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Resting Metabolic Activity in the Cingulate Cortex and Vulnerability to Posttraumatic Stress Disorder

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Abstract

Context—Recent neuroimaging research has revealed functional abnormalities in the anterior cingulate cortex, amygdala and hippocampus in posttraumatic stress disorder (PTSD).

Objective—To determine whether resting functional abnormalities found in PTSD are acquired characteristics or familial risk factors.

Design—Cross-sectional design including identical twins discordant for trauma exposure.

Setting—Academic medical center.

Participants—Combat-exposed veterans with PTSD (n=14) and their identical, combat-unexposed co-twins (n=14), as well as combat-exposed veterans without PTSD (n=19) and their identical, combat-unexposed co-twins (n=19).

Main Outcome Measures—We used positron emission tomography and [18F]-fluorodeoxyglucose to examine resting regional cerebral metabolic rates for glucose (rCMRglu).

Results—Veterans with PTSD and their co-twins had significantly higher resting rCMRglu in dorsal anterior cingulate/mid cingulate cortex (dACC/MCC) compared to non-PTSD veterans and their co-twins. Resting rCMRglu in dACC/MCC in the combat-unexposed co-twins was positively correlated with combat exposure severity, PTSD symptom severity, and alcohol use in their exposed twins.

Conclusions—Enhanced resting metabolic activity in dACC/MCC appears to represent a familial risk factor for developing PTSD after exposure to psychological trauma.

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Keywords

stress disorders; post-traumatic; twins; monozygotic; positron-emission tomography; fluorodexoyglucose F18; metabolism; cingulate gyrus

Neuroimaging studies of post-traumatic stress disorder (PTSD) have reported functional abnormalities in several brain regions, including anterior cingulate cortex (ACC), amygdala, and hippocampus. The ACC is a medial prefrontal structure consisting of several functional subdivisions.[1, 2] In healthy individuals, rostral regions of the ACC (rACC) are activated during emotional states and tasks that involve interference from emotional stimuli.[3–8] In contrast, dorsal regions of the ACC (dACC) have traditionally been thought to be involved in multiple cognitive processes such as performance monitoring, response selection, error detection, and decision making,[5, 6, 9, 10] although a role for the dACC in fear learning has recently been reported.[11] In PTSD, the rACC is hyporesponsive to trauma-related and other emotionally negative stimuli[12–23] and is hypoactive at rest.[24] In addition, rACC activation appears to be inversely related to PTSD symptom severity.[19, 21, 25] In contrast, the dACC appears to be hyperresponsive during fear conditioning, interference, and auditory oddball tasks in PTSD.[23, 26–28]

The amygdala is a medial temporal lobe structure that is involved in the detection of potential threat or biologically relevant predictive ambiguity in the environment.[29–31] In PTSD, the amygdala appears to be hyperresponsive during exposure to both trauma-related stimuli[32–38] and trauma-unrelated, emotional stimuli,[19, 21, 23, 39] as well as during the performance of neutral tasks,[24, 27] and even at rest.[40] Amygdala activation has been shown to be positively correlated with PTSD symptom severity[36, 37, 39, 41] and self-reported anxiety.[34]

The hippocampus is involved in explicit memory processes, as well as memory for fear extinction and context in Pavlovian fear conditioning.[42–45] Diminished hippocampal activation in PTSD has been observed during symptomatic states,[12, 13] administration of the alpha-2-antagonist yohimbine,[46] and memory tasks involving words, passages, or spatial locations.[47–50]

Most functional neuroimaging studies of PTSD have involved the examination of brain activation during symptom provocation or cognitive tasks. Fewer studies have examined resting brain activity in PTSD,[24, 40, 46, 51–53] and their findings have been inconsistent. Nearly all previous resting-state studies have measured regional cerebral blood flow using single photon emission computed tomography (SPECT) or positron emission tomography (PET). Only two previous PET studies have examined regional cerebral metabolic rates for glucose (rCMRglu) at rest in PTSD. One such study reported diminished rCMRglu in the temporal cortex in PTSD.[46] The other study found diminished rCMRglu in cingulate gyri, hippocampus, and insula among other regions, and increased rCMRglu in cerebellum, fusiform, temporal, and occipital cortices.[53]

The origin of functional neuroimaging abnormalities in PTSD is largely unknown. It is tempting to conclude that because PTSD is defined as a result of traumatic life event, all abnormalities associated with it were also caused by the event. However, PTSD is moderately heritable.[54–56] We studied identical twins who are discordant for combat exposure to determine whether resting rCMRglu abnormalities found in PTSD represent acquired signs of the disorder or familial risk factors for developing it upon traumatic exposure. Vietnam combat veterans with and without PTSD, as well as their combat-unexposed identical co-twins (without PTSD) were studied. We reasoned that resting

rCMRglu abnormalities found in the combat veterans with PTSD but not in their identical co-twins would reflect acquired characteristics of PTSD, whereas resting rCMRglu abnormalities present in both the combat veterans with PTSD and their co-twins would represent familial risk factors. Based on the studies reviewed above, we hypothesized that combat veterans with PTSD would show lower rCMRglu in rACC and hippocampus, and higher rCMRglu in dACC and amygdala compared to veterans without PTSD. However, given the dearth of informative research, we had no hypotheses regarding whether any rCMRglu abnormalities found to be associated with PTSD would represent acquired signs or risk factors. We chose to use PET over SPECT due to its superior spatial resolution. Measures of rCMRglu are closely coupled to neuronal function.[57]

Methods

Participants

Participants were drawn from a pool of identical twins who had participated in a previous study of physiological responses to loud tones. A description of the recruitment strategy and characteristics of the participant population has been reported elsewhere.[58] Thirty-three pairs of male monozygotic twins participated (66 participants in total). One "exposed" (Ex) twin had served in the Vietnam combat theater, whereas his "unexposed" (Ux) co-twin had not. Of the Ex twins, 14 developed current combat-related PTSD (P+), and 19 never did (P −), as determined by the Clinician Administered PTSD Scale (CAPS)[59] using criteria from the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV).[60] Thus, there were four participant cells as follows: *ExP+*: combat-exposed veteran with current, combat-related PTSD (n=14), and *UxP+*: his combat-unexposed co-twin (without PTSD) (n=14); as well as *ExP−*: combat-exposed veteran who never had combat-related PTSD (n=19), and *UxP−*: his combat-unexposed co-twin (also without PTSD) (n=19). The study was approved by the Partners Healthcare System (Boston, MA) Institutional Review Board. Written informed consent was obtained from each participant after a full explanation of the procedures.

Demographics and Psychometrics

Fifty-six participants were right-handed, and 3 (1 ExP+; 2 ExP−) were left-handed. (Handedness information was missing for 1 ExP+, 2 ExP−, 2 UxP+, 2UxP−.) None of the participants reported a history of major head injury involving loss of consciousness for more than 10 minutes, tumor, epilepsy, cerebrovascular accident, or other neurological disorder.

According to the Structured Clinical Interview for DSM-IV (SCID),[61] participants in the ExP+ group met criteria for the following current comorbid diagnoses: major depression (n=4), dysthymia (n=2), panic disorder (n=1), social phobia (n=3), specific phobia (n=1), GAD (n=1), eating disorder (n=1), alcohol dependence (n=1), and substance use disorder (n=2). Participants in the other groups met criteria for the following current diagnoses: major depression (n=1 in UxP+), dysthymia (n=1 in ExP− and n=2 in UxP−) social phobia (n=1 in UxP+), specific phobia (n=1 in UxP+ and n=1 in ExP−), eating disorder (n=1 in ExP −), alcohol dependence (n=1 in UxP+; n=2 in UxP−).

Thirteen participants (5 ExP+, 3 UxP+, 2 ExP−, 3 UxP−) were taking antidepressants at the time of study. Two (1 ExP+ and 1 UxP+) were taking benzodiazepines. These medications were included among the potentially confounding medications or drugs that were excluded in a sub-analysis reported below. Potentially confounding drugs or medications were defined as: antihistamines, sympathomimetics, sympatholytics, parasympathomimetics, parasympatholytics, skeletal muscle relaxants, hypotensive agents, vasodilating agents, pressor agents, beta-blockers, antiarrhythmics, calcium channel blockers, narcotics,

anticonvulsants, antidepressants, neuroleptics, benzodiazepines, other psychotherapeutic agents, cerebral stimulants, sedatives, and hypnotics.

Participants completed the Beck Depression Inventory (BDI),[62] the Michigan Alcohol Screening Test (MAST),[63] the Childhood Trauma Questionnaire (CTQ),[64] the Positive and Negative Affect Schedule (PANAS),[65] and a measure of the severity of combat exposure.[66] The latter scale, which has good reliability and validity, assesses the extent to which the veteran had experienced a variety of different situations in combat, including being wounded, ambushed, captured, etc.[66] (See Table 1 for demographic and clinical information.)

PET-FDG Procedures

The PET equipment and procedures have been described previously.[67] Participants were instructed to fast at least 6 hours prior to PET scanning. Blood glucose levels were checked immediately before intravenous administration of [18F]-fluorodeoxyglucose (FDG) (approximately 185 MBq, 5 mCi). Then each participant was instructed to sit quietly with eyes closed in a dedicated waiting room for a 40-minute uptake period. The participant was then escorted to an adjacent room that housed the HR+ PET scanner (CTI/Siemens Medical Solutions), which had an in-plane and axial resolution of 4.5 mm FWHM (full-width at half-maximum intensity), 63 contiguous slices with 2.5 mm separation, and a sensitivity of 200,000 cps/microcurie/mL [two dimensional (2D)] and 900,000 cps/microcurie/mL (3D). After entering the scanner, each participant's head was fitted with an inflatable cushion to minimize movement and aligned in the scanner relative to the canthomeatal line.

Magnetic Resonance Imaging (MRI) Procedures

Structural MRI scans were obtained from a Symphony/Sonata 1.5 Tesla whole body high-speed imaging device equipped for echo planar imaging (EPI) (Siemens Medical Systems, Iselin NJ) with a 3 axis gradient head coil. Head movement was restricted using expandable foam cushions. After an automated scout image was acquired and shimming procedures were performed to optimize field homogeneity, high-resolution structural MRI images (3D MPRAGE; TR/TE/flip angle=2.73sec/3.31ms/7°) with a 1.33 mm slice thickness were collected. Functional MR images were subsequently collected for separate studies, the results of which are to be reported elsewhere. PET scans preceded MRI scans by one day.

Data Analysis

Two types of analyses were employed: (1) those conducted on whole-brain voxelwise PET-FDG data and (2) those conducted on PET-FDG data extracted from functional regions of interest (ROIs). These two different types of data required somewhat different but parallel, two-factor analytic strategies. Conceptually speaking, in both types of analyses, we treated Exposed versus Unexposed co-twins as a repeated measure (i.e., Exposure). The twin pairs in which the combat-exposed twin had PTSD (P+) were treated as a separate group from the twin pairs in which the exposed twin never had PTSD (P−). We reasoned that a significant difference between these two groups (i.e., Main effect of PTSD Diagnosis) would be consistent with a familial risk factor (as long as there was also no interaction between PTSD Diagnosis and Exposure); in this case, the combat-exposed twin with PTSD (ExP+) would have the same functional abnormality as his unexposed co-twin without PTSD (UxP+). (Follow-up analyses were conducted to confirm differences between ExP+ and ExP− subgroups, and between UxP+ and UxP− subgroups.) A significant PTSD Diagnosis by Exposure interaction (reflecting an abnormality in the exposed twins with PTSD only) would indicate an acquired sign of PTSD. Lastly, a difference between all combat-exposed twins as compared to all combat-unexposed twins (i.e., a main effect of Exposure) in the

absence of an interaction would suggest that a functional abnormality is associated with exposure to combat and not PTSD per se.

Voxelwise Analyses—The whole-brain voxelwise analyses were conducted using the Statistical Parametric Mapping 2 (SPM2) software package (Wellcome Department of Cognitive Neurology, London, UK). Within SPM2, each participant's PET image was coregistered to his high-resolution structural MRI image. The resulting images were spatially normalized in a standard stereotactic space (Montreal Neurological Institute, MNI) and then smoothed (6mm FWHM). At each voxel, the rCMRglu data were normalized by the global mean and fit to a linear statistical model by the method of least squares. Hypotheses were tested as contrasts in which linear compounds of the model parameters were evaluated using *t* statistics, which were then transformed to *z*-scores.

We used an approach that consisted of two hierarchical levels of analysis, in which the second level's random-effects analysis absorbed the random effects from the first level. For the purpose of examining the main effect of PTSD Diagnosis, for each pair, the rCMRglu values of the Ex and Ux participants were averaged (first level), and then the P+ and P− pairs were contrasted (second level). For the purpose of examining the PTSD Diagnosis x Exposure interaction, for each pair, the rCMRglu values of the Ex and Ux participants were subtracted one from the other (first level), and then the P+ and P− pairs were contrasted (second level). For the purpose of examining the main effect of combat Exposure, the rCMRglu values of the Ex and Ux subjects were contrasted (first level only).

The statistical parametric maps resulting from the above voxelwise analyses were inspected for the main effect of PTSD Diagnosis, main effect of Exposure, and the PTSD Diagnosis x Exposure interaction in our a priori structures of interest (dACC, rACC, amygdala, hippocampus). The amygdala and hippocampus were defined by their anatomical boundaries, as visualized on the MNI structural MRI (T1) template within SPM. The superior and lateral boundaries of the ACC were also defined anatomically. The dACC was defined as the portion of the anterior cingulate gyrus superior to the corpus callosum, between y= 0 and y= +30mm.[68] The rACC was defined as the portions of the anterior cingulate gyrus that are anterior to the genu of the corpus callosum and where y>30mm. (Most, although not all, previous findings of diminished function in ACC in PTSD have occurred at y> 30mm.) Given our strong hypotheses, we applied a significance threshold of uncorrected, two-tailed $p < 0.001$ (z-score>3.29) to rCMRglu differences found in these structures. (Because the procedure of correcting p values based upon region size is biased toward finding significance in small structures, we chose to employ the above stated constant significance threshold.) To regions about which we had no a priori prediction, we applied a more conservative constant significance threshold of uncorrected, two-tailed $p < 0.00001$ (z-score>4.42).

Region of Interest Analyses—We extracted rCMRglu data from clusters surrounding significant voxels identified the SPM analyses. We then analyzed these clusters for the main effect of PTSD Diagnosis, main effect of Exposure, and their interaction using a mixed model that treated combat Exposure as a within-pairs repeated measure, Diagnosis as a between-pairs measure, and twin pairs as a random effect,[69] including the covariates described under Results. Additional correlational analyses were performed on the ROI data as appear below.

Results

Voxelwise Analyses

No voxels met significance thresholds for a main effect of Exposure or a PTSD Diagnosis x Exposure interaction. However, there were significant main effects of PTSD Diagnosis in the dACC, midcingulate cortex, and left inferior parietal cortex (Table 2). In each case, combat-exposed veterans with PTSD (ExP+) and their unexposed co-twins (UxP+) (combined) exhibited greater rCMRglu than combat-exposed veterans without PTSD (ExP−) and their unexposed co-twins (UxP−) (combined). With one exception, these results remained significant when we temporarily removed from the voxelwise analyses data from (1) participants with current mood disorders or substance use disorders (all z-scores > 3.80) (2) participants taking potentially confounding medications (as defined above) (all z-scores > 3.77), or (3) participants who were left-handed or with missing handedness information (all z-scores > 4.41). The exception was that the z-score of the left inferior parietal finding dropped below threshold after the above participant exclusions; for this reason, this brain region is not considered further below. No voxels exhibited significantly lower rCMRglu in the PTSD twin pairs (i.e., ExP+ and UxP+ groups) relative to the non-PTSD twin pairs (i.e., ExP− and UxP− groups). Comparisons between subgroups (ExP+ vs. ExP− and UxP+ vs. UxP−) are presented in Table 3 and are consistent with the main effect of PTSD Diagnosis.

Region of Interest Analyses

Dorsal Anterior Cingulate/Midcingulate Cortex—Inspection of the statistical parametric maps revealed that the most significant voxels in dACC and midcingulate cortex were part of a common cluster of k=109 voxels, henceforth designated the “dorsal anterior cingulate/midcingulate cortex” (dACC/MCC) ROI and shown in Figure 1, along with a bar graph of group means and standard errors. Individual subjects’ values from this ROI were extracted and plotted by pairs in Figure 2. The within-pair correlation across PTSD and non-PTSD groups was r=0.73, $p<10^{-6}$, indicating a high degree of familiality of the measure. (For non-PTSD subjects alone, r=0.71, p<0.001; for PTSD subjects alone, r=0.41, p=0.07. These correlations were not significantly different from each other, p=0.25)

For the dACC/MCC rCMRglu ROI, the PTSD main effect yielded F(1, 31.2)=18.0, p=0.0002. The following covariates were screened as potential confounders of this result by examining their association with the dependent measure using a screening threshold of p<. 0.20: weeks premature, birth weight, age, total score on the CTQ, education, BDI score, MAST score, PANAS scores, and severity of combat exposure (in the Ex twin). Only combat severity met this threshold. Adjusted for combat severity, the PTSD main effect yielded F(1, 30.4)=7.8, p=0.009. Parallel analyses in combat-exposed participants (ExP+ vs. ExP−) alone indicated that only birth weight and combat severity passed screening as potential confounders. Unadjusted, the PTSD main effect yielded F(1,31)=11.5, p=0.002; adjusted for birth weight, F(1,27)=9.2, p=0.005; adjusted for combat severity, F(1,30)=5.0, p=0.03. Parallel analyses in combat-unexposed participants (UxP+ vs. UxP−) alone indicated that only MAST score and combat severity passed screening as potential confounders. Unadjusted, the PTSD main effect yielded F(1,31)=28.2, p<0.0001; adjusted for MAST score, F(1,27)=28.2, p=0.0001; adjusted for combat severity F(1,30)=10.1, p=0.004.

Correlational Analyses with Clinical Variables—Significant correlations between dACC/MCC rCMRglu in the Ux co-twins and other variables of interest included: their *own* MAST scores: r=0.53, p=.003; their *Ex twins*’ MAST scores: r=0.38, p=0.04; their *Ex twins*’ combat severity scale scores: r=0.49, p=0.004; and their *Ex twins*’ lifetime CAPS

scores: r=0.64, p=0.0001 (Figure 3). The last of these correlations adjusted for Ex twins' MAST and combat severity scores yielded: partial r=0.53, p=0.003.

Discussion

The results presented here showed greater resting rCMRglu, indicative of greater resting metabolic activity, in the dorsal anterior cingulate/mid cingulate cortex of the combat exposed veterans with PTSD and their identical, combat-unexposed co-twins, compared with the combat-exposed veterans without PTSD and their co-twins. This finding remained significant after adjusting for potentially confounding factors. The finding of dACC/MCC hypermetabolism in combat veterans with PTSD is consistent with previous findings of increased activation in these structures in PTSD singletons,[23, 26–28] and further suggests that this functional abnormality may be a risk factor rather than an acquired characteristic of PTSD. The current finding appears to be inconsistent with that of a previous PET FDG study[53] that reported rCMRglu decreases in anterior cingulate in PTSD; however, because coordinates were not reported in that study, it is unclear whether those decreases occurred in rostral or dorsal portions of the anterior cingulate. One other previous PET FDG study[46] reported no rCMRglu difference in the cingulate between 10 Vietnam combat veterans with PTSD and 10 healthy trauma-unexposed participants. However, unlike the current study, the previous study used a structural region-of-interest approach, which involved extracting PET FDG data from manually traced brain structures. The "cingulate" region in that study did not appear to distinguish between different subdivisions of this structure (i.e., anterior vs. posterior, dACC vs. rACC). Extracting and analyzing PET FDG data from the entire cingulate gyrus could easily obscure possible group differences in specific subregions of the cingulate, such as the dACC.

We did not find evidence of resting rCMRglu main effects or interactions in the rACC, amygdala, or hippocampus. Most of the previous findings of abnormal function in these regions have occurred in neuroimaging studies that utilized emotional or cognitive tasks; perhaps abnormalities in these brain structures are more likely to be manifest when participants are engaged in such tasks. Furthermore, amygdala responses are known to habituate[70–72] over seconds to minutes, even in PTSD.[19, 37] It is possible that such habituation occurred during the 40-minute FDG uptake period, thus obscuring any possible group differences that may have existed early in the uptake period. Two previous resting PET-FDG studies[46, 53] reported no group differences between PTSD and comparison groups with regard to rCMRglu in the amygdala, although one of those studies reported diminished rCMRglu in the hippocampus.[53] The fact that some of our a priori brain regions of interest did not show abnormal glucose metabolic rates in PTSD at rest does not preclude their involvement in the pathophysiology of the disorder. In future research, we plan to use cognitive and emotional tasks during fMRI to further probe these structures using the present twin design.

The dACC (also referred to as the dorsal anterior mid cingulate cortex [2, 73]) appears to be involved in many cognitive processes, such as conflict monitoring, response selection, and error detection.[5, 10] However, it also appears to be involved in aversive conditioning,[11, 74] the anticipation and perception of pain,[75, 76] and task/stimulus-related heart rate responses.[77] In rhesus monkeys, increased dACC metabolism is positively correlated with increased freezing behavior in response to a human intruder.[78] In humans, dACC activation is positively correlated with neuroticism and interoceptive accuracy[79] and emotional awareness.[80] Increased rCMRglu in the dACC recently has been reported in individuals with the short (s/s) allele of the serotonin transporter gene,[81] the frequency of which has been found to be increased in PTSD.[82,83]

The Michigan Alcoholism Screening Test and the measure of combat severity were originally included in the design for use as covariates to control for potentially confounding variables. Additionally, we found that hypermetabolism in dACC/MCC in the combat-unexposed co-twins positively and significantly correlated with their own and their exposed twins' alcoholism histories, as well as their exposed twins' combat exposure severity and PTSD severity. Although not predicted, these results are of substantial interest in view of a study of 4072 male–male twin pairs, both of whom were in military service during the Vietnam War, that found that the same additive genetic influences that affect the level of combat exposure also influence the level of alcohol use and the level of avoidance/arousal and reexperiencing PTSD symptoms.[84] The authors concluded that the genetic influences that lead to exposure to combat also lead to increased alcohol use and PTSD symptoms, and further that some genetically transmitted personal characteristics, possibly including impulsivity and sensation seeking, influence the veteran's probability of being exposed to a high level of combat, to PTSD symptoms, and to alcohol use. The results of the present study suggest that resting dACC/MCC hypermetabolism may be an endophenotypic manifestation of these genetic influences and personality characteristics. Confidence in this conclusion, however, is limited by the lack of relevant personality measures in this twin sample, as well as the dearth of prior studies regarding the relationship between dACC/MCC glucose metabolism, alcoholism, and personality characteristics such as impulsivity. However, one functional magnetic resonance imaging (fMRI) study reported exaggerated dACC/MCC activation in detoxified alcoholics in response to alcohol-related vs. neutral pictures.[85] Another fMRI study that employed a perceptual face processing task found that activation of the dACC was positively correlated with impulsivity.[86]

If replicated in further twin or prospective singleton studies, the current findings could have specific theoretical implications. The finding of hypermetabolism in the dACC in PTSD is consistent with conditioning and extinction neurocircuitry models of PTSD,[87] which implicate the dACC in fear learning.[11] More generally, the identification of regional brain metabolic activity as a familial risk factor challenges the notion that the traumatic event is the sole etiologic factor in the development of PTSD (see[88]) and is broadly consistent with many previous findings suggesting that certain psychological and biological factors appear to increase risk for PTSD following exposure to trauma.[89] For example, smaller hippocampal volumes,[90] diminished neurocognitive function,[91, 92] and increased neurological soft signs [93] have been shown to be familial risk factors for the development of PTSD after psychological trauma. In contrast, diminished gray matter density in rostral ACC appears to be an acquired sign of PTSD.[94]

In summary, we found hypermetabolism in the dACC/MCC in individuals with PTSD and in their trauma-unexposed identical co-twins without PTSD. Enhanced resting metabolic activity in the dACC/MCC therefore appears to represent a familial risk factor for the development of PTSD after exposure to psychological trauma. The current study is limited by the presence of disorders other than PTSD, medication use in some participants, and missing handedness data in 7 of 66 participants; however, the finding of hypermetabolism in the dACC/MCC in the P+ pairs remained even when the above participants' data were temporarily excluded from the analyses. It is important to note that, in the absence of dizygotic twin participants, the current twin design cannot distinguish between genetic and environmental contributions to familial risk. Future research examining the relationship between dACC hypermetabolism and specific genotypes should help to address this issue. Future longitudinal studies will be needed to confirm that dACC hypermetabolism identified before trauma exposure increases the risk of PTSD after trauma exposure. Finally, despite the fact that PTSD and non-PTSD pairs differed significantly on rCMRglu values in the dACC/MCC, there was both variability within groups and overlap between groups. Although this pattern of findings is typical in functional neuroimaging studies of psychiatric

patient groups, it limits the ability to use rCMRglu in the dACC/MCC as a sole predictor of vulnerability to PTSD following psychological trauma. In future studies, factoring in other measures (such as genotypes) may increase separation between groups and the predictive power of the rCMRglu measure.

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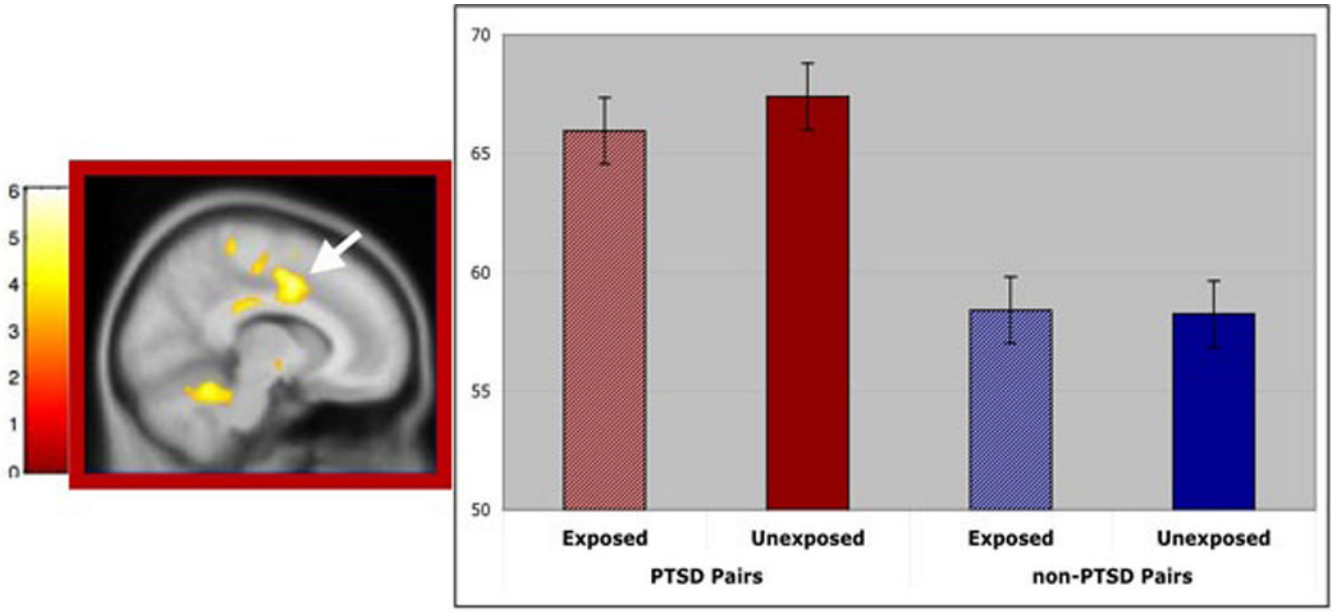

Figure 1.

Main effect of PTSD Diagnosis on regional cerebral metabolic rates for glucose (rCMRglu). This image shows resting rCMRglu in dorsal anterior cingulate/mid cingulate cortex that is greater in trauma-exposed twins with PTSD and their unexposed identical co-twins, compared with trauma-exposed twins without PTSD and their identical co-twins. FDG data are superimposed on a standard SPM2 T1 template and displayed according to neurological convention. The accompanying bar graphs present group means; error bars represent standard error of the mean. MNI=Montreal Neurological Institute

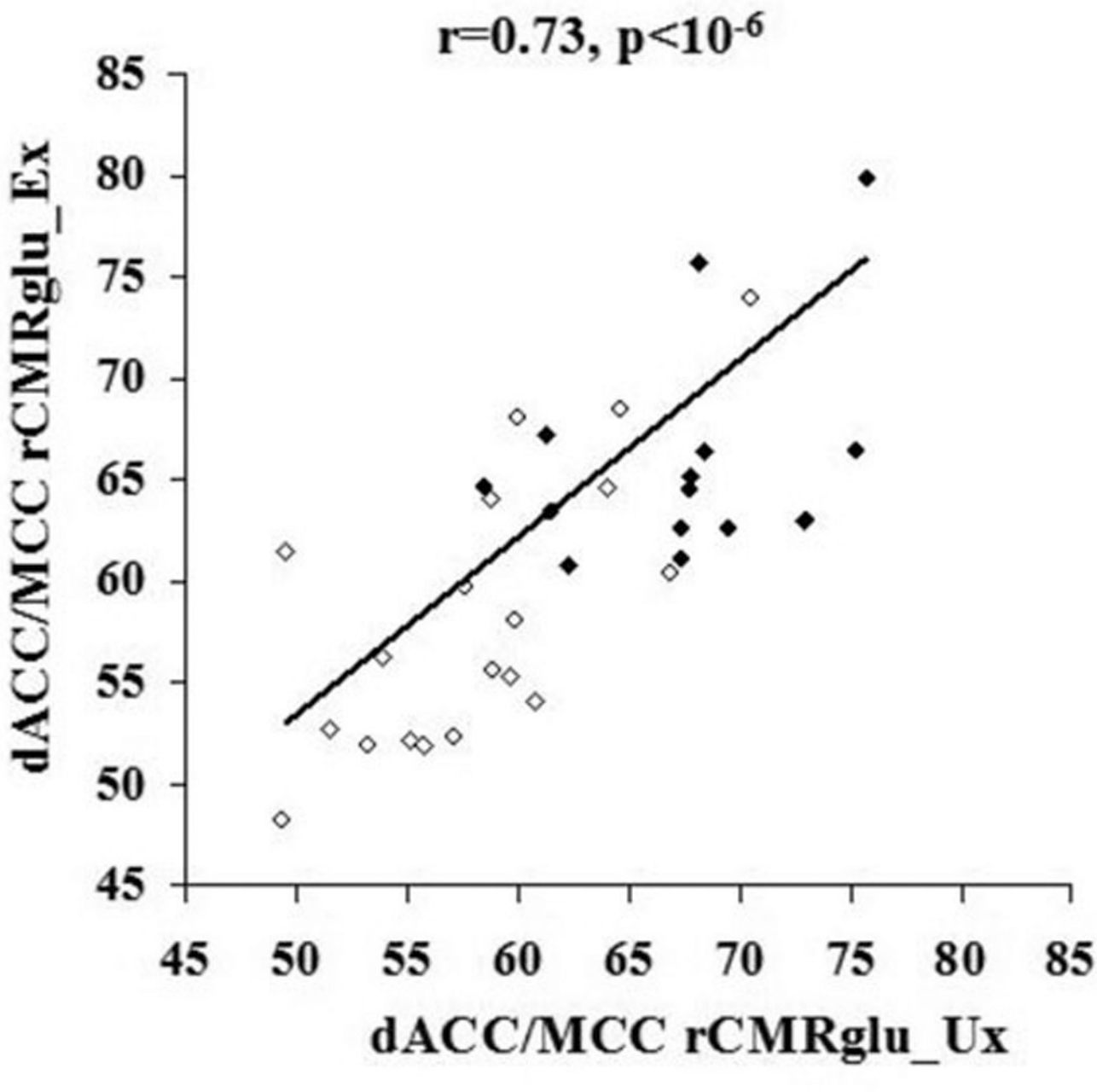

Figure 2.
rCMRglu correlation between co-twins. Individual subjects' rCMRglu values from the dorsal anterior cingulate/mid cingulate cortex cluster (k=109) plotted by pairs, with the value of the combat-unexposed (Ux) twin shown on the x-axis and that of the combat-exposed (Ex) twin on the y-axis; open circles represent non-PTSD pairs and closed circles PTSD pairs.

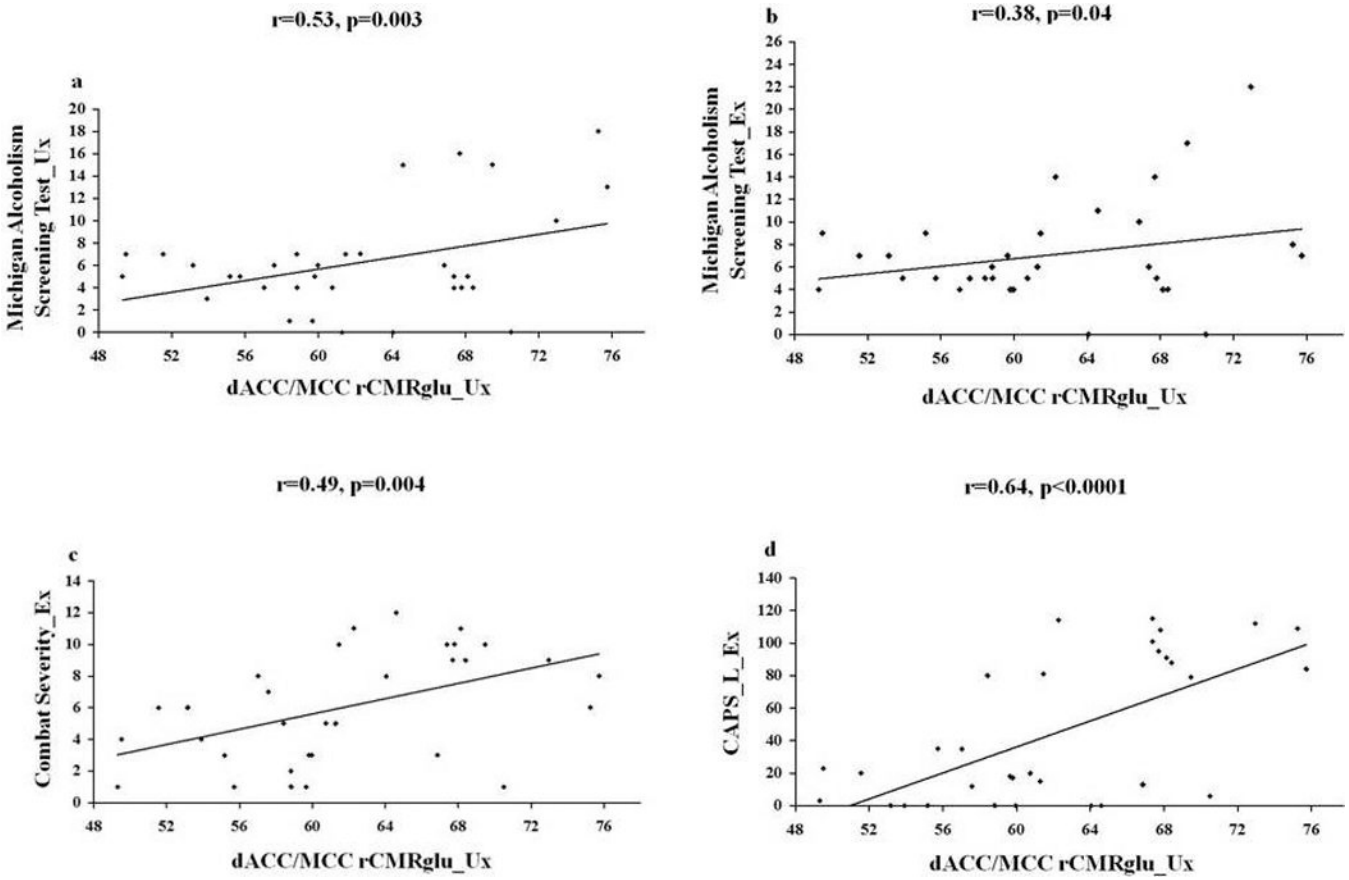

Figure 3.

rCMRglu correlations with clinical variables. The scatterplots show the zero-order correlations between rCMRglu values extracted from the dorsal anterior cingulate/ midcingulate cortex for combat-unexposed (Ux) co-twins and a.) their own Michigan Alcoholism Screening Test scores, b.) their combat-exposed (Ex) twins' Michigan alcoholism Screening Test scores; c.) their Ex twins' combat severity scores, and d.) their Ex twins' lifetime Clinician-Administered PTSD Scale scores.

Table 1

Group means (sd) of combat-exposed Vietnam veterans with and without PTSD and their combat-unexposed, identical co-twins

	PTSD Pairs*		Non-PTSD Pairs†		Mixed Model ANOVA					
	Exposed (n=14)	**Unexposed (high risk) (n=14)**	**Exposed (n=19)**	**Unexposed (low risk) (n=19)**	**Diagnosis *F(1,31)***	***p***	**Exposure *F(1,32)***	***p***	**Interaction *F(1,31)***	***p***
Age (years)‡	57.8 (2.8)		57.1 (2.2)		0.6	ns				
Education (years)	14.1 (2.4)	13.5 (2.3)	14.0 (1.9)	13.4 (1.8)	0.0[a]	ns	1.6[b]	ns	0.0[a]	ns
MAST#	9.3 (5.7)	8.4 (5.5)	6.3 (2.3)	5.6 (2.9)	4.7[c]	0.04	1.1[d]	ns	0.00[c]	ns
Combat everity¶	8.8 (2.0)		4.2 (3.0)		24.2	<.0001				
CAPS§-Current	66.0 (25.8)		6.6 (9.3)		86.4	.0001				
CAPS§- Lifetime	90.9 (25.5)		10.6 (12.0)		145.2	.0001				
BDI¥	12.2 (11.7)	2.9 (3.8)	3.1 (3.6)	4.4 (5.5)	3.7[e]	ns	7.3[f]	.02	12.8[e]	.002
CTQ❷	58.6 (8.7)	55.2 (17.8)	61.3 (8.3)	61.2 (2.9)	2.6	ns	0.5	ns	0.5	ns
PANAS£-Positive Affect	21.7 (7.9)	22.4 (5.4)	23.9 (8.9)	21.8 (5.7)	0.2[b]	ns	0.2[g]	ns	0.8[b]	ns
PANAS£-Negative Affect	17.0 (8.7)	11.5 (2.3)	11.8 (3.4)	10.9 (1.2)	6.5[b]	.02	7.4[g]	.01	3.7[b]	.07

*As determined by the presence of current, combat-related PTSD in the combat-exposed twin

†As determined by the absence of current or past, combat-related PTSD in the combat-exposed twin

‡As of January 1, 2005

#Michigan Alcoholism Screening Test (range 0–25)

¶18-item measure (range 0–18)

§Clinician-Administered PTSD Scale (range 0–136)

¥Beck Depression Inventory (range 0–63)

❷Childhood Trauma Questionnaire

£Positive and Negative Affect Schedule

[a]df=1,29;

[b]df=1,30;

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[c] df=1,28;

[d] df=1,29;

[e] df=1,27;

[f] df=1,28;

[g] df=1,31

Table 2

Main Effect of Diagnosis

	Region	Z-score	MNI Coordinates (x, y, z)
PTSD Pairs > non-PTSD Pairs			
	dACC	4.70	+10, +2, +42
	midcingulate cortex	5.03	+16, −2, +46
		4.65	−10, −4, +38
	left inferior parietal cortex	4.78	−46, −50, +28
Non-PTSD Pairs > PTSD Pairs			
	none		

Note: MNI = Montreal Neurological Institute.

Table 3

	Exposed Twins			Unexposed Twins		
	Region	**Z-score**	**MNI Coordinates (x, y, z)**	**Region**	**Z-score**	**MNI Coordinates (x, y, z)**
PTSD > non-PTSD:						
	dACC	3.16	+16, +8, +46	dACC	4.16	+8, +2, +44
					3.54	−6, 0, +38
					3.35	−8, +14, +36
	midcingulate cortex	3.49	+16, −4, +46			
Non-PTSD > PTSD:						
	none			none		

Note: MNI = Montreal Neurological Institute.