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Altered Cortical GABA in Female Veterans with Suicidal Behavior: Sex Differences and Clinical Correlates

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Abstract

Background—Suicide is a public health concern in the civilian and veteran populations. Stressful life events are precipitating factors for suicide. The neurochemical underpinnings of the association between stress/trauma and suicide risk are unclear, especially in regards to sex differences. We hypothesized that gamma-amino butyric acid (GABA), the major inhibitory neurotransmitter may be a neurochemical candidate that is critical in the association between stress and suicide risk in veterans.

Methods—Proton magnetic resonance spectroscopy (^{1}H MRS) at 3.0 Tesla was used to measure *in vivo* neurochemistry in the anterior cingulate cortex (ACC; predominantly the dorsal ACC) of 81 veterans (16 females), including 57 (11 females) who endorsed past suicidal ideation (SI) and/or suicide attempt (SA) and 24 (5 females) with no history of SI and/or SA. Suicidal behavior (SB) was defined as the presence of SI and/or SA.

Results—We observed no significant differences in GABA/ Creatine+phosphocreatine (Cr+PCr) between veterans with SB (SB+) and without SB (SB−). However, the female SB+ group showed significantly reduced GABA/Cr+PCr vs. the female SB− group. We observed a trend-level significant negative correlation between GABA/Cr+PCr and the defensive avoidance (DA) subscale on the Trauma Symptom Inventory (TSI) in the SB+ group. In contrast, the SB− group exhibited a positive relationship between the two variables. Furthermore, we found significant negative correlations between GABA/Cr+PCr and Hamilton Rating Scale for Depression (HAM-D) scores as well as between GABA/Cr+PCr and several subscales of the TSI in female veterans.

Conclusions—This study suggests that reduced GABA/Cr+ PCr ratio in the ACC, which may be related to altered inhibitory capacity, may underlie suicide risk in female veterans. Further, the

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negative association between GABA/Cr+PCr and stress symptomatology and depression scores suggests that MRS studies may shed light on intermediate phenotypes of SB.

Keywords

Stress; Suicide; Veterans; GABA; Magnetic Resonance Spectroscopy

Introduction

Suicide is a significant public health concern worldwide with more people dying by suicide than by homicides and wars combined [1]. In 2014, the age-adjusted suicide rate was 13.0 per 100,000 population in the United States [2]. While there is considerable debate regarding whether veterans are at an increased risk for suicide compared to the civilian population [3], there is no doubt that death by suicide is also a significant problem in male and female veteran populations. In 2014, an estimated 20 veterans died by suicide each day [4], suggesting a need for novel suicide prevention strategies in the veteran population. Suicide is a multifactorial phenomenon with several risk factors including mental illnesses and stressful/traumatic life events [5, 6]. Veterans are exposed to stressful events including combat-related trauma, which may contribute to the risk for suicide [7]. Although the biological mechanisms involved in the association between stress and suicide are not clear, converging lines of evidence implicate stress-related changes in brain morphology and neurochemistry in the etiology of suicide [8].

Important sex differences in suicidal behavior (SB) have been reported. For example, females are three times more likely to attempt suicide, but men are four times more likely to die by suicide than women, due in part to the more lethal methods used [9, 10]. Further, childhood trauma showed stronger associations with SB in female veterans as compared to males [11]. In agreement, women have a higher incidence of stress-related disorders such as post-traumatic stress disorder (PTSD) [12], suggesting that females may be more biologically vulnerable to the effects of stress [13]. Given new inclusionary policies, women are increasingly occupying military ranks and serving in combat roles [14]. Thus, it is of paramount importance to identify the neurobiological factors underlying the association between combat stress and suicide in order to develop additional suicide prevention strategies.

The gamma-amino butyric acid (GABA)ergic system may underlie the association between stress and SB given that prior evidence has shown links between GABA and stress responses as well as suicide [15–18]. GABA-related alterations in suicide have been reported at the neurochemical, cellular, and genetic levels [15]. For instance, quantitative polymerase chain reaction (PCR) studies showed that GABA-A receptor organization was altered in the frontal cortex, hippocampus, and amygdala in depressed individuals who died of suicide as compared to those who died due to other causes [19, 20]. Moreover, microarray-based investigations have revealed alterations in several GABAergic genes on a global level in the brain of depressed suicides [21, 22]. Furthermore, rodent and human studies have demonstrated stress-induced alterations in GABA transmission in the frontal cortex. For instance, chronic stress alters GABA-A receptor as assessed by radioligand binding [23], decreases GABA

synthesizing enzymes and GABA bioavailability, and impairs function of specific types of GABA interneurons in the cortex in rodent models [24]. In humans, a positron emission tomography (PET) study showed reduced GABA-A receptor binding in veterans with deployment-related PTSD [25]. Furthermore, lower serum GABA after trauma exposure predict development of PTSD [26]. Finally, a recent study reported that the *GABRA6* gene (encodes the GABA-A receptor alpha-6 subunit) variant plays an important role in mediating the effects of recent stress in the development of suicidal risk-related phenotypes [27]. Specifically, *GABRA6* T carriers showed an increased risk of specific elements of suicide risk after exposure to stressful life events [27]. Importantly, in the absence of stress, GABRA6 T carriers did not exhibit an increased risk for suicide-related phenotypes [27]. Collectively, these studies highlight that GABAergic transmission is dysregulated after stress as well as in suicide; and evidence suggests a complex interaction between the GABAergic system and stress associated with phenotypes related to SB [27].

There exist important sex differences with regard to stress-induced changes in GABAergic transmission [28]. For example, female rats show an increase in low-affinity GABA binding sites after swim stress but males do not [29, 30]. In humans, either a decrease [31] or no change [32] in frontal GABA has been reported in response to acute psychological stress using proton magnetic resonance spectroscopy (^{1}H-MRS). Interestingly, the study that reported no changes in GABA concentration after stress examined only male subjects [32] while the study reporting a decrease included both male and female subjects [31]. Sex differences in stress-induced alterations in the GABAergic system may be partly explained by differential levels of neurosteroids, which are under the control of ovarian hormones and play an important role in the GABAergic regulation of the hypothalamic-pituitary-adrenal (HPA) axis stress response [33]. Overall, these studies imply that there may be sex-specific differences in stress effects on GABA, which may influence the vulnerability of development of stress-related neurobiological disorders including SB.

^{1}H-MRS is an increasingly used non-invasive technique to measure *in vivo* neurochemistry [34]. Recent developments in the technique have made it possible to individually quantify glutamate, glutamine, and GABA, which is unreliable without specialized methods [35–37]. We examined GABA/Cr+PCr differences between SB+ and SB− groups in the ACC since this region has been implicated in imaging studies of suicide. For example, reduced ACC gray matter density measured by voxel-based morphometry was observed in MDD patients at high risk for suicide when compared to non high-risk MDD patients [38]. In addition, a meta-analysis showed increased ACC activation during emotional tasks and reduced ACC activation during cognitive tasks to be associated with SB [39]. In a study of combat-exposed veterans, those with SI showed more engagement of the ACC during error processing as compared to veterans without SI [40].

The purpose of the current study was to characterize the association between SB, stress and GABAergic transmission in the ACC using the ^{1}H-MRS technique in male and female veterans. On the basis of evidence supporting a role for GABA in stress and suicide [24, 26,31], we specifically hypothesized that veterans with SB (SB+) would exhibit lower GABA/Cr +PCr than veterans without SB (SB−). We further explored whether between group difference in GABA/Cr+PCr is related to stress response and sex.

Methods

Participants

Eighty-one veterans (16 females) were enrolled in the study. Participants were recruited from a local VA hospital as well as from the community via flyers. The Institutional Review Boards at the University of Utah and the George E. Wahlen Department of Veterans Affairs (VA) Medical Center approved this study. All subjects provided written informed consent as per the IRB and Declaration of Helsinki. Participants were compensated financially for their time. Combat and non-combat exposed veterans between the ages of 18 and 55, male or female, and of any race or ethnicity were included. Veterans with a history or current diagnosis of depression, PTSD, and substance use disorder were included. Further, we included veterans who were stable on current psychotropic medication regimen for more than 3 months. While it acknowledged that medications may have potential confounding effects the research team felt it would be unethical to ask participants to discontinue medication for the study; therefore, we included participants who were on antidepressants, anxiolytics, mood stabilizers and antipsychotic medications. Exclusion criteria included major sensorimotor handicaps, estimated full scale IQ<80, history of autism, claustrophobia, electroconvulsive therapy, significant medical or neurological illness that may affect cognitive function, with the exception of traumatic brain injury (TBI), and any MRI contraindications. Pregnant or lactating females were excluded. Further, the menstrual cycle was not assessed and laboratory assessments for hormone levels were not completed.

Procedures

Participants completed the Structured Clinical Interview for DSM-IV-TR (SCID-IV-TR), a clinician administered, semi-structured interview to determine general health functioning (GAF) as well as current and past mental health diagnoses [41]. The *Wechsler Abbreviated Scale of Intelligence-Second Edition* (WASI-II) [42] was administered to all participants to assess estimated IQ.

Participants also completed a clinical battery including the Columbia Suicide Severity Rating Scale (C-SSRS) [43], Hamilton Rating Scale for Anxiety and Depression (HAM-A, HAM-D) and the Trauma Symptom Inventory (TSI) [44, 45]. Finally, participants completed a ^{1}H-MRS scan at the visit.

The C-SSRS assesses lifetime presence of SI, plans, intensity of ideation and SA. SA includes an actual attempt, an interrupted attempt, or an aborted/self-interrupted attempt. Constructs on the C-SSRS have been found to be acceptable internal consistency as well as convergent, divergent, and predictive validity and predict SA in a 24-week follow-up period [43].

The TSI scale [46] is a widely used, 100 item self-report measure developed to assess post-trauma symptoms [47]. The TSI is used in the evaluation of acute and chronic posttraumatic symptomatology, including the sequelae of rape, spouse abuse, physical assault, combat experiences, major accidents, and natural disasters, as well as the lasting sequelae of childhood abuse and early traumatic events. The 10 TSI scales are the following: Anxious Arousal (AA), Anger Irritability (AI), Depression (D), Dissociation (Dis), Defensive

Avoidance (DA), Intrusive Experiences (IE), Tension Reduction Behavior (TRB), Impaired Self-reference (ISR), Sexual Concerns (SC), Dysfunctional Sexual Behavior (DSB). The TSI scale demonstrates good internal consistency and convergent validity in civilian as well as veteran populations [48–50].

The HAM-A and HAM-D are widely used rating scales to measure the severity of anxiety and depressive symptoms respectively [44]. It is based on the clinician's interview with the patient and probes symptoms such as depressed mood, guilty feelings, suicide, sleep disturbances, anxiety, and weight loss. Research has demonstrated a validity coefficient of . 85 [51]. The HAM-A is a rating scale developed to quantify the severity of anxiety symptomatology, and it is often used in psychotropic drug evaluations [45].

Magnetic Resonance Spectroscopic Imaging: Acquisition and Analysis

^{1}H-MRS measurements were performed using a 3.0 Tesla Siemens (Erlangen, Germany) Verio™ whole-body MRI scanner. Three-dimensional, high-resolution, magnetization-prepared, rapid gradient echo (MP-RAGE) MR images (TR/TE/TI = 2000/3.53/1100 ms; FOV = 256×256×224 mm; 1 mm isotropic resolution) were obtained to facilitate the positioning of an obliqued MRS voxel (25 × 25 ×30 mm^3) within predominantly gray matter of the ACC. The ^{1}H-MRS voxel was placed midline to primarily cover the dorsal anterior cingulate cortex on midsagittal T1-weighted images, with the anterior ventral edge of the voxel aligned with the centroid of the genu of the corpus callosum (Fig. 1). The MRS voxel was obliqued along the sagittal plane with its smallest dimension spanning the anterior–posterior axis and the largest dimension in the superior-inferior orientation.

Within-voxel B0 shimming was achieved using a manufacturer-supplied phase map procedure in combination with interactive manual shimming until a full-width at half-maximum (FWHM) of ≤ 11 Hz was observed for the real component of the ACC unsuppressed water signal. A PRESS sequence was used to acquire two-dimensional (2D) J-resolved 1H MRS spectra measurements, modified to enable TE stepping: TR/TE range = 2400 / 31–229 ms; signal averages per TE = 4; deltaTE = 2 ms; 3-pulse WET water suppression. The spectral data were obtained using a maximum-echo sampling scheme whereby the analogue-to-digital converter (ADC) on-time was fixed for all 100 TE steps [52]. Outer-volume suppression (OVS) was achieved using six saturation bands positioned at least 1.5-cm away from the MRS voxel faces and band saturation was achieved using hyperbolic secant adiabatic full passage RF pulses. A three-pulse water elimination through T_1-effects (WET [53]) scheme was interleaved with the OVS module for global water suppression. An additional water unsuppressed 2D J-resolved 1H MRS dataset was recorded from each voxel with 2 signal averages recorded for each TE step.

Tissue segmentation

To control for within-voxel tissue variability, skull-stripping and brain tissue-type segmentation was applied to all MP-RAGE images using the Brain Extraction Tools [54] and FAST [55] tools provided with the freely-available FMRIB software library [56]. MATLAB (TheMathWorks, Natick, MA) was used to extract the 3D volume corresponding to the positioned MRS voxel and calculate within-voxel gray matter (GM), white matter (WM) and

cerebrospinal fluid (CSF) tissue content for each subject. The within-voxel GM % was calculated as the ratio to the total brain matter, i.e., 100 X GM/(GM+WM).

MRS data processing

All 2D J-resolved 1H MRS data were quantified using the prior knowledge fitting (ProFit) algorithm without additional line broadening applied prior to spectral fitting. Before the 2D fast Fourier transformation (FFT), the raw 2D matrix was zero-filled to 200 points along the indirectly detected J dimension. The ProFit algorithm fits basis spectra from a total of nineteen metabolites to the raw 2D spectral surface without considering the effects of spatial localization [52, 57]. The basis set comprised of N-acetylaspartate (NAA), glycerophosphocholine (GPC), phosphorylcholine (PC), alanine (Ala), aspartate (Asp), glucose (Glc), glycine (Gly), lactate (lac), N-acetylaspartylglutamate (NAAG), ascorbic acid (Asc), phosphoethanolamine (PE), taurine (Tau), *scyllo*-inositol (sI), total creatine (Cr+PCr), glutamate, glutamine, GABA, myoinositol, and glutathione (GSH). Using identical 2D ^{1}H MRS methodology in 10 healthy volunteers, we previously have reported a within-subject coefficient of variation (CV) of 15 % and a between-subject CV of 24% for ACC GABA normalized to water[58]. All metabolites were expressed as metabolite/water ratios and corrected for the within-voxel CSF fraction using segmented MRI data as previously described [58,35]. All fitted metabolite areas were also normalized to total Cre (Cr+PCr). Metabolite/water and metabolite/Cr+PCr ratios thus are expressed as institutional units (I.u) and presented as the mean ± standard error mean (SEM).

Statistical analysis

Group differences in demographic, clinical and MRS measures between veterans with and without SB were evaluated using Student's *t*-test. One-way ANCOVA was used to adjust for age and sex when analyzing differences in demographic and clinical variables. Pearson's tests were used to assess relationships between clinical variables and neurochemical levels. Further, partial correlations were run with age as covariate. We conducted the correlation analysis in the combined sample rather than segregating participants by SB since symptoms of depression, anxiety, and stress may also exist in the SB− group. This is in line with the Research Domain Criteria (RDoC) approach [59] whereby behavioral constructs are evaluated along a continuum and not by diagnostic categories, which has increasingly been used in several studies [60, 61]. Non-parametric tests (Mann-Whitney U test and Spearman's correlation) were used if the measures failed test for normality, which was tested using the Shapiro-Wilk's test. The correlation analyses were exploratory in nature given the small sample size for female veterans and hence we did not correct for multiple comparisons. Thus, our hypothesis testing should be considered preliminary and not definitive. We used G*Power 3.1 to compute posthoc achieved power given an alpha=0.05 and our sample size. All other analyses were performed in SPSS 20 (IBM, Chicago, IL). *p* values less than 0.05 were considered significant.

Results

Clinical and demographic variables

Clinical and demographic characteristics for each group are shown in Table 1. There were no significant differences between SB+ and SB− groups with regard to age, education and IQ. Further, when adjusted for sex and age, IQ and education were not significantly different between the two groups. When analyzed separately, the female SB+ group did not differ significantly from the female SB− group with regard to age, education and IQ (p>0.05). As expected, the SB+ group had significantly higher scores of depression and anxiety on the HAM-D and HAM-A respectively, as compared to the SB− group. The scores on each of the TSI subscales were also significantly different between the two groups (SB+>SB−). When sex and age were included as covariates, the difference in HAM-A, HAM-D, and TSI subscales between the two groups continued to remain significant (p<0.05).

Tissue segmentation

Figure 1 displays tissue-segmented axial and sagittal images extracted from a 3D MP-RAGE dataset recorded from a single HC subject. Table 2 displays the within-voxel GM and WM content for both subject cohorts. We did not find significant differences between the two groups. Further, the CSF content within the ACC did not differ between the two groups (p=0.42). Within female veterans, the GM, WM, and CSF content did not differ significantly between the SB+ and SB− groups.

Group differences in metabolite ratios

Cr+PCr/H2O ratio did not exhibit significant differences between groups. When data was analyzed separately for females, we did not observe significant differences in Cr+PCr/H2O ratios between the SB+ and SB− groups. This was also true for when age was added as a covariate. Thus, Cr+PCr was used as a non-biased internal standard (denominator) and GABA/Cr+PCr was used as an outcome measure for this study.

No significant differences were found in the levels of GABA/Cr+PCr (t=0.12, p=0.9, Table 3) between SB+ and SB− groups. Ratios of other key metabolites are also reported (Tables 3, S1). However, when data was analyzed separately for males and females, we observed that female veterans with SB had lower GABA/Cr+PCr as compared to female veterans without SB (t-ratio=−2.35, p=0.039, Fig. 2, Table 3). When age was added as a covariate, the p value approached significance (p=0.06).

Correlation between GABA/Cr+PCr and clinical characteristics

In the SB+ group, we observed a trend towards a negative correlation between GABA/ Cr +PCr and TSI-DA subscale (Spearman's rho=−0.27, p=0.06, Fig. 3A). Interestingly, the relationship between GABA/Cr+PCr and the TSI-DA subscale was opposite in the SB− group (Spearman's rho=0.44, p=0.05, Fig. 3B). When age was included as a covariate, the relationship between GABA/Cr+PCr and the TSI-DA subscale approached significance in the SB+ (Spearman's rho=−0.25, p=0.08) group; however, the significant relationship was lost in the SB− group (Spearman's rho=0.35, p=0.1).

Since we observed significant group differences in GABA/Cr+PCr ratio in female veterans, we performed an exploratory analysis to investigate any potential relationship between GABA and clinical variables in female veterans. Significant negative relationships were observed between GABA/Cr+PCr and TSI-AA (Pearson's correlation coefficient=−0.6, p=0.03, Fig. 4A), TSI-AI (Pearson's correlation coefficient=−0.596, p=0.03, Fig. 4B), HAM-D (Pearson's correlation coefficient=−0.576, p=0.04, Fig. 4C), and C-SSRS scores (Spearman's rho=−0.53, p=0.05, Fig. 4D). With age as a covariate, the relationship between GABA/Cr+PCr and TSI-AA (Pearson's correlation coefficient=−0.66, p=0.02), TSI-AI (Pearson's correlation coefficient=−0.79, p=0.002) continued to remain significant while the correlation between GABA/Cr+PCr and HAM-D (Pearson's correlation coefficient=−0.54, p=0.07), and C-SSRS scores (Pearson's correlation coefficient=−0.53, p=0.07) showed a trend towards significance. Further, the negative association between GABA/Cr+PCr and HAM-A (Spearman's rho=−0.48, p=0.09), TSI-DA (Spearman's rho=−0.52, p=0.07) approached significance in our cohort of female veterans. With age included as a covariate, the association between GABA/Cr+PCr and the TSI-DA subscale (Spearman's rho=−0.57, p=0.05) was significant while the GABA/ Cr+PCr and HAM-A correlation (Spearman's rho=−0.5, p=0.09) continued to show a modest trend towards significance.

Power analysis

The final sample size had high power (1-β >0.90) to detect 1 large (d=0.8) and medium effect sizes (d=0.5) and medium power (1-β =0.72) to detect a small effect size (d=0.3).

Discussion

To the best of our knowledge, this is the first ^{1}H-MRS study in the ACC in veterans with SB. Specifically, we observed decreased ACC GABA/Cr+PCr in the female SB+ group (vs. female SB− group). Our results also indicated opposite direction of correlation between GABA/Cr+PCr and the TSI-DA in veterans with and without SB, though the correlation in SB+ only approached significance. In addition, we found significant negative correlations between GABA/Cr+PCr and clinical variables such as HAM-D, TSI-AI, TSI-AA, and C-SSRS scores in female veterans, suggesting that GABA/Cr+PCr in ACC may be sensitive to variation along a continuum of subclinical to pathologic depressive and stress symptoms. Caution is warranted in interpreting the findings given the small sample size of female veterans. Further, the ratio of male to female veterans in the study was significantly skewed towards males. These findings will have to be replicated in a larger cohort of female veterans as well as in a sample of equally distributed male and female veterans to draw firm conclusions.

Nonetheless, these results add to a burgeoning body of literature that has suggested a prominent role for GABA dysregulation in suicide [15]. GABA, the major inhibitory neurotransmitter is important in modulating excitation in the brain by controlling the firing rate of intrinsic cortical neurons [62]. Studies have reported alterations in GABA receptor subunit genes, as well as down regulation of GABA-A receptor in postmortem brain analyses of suicide decedents [19, 20]. Despite this evidence, studies reporting on *in vivo* brain GABA in individuals at high risk for suicide are scarce. Thus far, only two ^{1}H-MRS studies

have investigated *in vivo* brain GABA in individuals with SB [63, 64] but none involved a veteran population. Moreover, neither of the studies reported significant alterations in GABA/Cr+PCr in those with SB. The brain regions of interest in these studies were the dorsal prefrontal cortex [63] and the hippocampus [64] and neither of the studies analyzed MRS data separately by sex. Thus it may be possible that reduced GABA/Cr+PCr in female veterans with SB observed in the current study is specific to the ACC and the female sex. Importantly, we did not observe alterations in NAA/H2O and Cre/H2O, which are often seen in pathologies involving neuronal loss [65–67]. Thus, reduction in GABA may not be secondary to cell loss but instead may involve abnormalities in GABA synthesis and metabolism. Overall this is the first report to suggest that reduced ACC GABA/Cr+PCr ratio may play a role in heightened suicide risk in female veterans.

ACC GABA/Cr+PCr showed a trend-level negative correlation with the TSI-DA subscale in the SB+ group as opposed to a positive relationship between the two variables in the SB− group. The DA subscale measures posttraumatic cognitive and behavioral avoidance. Thus, the above results suggest that stress/trauma shows a trend towards affecting ACC GABA/Cr +PCr differently in veterans with and without SB, which may underlie higher scores of TSI-DA in veterans with SB.

Dysfunction of the GABAergic system has been implicated in depression, which is related to stress-related psychopathology and SB [15]. In support, we observed that ACC GABA/Cr+PCr ratios were inversely correlated with C-SSRS, TSI-AA, TSI-AI, and HAM-D scores in females. A negative correlation between C-SSRS scores and GABA is concordant with reduced GABA in female veterans with SB. The TSI-AA scale taps into symptoms of anxiety, including those associated with posttraumatic hyperarousal and the TSI-AA scale measures angry or irritable affect in the context of trauma [48]. Structural and functional neuroimaging studies have consistently implicated the ACC in mediating anxiety [68], hyperarousal and emotion dysregulation symptoms in response to stress/trauma [69, 70]. Thus, it seems logical to find a relationship between ACC neurochemistry and psychological mechanisms that influence responses to stress/trauma. Moreover, we also observed a negative correlation between GABA/Cr+PCr and HAM-D scores, which is largely consistent with the literature implicating GABAergic dysfunction in major depression. For example, MRS studies in depressed adults and adolescents exhibited GABA deficits in the brain [61, 71]. Decreased GABA has also been observed in the plasma [72] and CSF [73] of depressed individuals. Importantly, lower GABA has been associated with treatment resistant depression [74], which is characterized by more severe outcomes such as suicide. Finally, a recent study in depressed patients by Brennan and colleagues showed a significant association between the clinical response to citalopram at day 42 with a greater increase (or lesser decrease) in GABA/Cr+PCr in the ACC from baseline to day 3 and day 7 of treatment [75]. Thus, an antidepressant response is associated with early increases in GABA in the ACC, implicating reduced ACC GABA in the etiology of depressive symptoms. Taken together, these results suggest that deficits in ACC GABA associated with increased stress and depressive symptomatology may be a potential neurobiological explanation for the role of stress and trauma in promoting SB, at least in females.

The current study suggests that there may exist sex differences in the role of GABAergic transmission in SB; however, findings need to be replicated in a larger cohort. We found reduced GABA/Cr+PCr in the ACC in the female SB+ group when compared to the female SB− group. However, this finding was not observed for male veterans. Women, especially veterans have been under-represented in suicide research till date. Genetic and neurobiological differences may exist in SB between males and females. For instance, a genomics study investigating genes that change in expression between women with no SI and women with high SI showed that a number of biomarkers for SI change in the opposite direction than observed in men [76]. Sex differences in neurobiology underlying suicidality merits more attention and may be a first step in the direction of individualized/personalized medicine.

Several limitations need to be considered in the interpretation of the results. First, the sample size of female veterans was small, therefore the findings must be considered preliminary and the results must be replicated in studies with larger sample sizes and multiple testing procedures. The present study remains subject to the possibility of Type 1 error and larger populations will allow more rigorous statistical testing. Second, GABA neurotransmission is tightly regulated by the menstrual cycle in females [77]. The current study did not match female participants for menstrual cycle stage. Thus, it is possible that menstrual cycle stage may have affected the differences in GABA/Cr+PCr between the two groups. Third, veterans in the current study were not asked to stop taking prescription medications for ethical reasons and some participants suffered from substance use. Thus, we cannot rule out the confounding effects of medications and drugs of abuse on the observed differences. Fourth, GABA is an important neurochemical correlate of depression [78], anxiety [79], and PTSD [80], and the current cohort included participants with these disorders. Thus, the presence of past and/or current co-morbidities within the two groups may be potential confounds in the present study. Future studies should address this limitation by including both patient control and healthy control groups and rigorous assessments of illness severity across diagnostic domains. This study design will enable us to determine which neurochemical changes are due to the diathesis for SB and which are related to primary psychiatric disorders. Finally, the coefficient of variance (CV) for metabolite ratios to Cr+PCr in the ACC were higher than previously reported [52], which may reflect the heterogeneity of the population and hence the negative findings for other metabolites should be interpreted with caution.

In summary, this pilot study reports three preliminary findings. First, ^{1}H-MRS GABA/Cr +PCr in the ACC was reduced in female veterans with SB. Second, the direction of association between GABA/Cr+PCr and the TSI-DA was opposite in SB+ and SB− groups. Finally, in females, a number of TSI subscales and HAM-D showed a negative correlation with ACC GABA/Cr+PCr. The current study motivates future investigations into sex differences in the neurobiological underpinnings of SB as well as the association between stress/trauma and SB in a larger cohort of female veterans.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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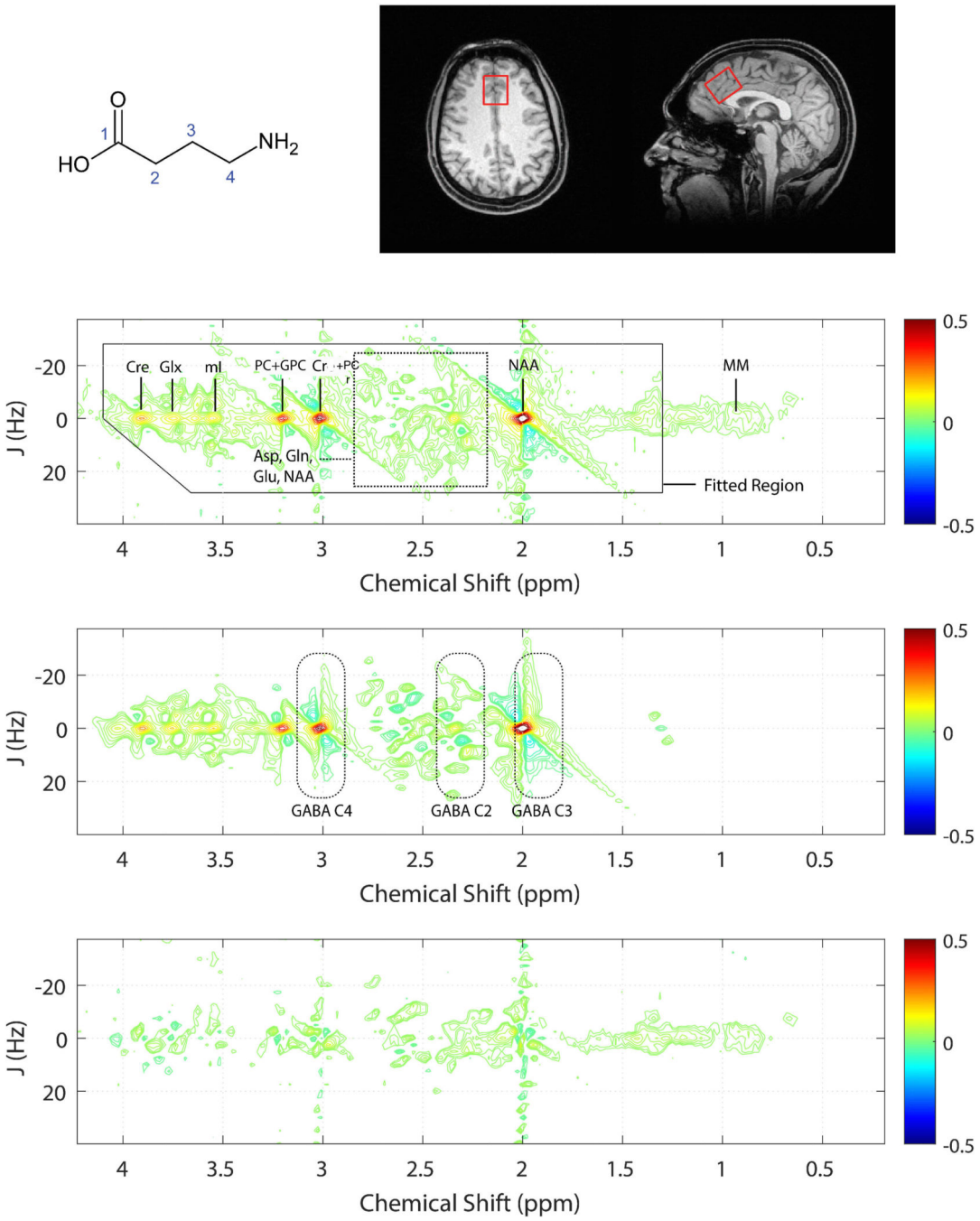

Figure 1.

Top left: GABA structure, Top right: Axial and mid-sagittal slices extracted from a tissue-segmented 3D MP-RAGE MRI dataset recorded from a single subject. Red rectangle depicts the positioning of the MRS voxel in the ACC. Fitted (top), raw (middle) and residuals (bottom) 2D-J 1H-MRS spectra analyzed using Prior Knowledge Fitting (ProFit). Dashed boxes indicate the 2D spectral regions where the GABA protons resonate. The color bars to the right show contouring amplitudes and signal phase. The raw data displayed shows

tentative signal assignments for the dominant metabolite resonances as well as macromolecules (MM).

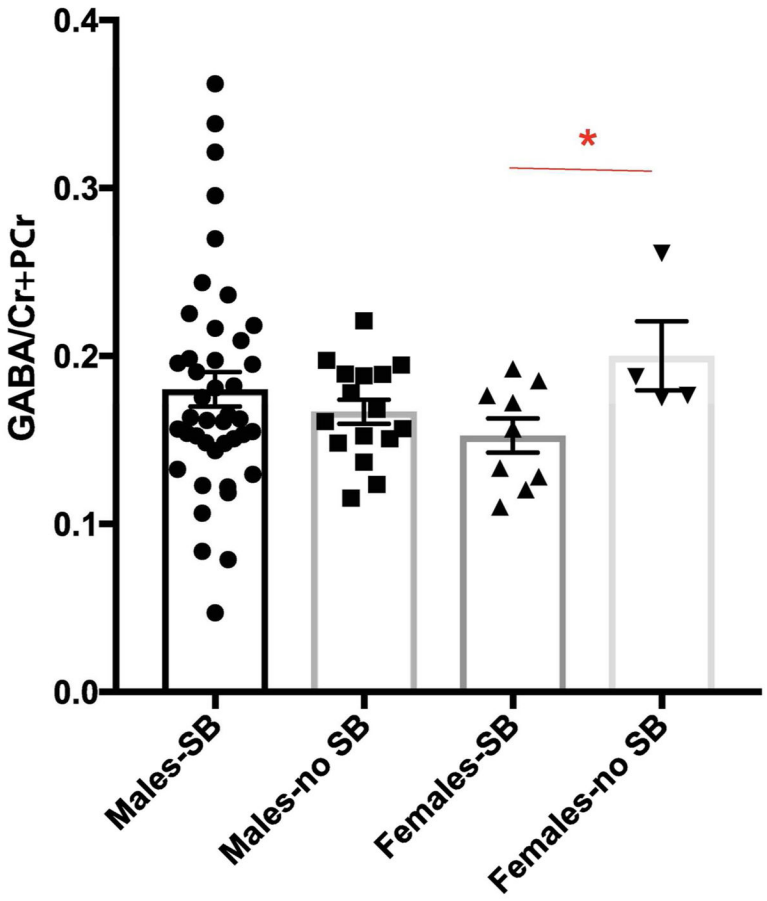

Figure 2.
The GABA/Cr+PCr ratio was significantly lower in female veterans who endorsed SB when compared to those who did not. * indicates $p<0.05$. Data is represented as mean ± S.E.M.

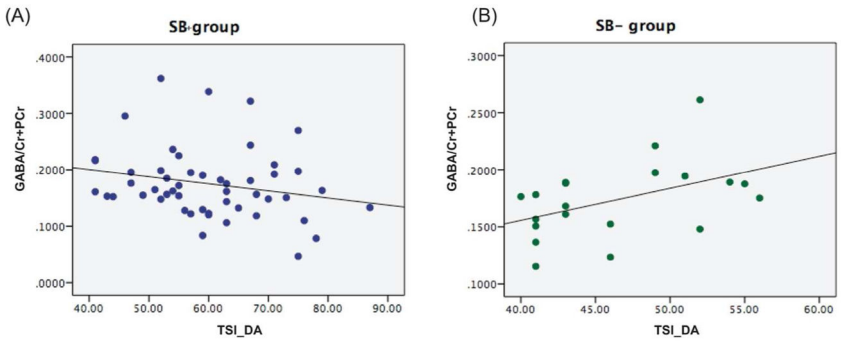

Figure 3.

Correlation of GABA/Cr+PCr and Defensive Avoidance (DA) subscale on the Trauma Symptom Inventory (TSI) measure in (A) SB+ group (B) SB− group.

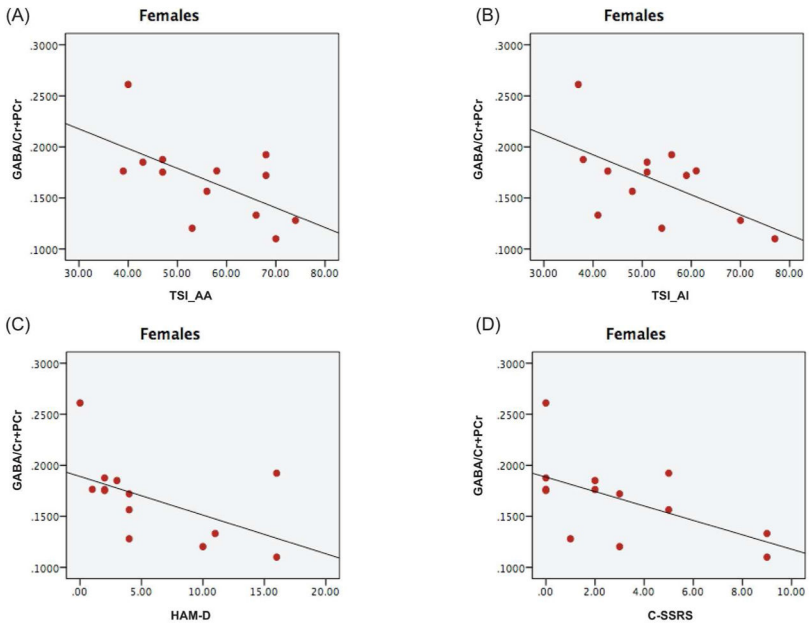

Figure 4.

Correlation of GABA/Cr+PCr and (A) Anxious Arousal (AA) subscale (B) Anger Irritability Subscale (AI) of the TSI measure (C) HAM-D scores (D) C-SSRS in female veterans.

Table 1

Demographic and clinical variables represented as mean ± S.D. (WASI=Wechsler Abbreviated Scale for Intelligence, HAM-D=Hamilton Rating Scale for Depression, HAM-A= Hamilton Rating Scale for Anxiety, TSI=Trauma Symptom Inventory, AA= Anxious Arousal, D=Depression, AI=Anger Irritability, TRB= Tension Reduction Behavior, IE= Intrusive Experience, DA=Defensive Avoidance, Diss= Dissociative Behavior, ISR= Impaired Self-Reference)

	SB+	**SB−**	***p*-value**
Sex	46 males, 11 females	19 males, 5 females	
Age	37.2 ± 9.1	36.2 ± 9.7	0.62
Education	15 ± 2.2	14.7 ± 1.7	0.57
WASI-IQ	110.8 ± 9.6	114.3 ± 11.1	0.16
HAM-D	9.8 ± 7.5	1.9 ± 2.5	<0.001**
HAM-A	10.1 ± 8.3	3.0 ± 4.1	<0.001**
TSI-AA	58.8 ± 11.7	48.1 ± 8.6	<0.001**
TSI-D	60.4 ± 11.5	46 ± 7.1	<0.001**
TSI-AI	56.7 ± 11.7	44.4 ± 6	<0.001**
TSI-TRB	58.3 ± 14	47.1 ± 4.3	<0.001**
TSI-IE	62.3 ± 12.5	50.6 ± 5.9	<0.001**
TSI-DA	59.9 ± 11.1	47.6 ± 6.2	<0.001**
TSI-Diss	59 ± 11.9	49.7 ± 7	<0.001**
TSI-ISR	58.7 ± 10.5	45.4 ± 5.5	<0.001**

Table 2

Tissue Fractions (GM and WM) calculated for both groups and brain regions under investigation. Values are expressed as expressed as group mean % fraction ± SD.

Brain Region	Group	GM	WM	p-value
ACC	SB+	69.44 ± 5	30.55 ± 5	0.52
	SB−	70.22 ± 3	29.78 ± 3	

Table 3

Key metabolite concentrations normalized to creatine in the ACC (mean ± standard error)(Institutional units).

	Male-SB+	Male-SB−	Female-SB+	Female-SB−	*p* value (SB+ vs.SB−)	*p* value (males SB+ vs.males SB−)	*p* value (females SB+ vs.females SB−)
NAA/Cr+PCr	1.34 ± 0.02	1.36 ± 0.04	1.41 ± 0.03	1.40 ± 0.07	0.79	0.76	0.92
GABA/Cr+PCr	0.18 ± 0.01	0.17 ± 0.007	0.15 ± 0.01	0.2 ± 0.02	0.9	0.44	0.04 *
Gln/Cr+PCr	0.26 ± 0.01	0.27 ± 0.03	0.22 ± 0.02	0.25 ± 0.006	0.35	0.49	0.37
Glu/Cr+PCr	1.12 ± 0.02	1.12 ± 0.03	1.15 ± 0.03	1.12 ± 0.12	0.99	0.86	0.73

NAA: N-Acetylaspartate, Cr+PCr: Creatine+phosphocreatine, GABA: Gamma amino butyric acid, Gln: Glutamine, Glu: Glutamate,

* indicates significance (t-test)