

## Higher cerebrospinal fluid homovanillic acid levels in depressed patients with comorbid posttraumatic stress disorder

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### Abstract

Major depression and posttraumatic stress disorder (PTSD) are often comorbid, resulting in more impairment compared than with either diagnosis alone. Both major depression and PTSD are thought to be associated with monoamine transmitter abnormalities. This study compared clinical features and cerebrospinal fluid (CSF) monoamine metabolites in drug-free depressed subjects with a current major depressive episode (MDE) without comorbid PTSD, subjects with a current MDE and comorbid PTSD, and healthy volunteers. Depressed subjects with comorbid PTSD had higher CSF homovanillic acid (HVA) levels compared with depressed subjects without comorbid PTSD or healthy volunteers. Higher HVA was present after adjustment for sex, lifetime aggression severity and depression scores, alcoholism, tobacco smoking, comorbid cluster B personality disorder, reported childhood abuse, and psychosis. We found no group difference in CSF 5-hydroxyindolacetic acid (5-HIAA) and 3-methoxy-4-hydroxyphenylglycol (MHPG) levels. Higher dopaminergic activity may contribute to alterations in memory and other cognitive functions, anhedonia, and hypervigilance observed in PTSD.

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### 1. Introduction

Major depression and posttraumatic stress disorder (PTSD) can be comorbid, resulting in more impairment compared than with either diagnosis alone (Kessler et al., 1995; Bleich et al., 1997; Kaufman and Charney, 2000; Oquendo et al., 2003a). Both major depression and PTSD are thought to be associated with monoamine neurotransmitter abnormalities (for reviews, see Katz et al., 1996; Hageman et al., 2001; Sher and Mann, 2003). Several studies suggest that the dopaminergic system is hyperactive in subjects with PTSD and may play a role in

the pathophysiology of certain PTSD symptoms, such as emotional numbing, anhedonia, and hypervigilance (Abercrombie et al., 1989; Yehuda et al., 1992; Finlay et al., 1995; Sudha and Pradhan, 1995; Lemieux and Coe, 1995; Katz et al., 1996; Bremner et al., 1999; Ventura et al., 2002; Charney, 2004). The study of cerebrospinal fluid (CSF) homovanillic acid (HVA) levels may further clarify the underlying pathophysiology of PTSD (Deutch and Young, 1995).

We examined clinical features and CSF HVA, 5-hydroxyindolacetic acid (5-HIAA), or 3-methoxy-4-hydroxyphenylglycol (MHPG) levels in drug-free unipolar depressed subjects with and without comorbid PTSD and healthy controls. To the best of our knowledge, this is the first study to compare CSF monoamine metabolites in depressed groups with and without comorbid PTSD and healthy controls.

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## 2. Material and methods

### 2.1. Subjects

Depressed subjects were recruited through advertising and referrals and admitted to a university hospital for participation in mood disorders research. Healthy controls were recruited by advertising. All subjects gave written informed consent as required by the Institutional Review Board for Biomedical Research. In all, 113 unipolar depressed subjects without comorbid PTSD, 12 unipolar depressed subjects with comorbid PTSD, and 27 healthy volunteers participated in the study. All depressed subjects met DSM-IV (American Psychiatric Association, 1994) criteria for a current major depressive episode (MDE). Participants were free from medications known to affect brain serotonin, dopamine, or norepinephrine systems for a minimum of 14 days. The drug-free interval was longer for drugs with a long half-life (6 weeks for fluoxetine and 4 weeks for oral antipsychotics). Among psychotropics, only small doses of short-acting benzodiazepines were permitted but not within 72 h of the lumbar puncture. Subjects were free from any substance use disorder for at least 2 months. The duration of the drug-free status of the subjects was established by a combination of urine and blood toxicological screenings, observation in hospital, and a history obtained from the participant, the participant's family, and the referring physician. Subjects were not permitted to smoke for 12 h before the lumbar puncture.

DSM-IV Axis I and Axis II disorders were diagnosed using the structured clinical interview I (SCID-I) and the structured clinical interview II (SCID-II; for DSM-IV, American Psychiatric Association, 1994), respectively. Healthy controls were free of psychiatric disorder based on the SCID nonpatient version (SCID-NP). All subjects had a physical examination and routine laboratory screening tests, including urine and blood toxicological screenings to rule out neurological or medical illness or illicit drugs that could affect their mental status or CSF monoamine metabolites.

Current severity of depression was assessed by the Hamilton depression rating scale (HDRS; Hamilton, 1960). Lifetime aggression was rated with the Brown–Goodwin aggression scale (Brown and Goodwin, 1986). Life events were scored on the St. Paul Ramsey life events scale (Lumry, 1978).

### 2.2. The lumbar puncture and cerebrospinal fluid monoamine metabolites assay

The lumbar puncture was performed at about 8:00 a.m. after the subject had been kept at bed rest and fasting from midnight. Cerebrospinal fluid was withdrawn from the L4–L5 interspace, with the subject in the left decubitus position. After the removal of 1 mL of CSF into the first sample tube, a further 15 mL of CSF was collected in the second and

third tubes. These tubes were then immediately transferred on ice water to be centrifuged at 4 °C, and the supernatant was pooled from the second and third tubes. The 15 mL of supernatant was divided into 1-mL aliquots for storage at –70 °C until assay. Cerebrospinal fluid amine metabolites were assayed in one of the 1-mL aliquots of the 15-mL sample.

Cerebrospinal fluid HVA, 5-HIAA, and MHPG were assayed by high-performance liquid chromatography with electrochemical detection (Scheinin et al., 1983). The within- and between-run coefficients of variance of the assay were less than 10%. The sensitivity of the assay was 0.5 pmol/injection. All samples were kept frozen at –70 °C until assay. Storage effects were not detected.

### 2.3. Statistical analyses

Demographic and clinical characteristics and CSF monoamine metabolites in depressed subjects with and without comorbid PTSD and healthy volunteers were compared using a general linear model, Mann–Whitney test, and the Chi-squared test, as appropriate. We used a general linear model to compare CSF HVA in the two depressed groups controlling for sex, aggression, depression (HDRS), alcoholism, tobacco smoking, cluster B personality disorders, reported childhood abuse, and psychosis because studies have suggested that these parameters may affect CSF HVA levels (Raleigh et al., 1992; Nordin et al., 1995; Seegal, 1985; Campanella et al., 1977; Lindstrom, 1985; Aberg-Wistedt et al., 1985; Houston et al., 1986; Almay et al., 1987; Jones et al., 1990; Faustman et al., 1991; Limson et al., 1991; Spiegel and King, 1992; Johnson et al., 1994; Soderstrom et al., 2001; Kapur and Mann, 1992; Brown and Gershon, 1993; Lykouras et al., 1994; Van Praag et al., 1975; Post et al., 1973; Chotai et al., 1998; Geraciotti, 1997; Daderman and Lidberg, 2002; Sher et al., 2003). All tests were two tailed, and significance required was  $p < 0.05$ .

## 3. Results

### 3.1. Demographic and clinical characteristics

The three groups were comparable in demographic characteristics with three exceptions (Table 1). The depressed group without comorbid PTSD had fewer years of education than controls. The depressed group with comorbid PTSD had more females compared with the depressed group without comorbid PTSD and healthy controls. There were fewer smokers among healthy volunteers than in both depressed groups. Among the 12 patients with PTSD, reported traumata precipitating PTSD were childhood abuse ( $N=7$  [58%]), physical threat to the patient ( $N=3$  [25%]), including intimate partner violence ( $N=1$  [8%]), and unknown ( $N=2$  [17%]).

Table 1  
Clinical characteristics of depressed subjects and healthy volunteers

Measure	Healthy controls (N=27)		Subjects without comorbid PTSD (N=113)		Subjects with comorbid PTSD (N=12)		Analysis		
	Mean (%)	SD	Mean (%)	SD	Mean (%)	SD	df	F/t/z/ $\chi^2$	p
Age (years)	36.6	12.9	36.4	12.4	36.7	8.8	2,149	0.004	0.99
Gender (%males)	48.1		45.1		8.3		2	6.4	0.04 <sup>a,b</sup>
Marital status (% married)	14.8		24.8		33.3		2	1.68	0.39
Total years of education	16.6	2.4	14.7	2.6	15.3	4.1	2,135	5.36	0.005 <sup>c</sup>
Hamilton depression rating scale	0.6	0.9	20.0	6.8	21.3	6.6	2,147	103.64	<0.0001 <sup>a,c</sup>
St. Paul Ramsey scale (life events)	2.6	1.5	4.0	1.2	3.8	0.4	2,122	10.35	<0.0001 <sup>a,c</sup>
Aggression history scale	13.5	3.2	18.9	6.2	19.5	6.2	2,141	8.95	<0.0001 <sup>a,c</sup>
Number of major depressive episodes	N/A	N/A	4.2	5.0	12.2	27.7		-0.23	0.98 <sup>d</sup>
Number of hospitalizations	N/A	N/A	2.8	6.0	12.9	22.4		-1.89	0.06 <sup>d</sup>
Age of onset of the first depressive episode	N/A	N/A	25.4	12.1	21.2	15.1	116	1.12	0.26
Age at first hospitalization	N/A	N/A	31.0	11.9	22.9	10.9	97	1.95	0.05
Cigarette smoking (%smokers)	8.0		38.7		33.3		2	8.71	0.01 <sup>a,c</sup>
Prevalence of a history of alcoholism (%)	N/A	N/A	41.6		16.7		1	2.82	0.09
Prevalence of Cluster B personality disorders (%)	N/A	N/A	49.0		75.0		1	2.9	0.09
Prevalence of a history of childhood abuse (%)	N/A	N/A	32.9		91.7		1	15.09	<0.0001

<sup>a</sup> Controls are different from depressed subjects with comorbid PTSD ( $p<0.05$ ).

<sup>b</sup> Depressed subjects without comorbid PTSD are different from depressed subjects with comorbid PTSD ( $p<0.05$ ).

<sup>c</sup> Controls are different from depressed subjects without comorbid PTSD ( $p<0.05$ ).

<sup>d</sup> Mann-Whitney test.

The depressed groups had comparable HDRS, Brown–Goodwin aggression scale, and St. Paul Ramsey life events scale scores but, as expected, higher scores than controls in all these scales. Depressed subjects with comorbid PTSD were more likely to have a reported history of childhood abuse than depressed subjects without comorbid PTSD ( $df=1$ ,  $\chi^2=15.9$ ,  $p<0.0001$ ). Subjects with comorbid PTSD had earlier age of first hospitalization ( $df=97$ ,  $t=1.95$ ,  $p=0.05$ ) and a higher number of hospitalizations ( $z=-1.89$ ,  $p=0.06$ ), but the differences did not reach statistical significance.

### 3.2. CSF monoamine levels

Table 2 gives results of monoamine metabolite assays for the three groups. CSF HVA levels were higher in depressed subjects with comorbid PTSD compared with depressed subjects without comorbid PTSD and healthy volunteers. The difference in CSF HVA levels between the

two depressed groups remained statistically significant after adjustment for sex, aggression, depression (HDRS) scores, alcoholism, tobacco smoking, cluster B personality disorders, childhood abuse, and psychosis ( $df=9$ ;  $F=2.2$ ;  $p=0.01$ ). We did not find any differences in CSF 5-HIAA and MHPG levels among the three groups. As expected, CSF HVA levels were correlated with CSF 5-HIAA ( $r=0.6$ ,  $p<0.0001$ ) and CSF MHPG ( $r=0.2$ ,  $p<0.02$ ) levels. We did not find any correlations between CSF monoamine metabolite levels and ratings on behavioral measures (data not shown).

## 4. Discussion

### 4.1. Clinical and demographic features

More women than men in our sample had PTSD. This observation is consistent with data suggesting a differential

Table 2  
CSF monoamine metabolites in depressed subjects and healthy volunteers

	Healthy controls (N=27)		Subjects without comorbid PTSD (N=113)		Subjects with comorbid PTSD (N=12)		Analysis		
	Mean	SD	Mean	SD	Mean	SD	df	F	p
HVA (pmol/mL)	197.2	69.5	192.7	72.4	252.6	95.2	2,149	3.57	0.03 <sup>a,b</sup>
5-HIAA (pmol/mL)	92.9	33.0	98.5	34.9	117.4	33.7	2,149	2.14	0.12
MHPG (pmol/mL)	47.4	26.5	43.4	16.6	39.0	12.5	2,149	0.96	0.39

<sup>a</sup> Controls are different from depressed subjects with comorbid PTSD ( $p<0.05$ ).

<sup>b</sup> Depressed subjects without comorbid PTSD are different from depressed subjects with comorbid PTSD ( $p<0.05$ ).

gender risk for stressor exposure, as well as for the subsequent development of PTSD when exposure is roughly comparable (for reviews, see [Golding, 1999](#); [Saxe and Wolfe, 1999](#)).

In our sample, depressed individuals with comorbid PTSD were more likely to have a reported history of childhood abuse than depressed individuals without comorbid PTSD. Indeed, in more than half of the cases, childhood abuse was a precipitant for PTSD. About one-third of those who have been abused or neglected during childhood develop PTSD ([Widom, 1999](#)). The prevention of childhood abuse and intimate partner violence may result in a significant reduction in morbidity from PTSD ([Murray, 1993](#); [Golding, 1999](#); [Widom, 1999](#); [Heim and Nemeroff, 2001](#)).

The fact that depressed subjects with comorbid PTSD tended towards earlier age of first hospitalization and a higher number of hospitalizations compared to depressed individuals without comorbid PTSD indicates a higher vulnerability to adversity in individuals with comorbid PTSD and underlines the importance of early recognition and appropriate treatment of individuals with PTSD that can produce a meaningful reduction in distress (for reviews, see [Katz et al., 1996](#); [Hageman et al., 2001](#); [Solomon and Johnson, 2002](#)).

#### 4.2. Biological findings

Our finding that CSF HVA levels were higher in depressed subjects with comorbid PTSD compared with depressed subjects without comorbid PTSD and healthy volunteers is consistent with reports suggesting elevated dopamine release and metabolism in PTSD ([Roth et al., 1988](#); [Abercrombie et al., 1989](#); [Kalivas and Duffy, 1989](#); [Keefe et al., 1990](#); [Imperato et al., 1991](#); [Yehuda et al., 1992](#); [Hamner and Diamond, 1993](#); [De Bellis et al., 1994](#); [Finlay et al., 1995](#); [Lemieux and Coe, 1995](#); [Sudha and Pradhan, 1995](#); [Bremner et al., 1999](#); [Glover et al., 2003](#)). Studies of subjects with combat-related PTSD, sexual-abuse-related PTSD, sexually abused girls, and severely maltreated children with PTSD found elevations in urinary dopamine relative to controls ([Yehuda et al., 1992](#); [De Bellis et al., 1994](#); [Lemieux and Coe, 1995](#); [De Bellis et al., 1999](#)). A recent study of urinary dopamine levels in mothers of childhood cancer survivors found that those with PTSD symptoms had higher urinary dopamine levels than mothers without PTSD symptoms and controls ([Glover et al., 2003](#)). It has also been reported that resting plasma dopamine levels were significantly higher in subjects with PTSD than healthy control subjects ([Hamner and Diamond, 1993](#)).

Animal studies also support the role of the dopaminergic system in the pathophysiology of acute and chronic stress ([Bremner et al., 1999](#)). In rats, mild and brief stress, as well as chronic stress, results in an increase in dopamine release and metabolism in the medial prefrontal cortex ([Kalivas and](#)

[Duffy, 1989](#); [Abercrombie et al., 1989](#); [Imperato et al., 1991](#); [Finlay et al., 1995](#); [Sudha and Pradhan, 1995](#)). Severe stress can result in elevated dopamine release and metabolism in the nucleus accumbens and striatum, as well as the medial prefrontal cortex ([Roth et al., 1988](#); [Abercrombie et al., 1989](#); [Keefe et al., 1990](#); [Imperato et al., 1991](#)). In a review of the neurobiology of PTSD, [Bremner et al. \(1993\)](#) suggested a possible role for the mesocortical dopaminergic system in memory and attention alterations. A role for dopamine in PTSD is also supported by the observation that the administration of cocaine and amphetamine, which both stimulate endogenous dopamine release, results in an increase in paranoid and vigilance behaviors ([Bremner et al., 1999](#)). Possibly, alterations in the dopaminergic system play a role in the pathophysiology of these symptoms in individuals with PTSD.

A recent study found that the dopamine transporter gene was associated with PTSD ([Segman et al., 2002](#)). This provides additional evidence for the involvement of the dopaminergic system in the etiology of PTSD. The significant elevation in peripheral dopamine beta-hydroxylase (DBH) activity in psychotic versus nonpsychotic PTSD patients and between psychotic PTSD patients and normal control subjects has been reported ([Hamner and Gold, 1998](#)). Because DBH activity is relatively stable, at least in adults, the differences obtained in peripheral DBH suggest genetic influences on who develops psychotic features in the context of trauma. Genetically determined variations in dopaminergic neurotransmission may mediate the pathological response to trauma and, in general, the vulnerability to the effects of stress. This is consistent with multiple reports suggesting that genetic factors are associated with susceptibility to PTSD (for reviews, see [Yehuda, 1999](#); [Radant et al., 2001](#)) and with evidence of a gene-by-environment interaction, in which an individual's response to environmental insults is moderated by his or her genetic makeup ([Caspi et al., 2003](#)).

However, in addition to the involvement of the dopaminergic system, multiple lines of evidence suggest that dysregulation of multiple neurotransmitter and neuroendocrine pathways, including serotonergic, noradrenergic, opioid, and hypothalamic–pituitary–adrenal systems plays a role in the pathophysiology of PTSD (for reviews, see [Katz et al., 1996](#); [Bremner et al., 1999](#); [Yehuda, 1999](#); [Hageman et al., 2001](#)). These neurochemical pathways do not function in isolation but rather within a remarkably intricate network of regional modulatory systems. For example, a distinctive abnormality of PTSD is hypothalamic–pituitary–adrenal (HPA) axis dysregulation. Studies have shown lower resting glucocorticoid levels in plasma, lower urinary cortisol excretions, lower glucocorticoid response to stress, up-regulation of lymphocyte glucocorticoid receptors, enhanced negative feedback to low-dose dexamethasone, and lower cortisol levels and the absence of an age effect on cortisol levels in response to fenfluramine administration in subjects with PTSD ([Munck et al., 1984](#);

Sapolsky et al., 1984; Yehuda et al., 1993; Yehuda et al., 1995; Hageman et al., 2001; Oquendo et al., 2003b; Sher et al., 2004). CSF corticotropin-releasing hormone and beta-endorphin concentrations were found to be higher in PTSD patients than in comparison subjects (Bremner et al., 1997; Baker et al., 1997; Baker et al., 1999). The HPA axis interacts with the dopamine system. Dexamethasone administration increases plasma-free dopamine and plasma HVA in healthy volunteers (Rothschild et al., 1984; Wolkowitz et al., 1986; Reus and Wolkowitz, 2003). In rats, corticosteroid administration reduces dopamine re-uptake (Gilad et al., 1987). There are also pronounced bidirectional relationships between the HPA axis and the serotonergic system (McEwen, 2003). There has been considerable interest in alterations in memory and other cognitive functions in PTSD (for reviews, see Bremner et al., 1999; Brewin, 2001). Both dopaminergic and HPA pathways, as well as opioid and gamma-aminobutyric acid systems, affect memory and learning and abnormalities in these neurobiological systems may contribute to cognitive symptoms observed in PTSD.

The fact that the PTSD group was small and had a greater number of females is a limitation of our study. Future studies of neurobiology of PTSD should include, if possible, larger sample sizes and equal numbers of males and females.

The results of our study underline the importance of taking into account comorbidity in mood disorder research. It is possible that, in some studies, subjects with comorbid PTSD constitute a meaningful subgroup of subjects with major depression. The variability in the rates of comorbid PTSD in different patient populations may affect both clinical and biological results of research studies (Oquendo et al., 2003b).

The results of our study show that depressed individuals with comorbid PTSD are more likely to have a reported history of childhood abuse and need more treatment than depressed individuals without comorbid PTSD. The depressed group with comorbid PTSD has higher CSF HVA levels than the depressed group without comorbid PTSD and the control group. Future research is needed to study biological parameters when PTSD is not comorbid with other conditions, as well as in major depression with and without comorbid PTSD. Biological studies of PTSD may contribute to the development of new pharmacological treatments for PTSD, such as D<sub>1</sub> and D<sub>2</sub> receptor antagonists.

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