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ANXIETY IN MAJOR DEPRESSION AND CEREBROSPINAL FLUID FREE GAMMA-AMINOBUTYRIC ACID

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Abstract

Background—Low gamma-aminobutyric acid (GABA) is implicated in both anxiety and depression pathophysiology. They are often comorbid, but most clinical studies have not examined these relationships separately. We investigated the relationship of cerebrospinal fluid (CSF) free GABA to the anxiety and depression components of a major depressive episode (MDE) and to monoamine systems.

Methods and Materials—Patients with a DSM-IV major depressive episode (N = 167: 130 major depressive disorder; 37 bipolar disorder) and healthy volunteers (N = 38) had CSF free GABA measured by gas chromatography mass spectroscopy. Monoamine metabolites were assayed by high performance liquid chromatography. Symptomatology was assessed by Hamilton depression rating scale.

Results—Psychic anxiety severity increased with age and correlated with lower CSF free GABA, controlling for age. CSF free GABA declined with age but was not related to depression severity. Other monoamine metabolites correlated positively with CSF GABA but not with psychic anxiety or depression severity. CSF free GABA was lower in MDD compared with bipolar disorder and healthy volunteers. GABA levels did not differ based on a suicide attempt history in mood disorders. Recent exposure to benzodiazepines, but not alcohol or past alcoholism, was associated with a statistical trend for more severe anxiety and lower CSF GABA.

Conclusions—Lower CSF GABA may explain increasing severity of psychic anxiety in major depression with increasing age. This relationship is not seen with monoamine metabolites,

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suggesting treatments targeting the GABAergic system should be evaluated in treatment-resistant anxious major depression and in older patients.

Keywords

cerebrospinal fluid; gamma-aminobutyric acid; major depression; anxiety

INTRODUCTION

Major depressive disorder (MDD) is associated with low levels of brain, plasma and cerebrospinal fluid (CSF) gamma-aminobutyric acid (GABA). Plasma GABA levels have been reported to be low in 35–40% of depressed patients.[1] Most studies have found lower levels of CSF GABA in patients with major depression compared with control groups (see Table 1 for summary). Occipital cortical GABA measured by magnetic resonance spectroscopy (MRS) is lower in major depression[2, 3] compared with healthy volunteers and remitted patients,[4] suggesting that low GABA is mood-state-dependent. Low occipital cortical GABA appears to be associated with melancholic features. Morphometric studies have found fewer GABA neurons or less neuronal density in regions of the brain such as prefrontal cortex, anterior cingulate and dentate gyrus in MDD and bipolar disorder.[5–7] Some animal models of depression have a deficit of GABAergic function[8, 9] and antidepressants upregulate GABA-B binding in prefrontal cortex.[10]

Conversely, several types of antidepressants enhance GABAergic function. Electroconvulsive therapy raises seizure threshold and enhances GABAergic function.[11–13] Some anticonvulsant medications, such as lamotrigine, have antidepressant effects and enhance GABAergic action.[14, 15] Anticonvulsants with antimanic and mood stabilizing properties, but no evidence of antidepressant effects, such as carbamazepine, have no effect on CSF GABA.[16] Selective serotonin reuptake inhibitor antidepressants (SSRIs) cause an acute increase in brain GABA levels.[17, 18]

Depression and anxiety often occur together[19–22] and GABA regulates anxiety.[23–29] Brain imaging studies have found less binding to the benzodiazepine-GABA receptor in anxiety disorders[23–29] and lower cortical GABA levels using MRS.[30] This raises a question as to whether GABA is related to mood disorders as whole or to the anxiety component of both mood and anxiety disorders.

Studies in psychiatric and healthy human subjects report that CSF GABA levels decrease with age,[31–37] but there is debate about whether that is the case for cortical GABA levels.[2, 30] Anxiety and psychomotor agitation with depression are more severe in older patients, but the reason is unknown.[38] We hypothesized that an age-related decline in brain GABA contributes to the more severe anxiety seen in older depressed patients. Accordingly, the purpose of this study was to investigate the relationship between CSF free GABA levels, depression, and anxiety in the context of major depressive episodes. Our second hypothesis was that low GABA levels contribute to more severe anxiety associated with a major depressive episode (MDE) independent of age. To determine whether GABA levels are low in major depressive episodes we compared MDE to healthy volunteers. We also explored the relationship of CSF free GABA to subtypes of mood disorders and a history of comorbid

alcoholism or suicide attempts. To test these subgroups, we examined a much larger sample of depressed subjects than in previous studies. Finally, since monoamines are also associated with mood disorders and with anxiety disorders, we examined the relationship of monoamine metabolites in CSF to free GABA levels.

METHODS AND MATERIALS

RECRUITMENT

Patients with a DSM-IV mood disorder (*N* = 167: 130 with MDD and 37 with bipolar disorder depression) presenting to a university psychiatric hospital for evaluation and treatment of an episode of major depression were recruited into the study. All participants gave written informed consent as required by the Institutional Review Board (IRB) for Biomedical Research. The duration of the drug-free status of patients was established by a combination of drug screen and interview. Patients were off medication for a minimum of 14 days, and longer for antipsychotics (medication free for >28 days) and fluoxetine (off >35 days) before lumbar puncture. Thirty-five depressed patients (29/130 MDD and 6/31 bipolar) received lorazepam for the management of anxiety (average daily dose = 1.6 mg) during the 14 days prior to lumbar puncture. Current, but not past, alcohol or substance use disorders were exclusion criteria. Healthy volunteers (*n* = 38) were recruited by advertising and screened to rule out Axis I and cluster B personality disorders and a first-degree relative with a mood or schizophrenia spectrum disorder.

CLINICAL MEASURES

DSM-IV Axis I disorders were diagnosed using the Structured Clinical Interview I (SCID-I) for DSM-IV in patients and the Structured Clinical Interview for DSM-IV for normal persons (SCID-NP) in healthy volunteers. Patients and healthy volunteers had a physical examination and routine laboratory screening tests (CBC, SMAC, and urine analysis) to detect neurological disease and active physical disease that could affect their mental status or CSF GABA. All were assessed by the 17-item Hamilton Depression Rating Scale (HDRS)[39] and the Brief Psychiatric Rating Scale (BPRS).[40] The items of Agitation, Psychic Anxiety, Somatic Anxiety, and Hypochondriasis from the HDRS were used to measure the presence of anxiety symptoms in the context of major depression. Clinical ratings were performed in both patients and controls but only patient data are reported for the relationship to psychopathology and to monoamines and age.

SAMPLE COLLECTION LUMBAR PUNCTURE AND ASSAYS

The lumbar puncture procedure was identical for patients and normal volunteers and performed at approximately 08:00 h after bed rest and fasting from midnight. Women were tapped during the first half of the menstrual cycle. CSF was withdrawn from the L3–L4 interspace with the participant 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. The tubes were immediately transferred on to ice water to be centrifuged at 4°C and the supernatant from tubes 2 and 3 pooled. The 15 mL of supernatant was promptly divided into 1-mL aliquots and stored at −70°C until assay. CSF free GABA monoamine metabolites

were assayed in one of the 1-mL aliquots of the 15-mL sample. Monoamine metabolites were assayed using our previously published method.[41]

An AGILENT Chemstation data system was used to control a HP 5988B gas chromatography-mass spectrometer (GC-MS), to quantify free GABA. The GC-MS with a DB-1 column (15 m × 0.25 mm I.D., 0.25 μm) was operated in NCI mode using methane: ammonia (95:5) as the reagent gas. The column was programed from 80°C(holding for 1 min) to 160°C at an increasing rate of 22°C/min and then to 260°C at the rate of 30°C/min. The ion-source temperature was 200°C, and the temperatures of injector (splitless) and the interface between the chromatograph and spectrometer were set to 265°C.

The extraction method was modified from a previous publication.[42] An internal standard GABA-d_6 (15 ng) was added to a CSF sample (0.2 mL) followed by addition of 0.8 mL 1 M phosphate buffer (pH 11.5) and 50 μl methyl chloroformate. After shaking for 10 min, 150 μl 6 N HCl and 4 mL ethyl acetate were added. The mixture was mixed for 5 min and centrifuged. The supernatant was transferred to a round bottom tube and dried down. To the residue, 10 μl triethylamine and 100 μl 15% pentafluorobenzylbromide in acetonitrile were added. The mixture was allowed to stand at room temperature for 15 min, and extracted with 200 μl 0.5 N HCl and 1 mL hexane. The supernatant was transferred and dried down. The residue was dissolved in 30 μl ethyl acetate and 2 μL injected for GC-MS analysis. Intra- and inter-assay coefficient of variance in six consecutive assays was <6% and <8%, respectively, for concentrations of 6, 12, and 24 ng/mL.

STATISTICAL ANALYSIS

SPSS version 21 was used for statistical analyses. Free CSF GABA values were log transformed to normalize the variance. Correlations between CSF GABA and monoamine metabolite levels, age, and clinical measures, were analyzed in patients using Spearman's correlation coefficient (rho). Comparisons of CSF GABA and monoamine metabolite levels, anxiety, and depression measures between subgroups were carried out using a generalized linear model or ANCOVAs to control for effects of age, diagnosis and sex. Data in tables and text on GABA and monoamine levels are shown as untransformed values but some statistical test results are also reported for log-transformed data, although statistically significant findings remained the same with non-transformed data.

RESULTS

Table 2 reports demographics, psychopathology measures, and CSF GABA levels in the mood disorders group (Table 2A) and the healthy volunteers (Table 2B). The 17-item HDRS and BPRS scores for the depressed group indicate a moderate degree of severity in depression and general psychopathology (20 ± 6.1 and 35.5 ± 7.7, respectively), and 56% of depressed subjects had a history of a suicide attempt. The healthy volunteers had no Axis I or cluster B Axis II diagnosis and minimal psychopathology scores on the HDRS or BPRS, although one individual had a history of alcoholism.

Table 3 gives CSF free GABA correlations with age, anxiety, and depression ratings. CSF GABA correlated negatively with age and HDRS psychic anxiety, but not with HDRS

psychomotor agitation. Age correlated positively with HDRS psychic anxiety, but did not correlate with HDRS agitation and tension. Psychic anxiety correlated negatively with CSF GABA, even after controlling for age effects. No correlation was observed between CSF GABA and HDRS depression severity, even excluding anxiety symptoms. Brown-Goodwin Life-time Aggression History scores did not correlate with CSF GABA.

In a generalized linear model with CSF GABA as the dependent variable, sex, and diagnoses as independent variables and age as a covariate, CSF differed between diagnostic groups ($F = 3.513$, $P = .032$) and by sex ($F = 5.642$, $P = .018$). The group effect was explained by lower CSF free GABA in major depressive disorder (MDD) compared with bipolar disorder (15.1 ± 7.1 vs. 18.7 ± 12.3, $t = -1.987$, df = 165, $P = 0.049$ for log-transformed data and $t = -2.256$, df = 165, $P = 0.025$ for untransformed data). CSF GABA mean level was comparable between healthy volunteers and bipolar disorder (17.4 ± 7.6 vs. 18.7 ± 12.3, $P > .05$). The sex effect was due to lower CSF free GABA levels in males compared with females (estimated marginal means are 15.3 vs. 18.5). CSF GABA levels were also comparable between mood disorder suicide attempters and nonattempters.

As expected depressed subjects prescribed benzodiazepines within days of the lumbar puncture had a trend for more anxiety (HDRS psychic anxiety 1.8 ± 1.4 vs. 1.5 ± 1.0, $t = 1.942$, df = 159, $P = .054$), and for lower CSF GABA compared to depressed subjects who were not prescribed benzodiazepines ($14.9 \pm 0.12.1$ vs. 16.3 ± 6.9, $t = -1.867$, df = 159, $P = .066$).

Regarding CSF monoamine metabolites, GABA correlated positively with HVA, 5-HIAA (trend level) and MHPG, controlling for age, sex, and diagnosis (Table 4). CSF HVA had a significant positive correlation with CSF 5-HIAA. CSF 5-HIAA and MHPG levels did not correlate with depression or anxiety severity, but lower CSF HVA correlated with higher psychic anxiety (Table 4). CSF monoamine metabolite levels did not differ between diagnostic groups controlling for age and sex (data not shown).

DISCUSSION

We found CSF GABA levels were lower in MDD compared with healthy volunteers and bipolar depression, controlling for effects of age and sex. Within those with a current major depressive episode, CSF GABA had a negative correlation with psychic anxiety, but not psychomotor agitation and somatic anxiety. We found no relationship between severity of depression and GABA levels. Such a relationship between the GABAergic system and the psychic anxiety component of major depression, and not with other depression symptom components, was the a priori hypothesis of this study. This correlation with CSF free GABA may explain the age effect on anxiety severity in MDE, and also contribute to the severity of psychic anxiety in MDE independently of the age effect. This present study examined a much larger sample than previous published studies (Table 1), lending confidence to the findings.

Our finding of lower CSF free GABA levels in MDD compared with healthy volunteers is consistent with results from other studies that examined both CSF and brain GABA in vivo

(Table 1). Our findings suggest that low CSF GABA is restricted to MDD and not seen in bipolar disorder, and it is related to the severity of psychic anxiety and not other depressive symptoms. Goddard et al.[30] reported low occipital GABA levels in patients with panic disorder as measured by magnetic resonance spectroscopy (MRS), and a blunted response of occipital cortex GABA in response to acute benzodiazepine administration in panic disorder compared to healthy volunteers.[43] Car accident survivors who develop posttraumatic stress disorder have lower plasma GABA levels than accident victims who do not,[44] further indicating that there is a GABA deficit associated with anxiety. Others[45] found no difference in CSF GABA in panic disorder compared to neurological controls, but studied a small sample.

We found that the increasing severity of the anxiety component of depression with age is explained by the greater severity of psychic anxiety, and not by other symptoms of depression or by psychomotor agitation or somatic anxiety. The relationship of anxiety to low CSF GABA in our study was also confined to psychic anxiety and not psychomotor agitation or somatic anxiety. Others[46] found a relationship of CSF GABA to severity of depression, but did not control for severity of anxiety. Roy et al.[47] found lower CSF GABA in depressed alcoholics, who were more anxious and had made more suicide attempts, compared to never-depressed alcoholics. In a later prospective study, they reported no association between future suicidal behavior and CSF GABA, suggesting, in agreement with our findings, that anxiety was the main basis for the association with low CSF GABA.[48] Honig et al.[49] found a negative correlation of CSF GABA with severity of depression and no correlation with anxiety but their small sample (N = 14), had limited statistical power.

When two MRS studies[2, 3] that did not find a relationship of depression severity to occipital GABA were combined, a negative correlation was observed. The latter study found low cortical GABA was particularly associated with melancholic and psychotic features in depressed subjects, but did not report an effect of anxiety or agitation.[3] Berrettini et al.[32] suggested that low CSF GABA is mood-state-dependent because euthymic patients had normal levels, as did Hasler[4] who observed no difference in cortical GABA between drug-free remitted major depression patients and controls. Neither study evaluated the role of the anxiety component. We did not study euthymic mood disorder patients.

In agreement with other studies examining CSF GABA levels[32, 33, 46, 50] and brain GABA[2] in psychiatric samples, and with studies conducted in normal human subjects,[31–37] we found a negative correlation of CSF GABA with age. The occurrence of anxiety symptoms in the context of depression, particularly in older patients has been documented.[19–22, 51, 52] The frequent coexistence of depression and anxiety in elderly has been termed a “depression-anxiety syndrome.”[53] No previous study examined the effect of age on the relationship of anxiety features in major depression to GABA levels. Goddard et al.[30] found no correlation of occipital GABA levels in panic disorder patients with age, when patients with mood disorders were excluded from the study. That excluded group was precisely our sample of interest. It is unlikely that results in brain and CSF should differ much, because brain and CSF free GABA levels are very strongly correlated in rat studies.[54]

In our depressed patient sample, age was negatively correlated with CSF GABA levels and positively correlated with psychic anxiety. After controlling for age, psychic anxiety remained significantly negatively correlated with CSF GABA. If this finding with psychic anxiety score is correct, it is consistent with GABA having two related effects. One GABA effect is on the severity of anxiety in major depression, and the second GABA effect is where it mediates the effect of age upon anxiety in major depression. Correlations cannot inform us about causal directions or pathways, but we hypothesize that the age-related decline in CSF GABA levels leads to, or permits, greater severity of psychic anxiety seen with increasing age in patients with major depression. Another possibility is that GABA levels are lower in response to the anxiety. If so, that would be the opposite of the expected direction for a homeostatic response and so seems a less probable explanation. Previous studies have not reported a relationship between GABA and age-related increased severity of anxiety in major depression, perhaps because most such studies did not evaluate the effects of age (see Table 3), or a narrow age range may prevent detection of a relationship to age-dependent anxiety and GABA effects.

Imaging studies have evaluated anxiety and the central benzodiazepine-GABA(A) receptor and many have found less benzodiazepine binding.[23–28, 55] Magnetic resonance proton spectroscopy indicates lower GABA levels in the cortex of subjects with unipolar depression,[2] and in anxiety disorders.[30] Anxiety symptoms, as part of major depression, may contribute to the finding of both low CSF and brain GABA in major depression.

Psychomotor agitation and somatic anxiety items from the HDRS were not related to either age or CSF GABA, raising the possibility that these forms of anxiety may be mediated through other mechanisms or neurotransmitters such as serotonin or norepinephrine. We found that CSF GABA correlated robustly with CSF HVA and CSF MHPG, and showed a statistical trend in the same direction for CSF 5-HIAA, perhaps reflecting shared transport in and out of CSF. CSF 5-HIAA and MHPG were not correlated with anxiety or depression scores but lower HVA correlated with more severe somatic but not psychic anxiety (Table 4). There have been few studies of CSF HVA, 5HIAA, and MHPG and anxiety, and none that included CSF GABA. Sullivan et al.[56] found no relation of CSF HVA to panic disorder, although high CSF 5-HIAA was present in depressed patients with panic disorder. Sher et al.[57] found higher CSF HVA in patients with comorbid PTSD and MDD, compared with MDD alone, and healthy volunteers, but did not examine its relationship to anxiety severity. In PET studies, Bonne et al.[58] reported no difference in 5-HT^{1A} receptor binding in PTSD compared to healthy volunteers. In contrast, Sullivan et al.[59] found higher binding in PTSD and a negative correlation between 5-HT_{1A} binding and somatic anxiety, and a positive correlation with psychic anxiety. Those findings indicate independent biologic processes may be involved in panic attacks, PTSD and psychic and somatic anxiety manifestations, consistent with our GABA findings with psychic anxiety.

We found that females had higher CSF free GABA than males when controlling for both age and diagnostic category. Other studies report sex differences in brain GABA levels[60] and in the impact of estradiol on the excitatory phase of GABA function in the developing brain.[61] Considering sex effects in studies of GABA and anxiety/depression is important.

This study has limitations. We performed exploratory comparisons without Bonferroni correction such as analyses of effects of alcoholism, suicide attempt history or previous benzodiazepine use, and these require independent replication. The degree of mood state dependence of low CSF GABA levels remains to be determined. Seventeen percent of our subjects had taken benzodiazepines within 14 days of the lumbar puncture. However, CSF GABA did not correlate with time off benzodiazepines. Others report no effect of alprazolam on CSF GABA.[45] We did find that subjects who took benzodiazepines within days of the lumbar puncture showed a statistical trend to be both more anxious compared to those who did not take benzodiazepines and have lower CSF GABA levels. Finally, the anxiety items on the HDRS are not as refined as some other rating scales that focus on anxiety symptoms, but we had limited the number of rating scales because of concerns over subject burden.

Understanding of the specific biochemical or neurotransmitter correlates of components of the psychopathology that constitute an episode of major depression is enhanced by the results of our study, which suggest that low CSF GABA levels in major depression may reflect the anxiety but not the depressive components of the disorder. Prominent anxiety in major depression is more common in older patients and has been associated with treatment resistance. Treatment of anxious depression may therefore warrant consideration of medications that enhance GABAergic function.

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TABLE 1

Studies of CSF GABA and psychopathology

Author	Control group	Patient group	Age corrected	CSF GABA	Medication status/comments
[16]	Normal volunteers *N* = 10	"Manic Depression" (2 unipolar; 7 bipolar) *N* = 9	No	No difference and not correlated with psychopathology	Drug free
[62]	Neurologic controls *N* = 20	Unipolar and bipolar depression *N* = 17	Not specified	Lower in depressed subjects	Drug free
[46]	Normal controls *N* = 29	Psychiatric patients *N* = 58	Yes (age-related decline)	Lower depressed subjects	Drug free
[63]	Normal controls *N* = 8	Depressed inpatients *N* = 13	No	Lower in depressed inpatients. No correlation with severity, age or sex. Bipolar lower than unipolar	Drug free
[50]	Normal controls *N* = 39	Euthymic bipolar and unipolar patients *N* = 9	Yes (age related decline)	Lower in euthymic bipolar and unipolar subjects. Higher on lithium	Drug free
[31]	Normal controls *N* = 38	Mood disorders and schizophrenia *N* = 76	No	Lower in depressed subjects	Drug free
[32]	Normal controls *N* = 34	Euthymic bipolar subjects (15 of whom provided unmedicated sample) *N* = 25	Yes (age related decline)	No difference	Some on lithium
[33]	Unipolar depression with melancholia *N* = 13 Bipolar depression *N* = 7	Unipolar depressed w/o melancholia *N* = 5	Yes (age related decline)	No difference	Drug free; depressed were older than controls
[64]	Normal controls *N* = 13	Pathological gamblers *N* = 17	Yes (no age effect)	No difference in gamblers and no difference in depressed vs. nondepressed gamblers	Drug free
[45]	Neurological controls *N* = 6	Subjects with Panic Disorder *N* = 11	No (despite age correlation)	No difference and no effect of alprazolam or imipramine treatment	Drug free

TABLE 2

Clinical and demographic characteristics and CSF GABA levels

(A) Mood Disordered Patients Variable	Total mean sample (*N* = 167) *N* (%) OR ± SD
Age (yr)	36.3 ± 11.4 (*n* = 167)
Male	69 (49%) (*n* = 167)
Suicide attempter	94 (56%) (*n* = 167)
Bipolar disorder	37 (22%) (*n* = 167)
Past alcohol use disorder (yes)	71 (43%) (*n* = 167)
HDRS	20.0 ± 6.1 (*n* = 167)
BPRS	35.5 ± 7.7 (*n* = 164)
Brown-Goodwin lifetime history of aggression scale	19.6 ± 5.7 (*n* = 164)
CSF free GABA (pmol/mL)	15.9 ± 8.5 (*n* = 167)
Log CSF free GABA	1.1 ± 0.2 (*n* = 167)
(B) Healthy volunteers Variable	**Total sample (*N* = 38), *N* (%) OR mean ± SD**
Age (yr)	34.8 ± 13.3 (*n* = 38)
Male	22 (58%) (*n* = 38)
Suicide attempter	0 (0%) (*n* = 38)
Bipolar disorder	0 (0%) (*n* = 38)
Past alcohol use disorder (yes)	1 (3%) (*n* = 38)
HDRS	0.6 ± 0.9 (*n* = 38)
BPRS	19.9 ± 2.2 (*n* = 38)
Brown-Goodwin lifetime history of aggression scale	14.2 ± 4.1 (*n* = 37)
CSF free GABA (pmol/mL)	17.4 ± 7.6 (*n* = 38)
Log CSF free GABA	1.2 ± 0.2 (*n* = 38)

TABLE 3

Correlations of age and CSF GABA with clinical features in mood disordered patients

Variable	Coefficient significance degree of freedom	CSF GABA	Age	Correlation between GABA and clinical variables controlling for age
Age	Rho	−0.377		
	p	5.02×10^{-7}		
	d.f.	165		
	n	167		
Agitation (HDRS)	Rho	−0.070	0.059	−0.052
	p	0.366	0.451	0.504
	d.f.	165	165	164
	n	167	167	167
Psychic anxiety (HDRS)	Rho	−0.278	0.191	−0.227
	p	2.76×10^{-4}	0.014	0.003
	d.f.	165	165	164
	n	167	167	167
Somatic anxiety (HDRS)	Rho	−0.002	0.033	0.012
	p	0.982	0.668	0.881
	d.f.	165	165	164
	n	167	167	167
Hypochondriasis (HDRS)	Rho	0.050	0.030	0.067
	p	0.518	0.690	0.391
	d.f.	165	165	164
	n	167	167	167
HDRS	Rho	−0.079	0.139	−0.030
	p	0.308	0.074	0.705
	d.f.	162	165	164
	n	164	167	167
HDRS no anxiety ITEMS	Rho	−0.029	0.095	0.008
	p	0.709	0.220	0.924
	d.f.	165	165	164
	n	167	167	167
Brown-Goodwin life-time aggression history score	Rho	0.006	−0.159	−0.057
	p	0.935	0.042	0.473
	d.f.	162	162	161
	n	164	164	164

TABLE 4

CSF GABA, monoamine metabolites and age and depression partial correlations: controlling for age, sex and diagnosis in mood disordered patients and healthy volunteers

Variable	Coefficient significance degrees of freedom	CSF GABA	HDRS17[a]	Psychic anxiety	Somatic anxiety
CSF HVA	Rho	0.259	−0.123	−0.107	−0.151
	p	.000	0.084	0.132	0.033
	d.f.	196	196	196	196
CSF 5-HIAA	Rho	0.122	0.014	−0.003	−0.105
	p	0.086	0.845	0.970	0.142
	d.f.	196	196	196	196
CSF MHPG	Rho	0.156	−0.013	−0.052	−0.066
	p	0.028	0.855	0.468	0.359
	d.f.	196	196	196	196

[a]HDRS17 is the 17-item Hamilton Depression Rating Scale and the anxiety items are from the HDRS.