in controls and a reduction in the strength of the left turning bias in the trauma sample. Within the trauma group, rationale for a difference between those with and without PTSD symptoms is less clear. If individuals with PTSD symptoms have a pre-existing vulnerability to stress and/or experience more acute stress (in the form of flashbacks and intense distress at exposure to trauma cues), perhaps the greatest reduction in left turning bias should be seen among women *with* compared to those without PTSD symptoms.

Third, exploratory analysis sought to examine the relationship between turn bias and urinary DA levels. Although it is unlikely that peripheral measures of DA reflect asymmetry in dopaminergic activity, as indicated by turn bias, our aim was to test this assumption.

2. Materials and methods

2.1. Participants

Participants included 23 mothers of pediatric cancer survivors with ($n = 15$) and without PTSD symptoms ($n = 8$) and control mothers of healthy children ($n = 9$). Urine samples were lost for three mothers, resulting in one less subject per group for all analyses involving urinary DA. Trauma mothers were identified through the UCLA tumor registry information and sent an initial letter outlining the study. Interested trauma mothers were asked to return a postage-paid letter giving permission for researchers to telephone them with further information. Trauma mothers were asked to participate only if their child was (a) alive, (b) off active cancer treatment for at least 1 year, and (c) considered a cancer "survivor" with no current relapse. Control mothers were identified through advertisements posted throughout the UCLA campus. The study was approved by the UCLA Institutional Review Board.

Subjects were prescreened during a telephone interview for general health and medication use and excluded if they reported a chronic health problem or medication use known to influence neuroendocrine function. Subjects were instructed to refrain from substance (tobacco, alcohol, or drugs) or any medication use 24 h prior to urine collection and this information was verified again after collection. Subjects also reported on sleep quality on the night of the urine collection.

2.2. Procedures

All participants were administered the Posttraumatic Stress Diagnostic Scale (PDS) [13]. This widely used instrument assesses PTSD based on DSM-IV criteria [1]. Internal consistency is high ($\alpha = 0.92$ for symptom items), and the instrument shows good sensitivity (0.82) and specificity (0.77) [13]. Subjects were also administered the Beck Depression Inventory (BDI) to assess potential effects of symptoms of co-morbid depression [2].

DA levels were assessed from a 12-h overnight urine collection conducted within days of the assessment of turn bias (but not the same day).

Turn bias was assessed using the method reported by Yazgan et al. [25]. Subjects were told before testing that they would be performing a task for the purposes of investigating gait. Participants were escorted into a symmetrical room. From the middle of the room, they were instructed to walk back and forth between two points 5 m apart. To avoid the possibility of an environmental cuing effect, the experimenter stood at the middle starting point and the room was spacious and symmetrical (i.e. no pictures or windows on either wall). The procedure was stopped after participants completed five turns.

For further information regarding the sample, procedures, and assay information see Glover and Poland [16].

2.3. Statistical analyses

Shapiro Wilks tests for normality indicated normal distributions for urinary DA. Natural log transformation was used to correct for nonhomogeneity of variance. Subsequent Levene statistics indicated variances were not significantly different across groups.

To separate effects of trauma exposure versus PTSD symptoms specifically, two planned contrasts compared (a) controls versus trauma subjects with *and* without PTSD (effect of trauma exposure) and (b) trauma subjects with and without PTSD (effect of PTSD). Age was entered as a covariate in the urinary DA analysis. To test whether limited sample size precluded detection of group effects in the three-group ANCOVA, a two-group ANCOVA was also performed, comparing PTSD subjects versus all non-PTSD subjects (trauma mothers without PTSD and controls).

Following methods by Bracha et al. [6], turn bias was computed by dividing the number of left turns by the total number of turns (percentage of leftward turns) out of five trials. Dichotomous coding assigned >50% leftward turns as left biased and <50% leftward turns as right biased. Yazgan et al. [25] found that left-handed participants did not show

the left turn bias found in right-handed participants. Due to the small number of left-handers in the sample ($n = 4$), the sample was stratified by handedness and chi-square results on frequency of left turn bias is reported only for right-handed participants ($N = 28$: $n = 8$, 12, and 8 for T-No PTSD, T-PTSD, and controls, respectively).

Correlational analyses explored the relationship between the percentage of leftward turns and urinary DA levels.

All analyses were repeated with total scores on the BDI [2] as a covariate to determine whether effects were influenced by symptoms of co-morbid depression.

3. Results

3.1. Sample characteristics

A majority of subjects were married (81.3%), middle to upper class in economic status (75.4%) and Caucasian (67.7%). Remaining subjects identified themselves as Latina (12.9%), Black (3.2%), Asian (6.5%), or "other" (9.7%). Groups did not differ on these demographic variables but there was a significant difference in age across groups [$F(2, 26) = 4.32$, $P = 0.02$]. Contrasts revealed the trauma groups were not different from each other (mean, S.D.: 42 ± 7.5 years), but were older than controls (mean, S.D.: 34.4 ± 5.2 years), [$F(1, 28) = 8.72$, $P = 0.006$].

The children of trauma mothers were diagnosed with cancer at the average (mean ± S.D.) age of 8.8 ± 5.5 years. At the time of the study, all children were off active treatment and the initial "trauma" of the cancer diagnosis had occurred 1–12 years previously (mean, S.D.: 4.5 ± 2.7 years).

3.2. Urinary DA

As expected, the trauma plus PTSD group showed an elevation in DA (μg/l) (mean, S.D.: 242.64 ± 179.8) compared to traumatize mothers without PTSD (mean, S.D.: 108.3 ± 51.2) and controls (mean, S.D.: 129.5 ± 68.03). The ANCOVA verified a group difference in DA (μg/l) [$F(2, 28) = 3.53$, $P = 0.05$] and planned contrasts indicated this effect was not due to trauma exposure per se (trauma versus controls $P = 0.16$) but a result of PTSD specifically (T-PTSD versus T-No PTSD $P = 0.06$). A two-group ANCOVA confirmed that the trauma plus PTSD group had higher urinary DA than those without PTSD (controls and trauma mothers) [$F(1, 28) = 7.22$, $P = 0.01$]. This same pattern occurred when analyses excluded left-handed participants.

3.3. Turn bias

A left turn bias (i.e. >50% leftward turns out of five trials, see Table 1) predominated only among control mothers, as hypothesized. A binomial test of the null hypothesis (equivalent proportions of left versus right turns) was rejected for controls ($P = 0.008$) but not trauma mothers ($P = 0.50$). Chi-square analysis further indicated that the proportion of subjects with a left turn bias was greater in controls (100%) compared to trauma mothers (60%) [$\chi^2(1, N = 28) = 4.48$, $P = 0.03$].

Within the trauma groups, results were unexpected. Contrary to our hypothesis, trauma mothers without PTSD symptoms showed a trend for the lowest proportion of left turn bias (37.5%) compared to trauma mothers with PTSD symptoms (75%) [$\chi^2(1, N = 20) = 2.81$, $P = 0.09$]. The majority of left-handed participants (75%) had a left turn bias, but the small sample of left-handers precluded statistical analysis by group. See Table 1.

3.4. Urinary DA and turn bias

Exploratory correlations between percentage of left turn bias and urinary DA levels showed no relationship for either trauma group or the whole sample (Pearson $r < 0.12$).

Table 1
Number of left turns over five trials across groups

T-PTSD ($m = 12$)		T-No PTSD ($m = 8$)		Controls ($m = 8$)	
Case no.	No. of left turns	Case no.	No. of left turns	Case no.	No. of left turns
1.	*3*	*1.*	*5*	*1.*	*4*
2.	*3*	*2.*	*5*	*2.*	*4*
3.	*5*	*3.*	*4*	*3.*	*4*
4.	*5*	4.	2	*4.*	*3*
5.	*3*	5.	2	*5.*	*3*
6.	*3*	6.	2	*6.*	*3*
7.	*3*	7.	2	*7.*	*3*
8.	*3*	8.	2	*8.*	*3*
9.	*3*				
10.	2				
11.	2				
12.	0				

Total no. of left turning: 9 of 12, 3 of 8, and 8 of 8 for T-PTSD, T-No PTSD, and controls, respectively.
Group (%) for left turning: 75, 37.5, and 100% for T-PTSD, T-No PTSD, and controls, respectively.
Italics number cases dichotomized as left turners.

Results for urinary DA, turn bias, or their relationship were not altered by BDI depression scores.

3.5. Urinary DA, turn bias, and PDS severity

Exploratory correlations between PDS [13] severity and turning or urinary DA showed no relationship for either trauma group or whole sample (Pearson $r < 0.10$).

4. Discussion

These data lend further support for investigation of the role of DA in trauma-exposed groups. This is the first report of urinary DA levels among females with PTSD symptoms who were traumatized as adults. The urinary DA elevation found in mothers with PTSD symptoms replicates and extends previous findings among males and females traumatized as children [9,18] and males traumatized as adults [26]. The finding that the DA elevation is exclusive to the PTSD group further replicates the only other DA study comparing individuals with versus without PTSD symptoms [18].

The reduced left turn bias found in trauma mothers supports the hypothesis of hemispheric imbalance in dopaminergic activity in individuals who have been exposed to extreme stress [11,14,24]. However, whereas the urinary DA elevation was exclusive to those with PTSD symptoms, reduced left turn bias was not.

In fact, left turn bias was most reduced in the trauma group without PTSD symptoms. The lack of correlation between urinary DA levels and turn bias rates in either trauma group supports the assumption that separate mechanisms govern these variables. The present data further suggest that DA perturbations are present in all previously traumatized individuals, but differ in form as a function of current PTSD symptoms. This is consistent with cortisol data reported by Glover and Poland [16] from this sample. Whereas mothers with PTSD symptoms had significantly lower urinary cortisol than either comparison group ($P = 0.05$), those without PTSD symptoms showed a trend toward higher cortisol than controls ($P = 0.11$).

This preliminary report suggests further exploration of DA in trauma samples may be informative. Future turn bias studies with larger trauma samples should also include males, based on evidence of a gender difference and menses stage effects in turn bias [20,21]. Also, inclusion of cerebral indicators of DA (e.g. cerebral spinal fluid homovanillic acid, as suggested by Deutch and Young [11]) may lead to further understanding of the etiology or neuroendocrine sequelae of trauma exposure and PTSD.

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References

[1] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Press; 1994.
[2] Beck AT, Steer RA. Internal consistencies of the original and revised Beck Depression Inventory. J Clin Psychol 1984;40:1365–7.
[3] Bracha HS. Asymmetric rotational (circling) behavior, a dopamine-related asymmetry: preliminary findings in unmedicated and never-medicated schizophrenic patients. Biol Psychiatry 1987;22:995–1003.
[4] Bracha HS, Seitz DJ, Otemaa J, Glick SD. Rotational movement (circling) in normal humans: sex difference and relationship to hand, foot and eye preference. Brain Res 1987;411:231–5.
[5] Bracha HS, Shults C, Glick SD, Kleinman JE. Spontaneous asymmetric circling behavior in hemi-Parkinsonism; a human equivalent of the lesioned-circling rodent behavior. Life Sci 1987;40:1127–30.
[6] Bracha HS, Livingston RL, Clothier J, Linington BB, Karson CN. Correlation of severity of psychiatry patients' delusions with right hemispatial inattention (left-turning behavior). Am J Psychiatry 1993;150:330–2.
[7] Carlson JN, Fitzgerald LW, Keller Jr RW, Glick SD. Lateralized changes in prefrontal cortical dopamine activity induced by controllable and uncontrollable stress in rats. Brain Res 1993;630:178–87.
[8] Carlson JN, Visker KE, Keller Jr RW, Glick SD. Left and right 6-hydroxydopamine lesions of the medial prefrontal cortex differentially alter subcortical dopamine utilization and the behavioral response to stress. Brain Res 1996;11–9.
[9] De Bellis MD, Baum AS, Birmaher B, Keshavan MS, Eccard CH, Boring AM, et al. Developmental traumatology part I: biological stress systems. Biol Psychiatry 1999;45:1259–70.
[10] Deutch AY, Roth RH. The determinants of stress-induced activation of the prefrontal cortical dopamine system. Prog Brain Res 1990;85:367–402.
[11] Deutch AY, Young CD. A model of the stress-induced activation of prefrontal cortical dopamine systems: coping and the development of post-traumatic stress disorder. In: Friedman MJ, Charney DS, Deutch AY, editors. Neurobiological and clinical consequences of stress: from normal adaptation to PTSD. New York: Raven Press; 1995. p. 163–75.
[12] Fedrowitz M, Potschka H, Richter A, Loscher W. A microdialysis study of striatal dopamine release in the circling rat, a genetic animal model with spontaneous lateralized rotational behavior. Neuroscience 2000;97:69–77.
[13] Foa EB, Cashman L, Jaycox L, Perry K. The validation of a self-report measure of posttraumatic stress disorder: the posttraumatic diagnostic scale. Psychol Assess 1997;9:445–51.
[14] Friedman EH. The neurobiology of posttraumatic stress disorder (PTSD). Biol Psychiatry 1994;35:500.
[15] Glick SD, Ross DA, Hough LB. Lateral asymmetry of neurotransmitters in human brain. Brain Res 1982;234:53–63.
[16] Glover DA, Poland RE. Urinary cortisol and catecholamines in mothers of child cancer survivors with and without PTSD. Psychoneuroendocrinology 2002;27:805–19.
[17] Krahe TE, Filgueiras CC, Schmidt SL. Effects of rotational side preferences on immobile behavior of normal mice in the forced swimming test. Prog Neuropsychopharmacol Biol Psychiatry 2002;26:169–76.

[18] Lemieux AM, Coe CL. Abuse-related posttraumatic stress disorder: evidence for chronic neuroendocrine activation in women. Psychosom Med 1995;57:105–15.
[19] McEwen BS. The neurobiology and neuroendocrinology of stress: implications for post-traumatic stress disorder from a basic science perspective. Psychiatr Clin North Am 2002;25:469–94.
[20] Mead LA, Hampson E. A sex difference in turning bias in humans. Behav Brain Res 1996;78:73–9.
[21] Mead LA, Hampson E. Turning bias in humans is influenced by phase of the menstrual cycle. Horm Behav 1997;31: 65–74.
[22] Mizoguchi K, Yuzurihara M, Ishige A, Sasaki H, Chui DH, Tabira T. Chronic stress-induced impairment of spatial working memory because of prefrontal dopaminergic dysfunction. J Neurosci 2000;20:1568–74.
[23] Pani L, Porcella A, Gessa GL. The role of stress in the pathophysiology of the dopaminergic system. Mol Psychiatry 2000;5:14–21.
[24] van der Kolk BA, Boyd H, Krystal J, Greenburg M. Posttraumatic stress disorder as a biologically based disorder, implications of the animal model of inescapable shock. In: van der Kolk BA, editor. Posttraumatic stress disorder, psychological and biological Sequela. Washington, DC: American Psychiatry Association Press; 1984. p. 124–36.
[25] Yazgan MY, Leckman JF, Wexler BE. A direct observational measure of whole body turning bias. Cortex 1996;32:173–6.
[26] Yehuda R, Southwick S, Giller EL, Ma X, Mason JW. Urinary catecholamine excretion and severity of PTSD symptoms in Vietnam combat veterans. J Nerv Ment Dis 1992;180:321–5.
[27] Zimmerberg B, Glick SD, Jerussi TP. Neurochemical correlate of a spatial preference in rats. Science 1974;185:623–5.