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Cavum Septum Pellucidum in Monozygotic Twins Discordant for Combat Exposure: Relationship to Posttraumatic Stress Disorder

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Abstract

Background—Abnormally large cavum septum pellucidum has been reported in posttraumatic stress disorder; however, the origin of this association is uncertain.

Methods—We utilized magnetic resonance imaging to measure cavum septum pellucidum in pairs of identical twins discordant for combat exposure in Vietnam.

Results—Presence of abnormal cavum septum pellucidum was significantly correlated between exposed and unexposed twins, indicating that it is partially determined by heredity and/or shared environment. There was a greater proportion of cavum septum pellucidum in combat-exposed twins with posttraumatic stress disorder and their noncombat-exposed co-twins.

Conclusions—The presence of abnormally large cavum septum pellucidum is a familial vulnerability factor for posttraumatic stress disorder.

Keywords

Septum pellucidum; stress disorders; posttraumatic; magnetic resonance imaging; twins; monozygotic

Cavum septum pellucidum (CSP) is a space, or cavum, between two thin translucent leaflet membranes in the brain composed of white matter and surrounded by the gray matter of the septum pellucidum. In normal development, the fusion of the septi pellucidi occurs within 3 to 6 months of birth due to rapid growth of midline and limbic structures, including the corpus callosum and hippocampal formation. Incomplete fusion results in the persistence of CSP, which may reflect neurodevelopmental abnormalities in these regions (Rakic and Yakovlev 1968; Sarwar 1989; Shaw and Alvord 1969). High-spatial-resolution magnetic resonance imaging (MRI) studies (Fukuzako et al 1996; Hagino et al 2001; Kwon et al 1998; Nopoulos et al 1997; Rajarethinam et al 2001) have found a prevalence of some degree of CSP, ranging

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from 38% to 85% in normal adults, suggesting that a small CSP is a normal variant; however, an abnormally large CSP occurs more frequently in schizophrenics, especially males (Kwon et al 1998; Nopoulos et al 1997; Rajarethinam et al 2001).

A number of studies (reviewed in Gilbertson et al 2002) have reported diminished hippocampal volume in posttraumatic stress disorder (PTSD), especially in combat veterans. Given the role played by hippocampal development in closing the CSP, these results suggest that PTSD subjects may also show abnormally large CSP. In the single study that addressed this issue in the literature, Myslobodsky et al (1995) reported the presence of CSP in 50% of Israeli combat veterans with PTSD compared with 14% in normal volunteers matched for age, socioeconomic background, and military experience. These authors concluded that CSP may be an antecedent marker for psychopathological vulnerability to stress.

Gilbertson et al (2002) found reduced hippocampal volume in both combat veterans with PTSD and their noncombat-exposed identical twins, compared with combat veterans without PTSD and their noncombat-exposed identical twins. This finding supports the proposition that smaller hippocampi are a familial risk factor for PTSD. In this study, we examined the presence of abnormal CSPs in this same twin sample.

Methods and Materials

Subjects

Subjects were members of 48 male monozygotic (identical) twin pairs discordant for combat exposure in Vietnam. This means that within each pair, one “exposed” twin had participated in military combat, whereas his unexposed co-twin had not. Among the exposed twins, 24 met DSM-IV criteria for current combat-related PTSD, and 24 had never met criteria for combat-related PTSD (non-PTSD). The means of ascertainment and recruitment of the subjects, as well as information regarding their combat severity, frequency of noncombat traumatic events, presence of other mental disorders, and substance use, have been presented in detail elsewhere (Gilbertson et al 2002; Orr et al 2003). The same MRI scans that were used to quantify hippocampal volume in the study of Gilbertson et al (2002) were used to quantify CSP here. This means that the subjects in the present study are the same as those in that report with an exception. Whereas the Gilbertson et al (2002) study data analysis approach (analysis of variance) discarded both members of a twin pair if data were missing from one of its members, in the present study, we applied a random effects, mixed model analysis, which allowed us to include CSP data from singletons (i.e., subjects whose twin’s data were missing). The psychodiagnostic and neuroimaging procedures were described in detail in a written informed consent document that had been approved by the relevant Institutional Review Boards. This document was provided to the subject to read and further explained by a doctoral-level psychologist, who then answered any questions. All subjects signed the consent document before participation.

PTSD Diagnosis

The Clinician-Administered Post-Traumatic Stress Disorder Scale (CAPS) (Weathers et al 2001) was used to make a categorical diagnostic determination of the presence or absence of combat-related PTSD (current vs. never had) in the exposed twin. In our hands, the interrater, test-retest reliability of total CAPS score was .94 (intraclass correlation coefficient). Due to ambiguous predictions, exposed subjects with past but not current PTSD were excluded.

MRI Acquisition and Processing

The MRI acquisition protocol and the postprocessing of images have been described by Kwon et al (1998). Briefly, we obtained 1.5-mm-thick coronal slices that were derived from a series

of contiguous slices using a Spoiled GRASS (SPGR) sequence (i.e., repetition time = 35 milliseconds, echo time = 5 milliseconds, voxel dimensions = .9375 × .9375 × 1.5 mm). An anisotropic diffusion filter (k = 13 for SPGR and 90 for proton/T2 images, iteration = 3) was applied to the images to reduce noise before processing each set of scans. Images were aligned using the line between the anterior and posterior commissures (anterior commissure-posterior commissure line [AC-PC]) and the sagittal sulcus to correct head tilt and were also resampled to make voxels isotropic (sides measured .9375 mm). The presence or absence of CSP was then scored on each of these slices.

Cavum Septum Pellucidum Quantification

The means of quantifying CSP have been described by Kwon et al (1998). Briefly, for each subject, the number of slices containing CSP was counted on a series of coronal images without knowledge of diagnosis. When a certain slice appeared to have a partial volume effect, the slice was scored as containing the CSP. This definition may be too inclusive, but it is objective and enables reliable measurement. Since the images were .9375 mm thick, without gaps, the multiplication of the rating by .9375 was a reflection of the anterior-to-posterior extent of the cavum, although partial volume effects render this an approximation. For example, a CSP seen on six slices would be approximately 5.6 mm long. Previously, the interrater reliability for CSP slice count determined by this technique was found to be .93 to .97 (Kwon et al 1998). We reevaluated this in the present study by having a second rater rescore 15 of the subjects' number of slices containing CSP.

Because the high-spatial-resolution MRI studies reviewed above suggest that the presence of a very small CSP has no pathologic significance, it is important to distinguish CSPs considered to be larger than normal variants. To do this, we set an a priori criterion based on previous work (Kwon et al 1998), whereby CSP was considered to be abnormal if it was visualized on six or more slices (≥5.6 mm).

Statistical Analysis

Continuous data were analyzed by means of a mixed model that treated dichotomous PTSD diagnosis (i.e., PTSD vs. non-PTSD in the combat-exposed twin) as a between-pairs fixed effect, combat exposure as a within-pair fixed effect, and twin pairs as a random effect (Little et al 1996). The categorical data for proportion of subjects with an abnormal CSP were analyzed in a parallel manner using generalized estimating equations (Liang and Zeger 1986). A significant PTSD diagnosis effect in the absence of a PTSD diagnosis × combat exposure interaction would be consistent with abnormal CSP as a familial vulnerability factor for PTSD. In contrast, a significant interaction (with a higher frequency of abnormal CSP in the exposed PTSD veterans than in the other three groups) would be consistent with abnormal CSP as an acquired PTSD sign. Because the predictions for abnormal CSP were clearly directional (i.e., there was no reason to entertain the possibility of a lower proportion of CSP in PTSD pairs than in non-PTSD pairs or in exposed veterans than in unexposed veterans), one-sided $p < .05$ was regarded as indicating statistical significance for the tests.

Results

Interrater reliability for CSP slice count in the current sample was .88 (intraclass correlation coefficient).

Magnetic resonance imaging data were unavailable in four combat-exposed, PTSD subjects for the following reasons: two had shrapnel that prohibited scanning, one developed an acute medical condition that precluded scanning, and one developed claustrophobia in the scanner. Magnetic resonance imaging data were unusable in one exposed twin without PTSD who had

a brain tumor and in one unexposed co-twin (of an exposed twin with PTSD) who had had past brain surgery.

Table 1 presents the remaining subjects' demographic, psychometric, whole brain volume, and CSP data, along with the results of the statistical analyses. There were no significant main effects or interactions for age or education. As would be expected, exposed PTSD subjects had larger total combat-related CAPS scores than exposed, non-PTSD subjects. Although the PTSD diagnosis × combat exposure interaction for whole brain volume showed a trend toward statistical significance ($p = .07$), the pattern of the PTSD veterans' and the co-twins of the non-PTSD veterans' mean whole brain volumes both being lower than those of the non-PTSD veterans and the co-twins of the PTSD veterans makes this trend uninterpretable and unlikely to be of any significance. With regard to the proportion of subjects with an abnormal CSP, the PTSD diagnosis main effect was $\chi^2 = 2.8$, $p = .09$ (two-sided), or $p < .05$ (one-sided). In contrast, the combat exposure main effect and the PTSD diagnosis × combat exposure interaction were not significant.

The correlation between presence (or absence) of an abnormal CSP in exposed and unexposed twins collapsed across exposed twin's PTSD diagnosis was calculated by means of the **Φ** coefficient (which is the equivalent of a Pearson product moment correlation between two dichotomous variables and also referred to as Yule's d). For this analysis, $\mathbf{\Phi} = .35$, $n = 42$, $p = .01$ (one-sided). There was no difference in mean (SD) hippocampal volume in the 20 subjects with an abnormal CSP: 7.4 (1.3) mL versus the 67 subjects without an abnormal CSP: 7.3 (.8) mL, $t(85) = .4$, $p = .67$ (hippocampal volume data missing in three subjects).

Discussion

The presence of an abnormal CSP was significantly correlated between exposed and unexposed twins, collapsed across diagnostic groups. This correlation indicates that the presence of an abnormal CSP is partially of familial determination, where familial means due to hereditary and/or environmental factors shared by the twins. To our knowledge, this is the first time that this finding has been reported; however, that this association accounted for only 12% ($.35^2$) of the variance suggests an additional determining role for unique environmental factors on abnormal CSP. (Not all congenital variations are familial as defined here, i.e., unique environmental factors that may distinguish identical twins can play a role even in utero.) There was no observed association between CSP and hippocampal volume.

The pattern of group results for abnormal CSP, viz., a significant PTSD diagnosis main effect in the absence of a combat exposure main effect or an interaction, supports the conclusion that the presence of an abnormal CSP is a familial risk factor for PTSD, as suggested by Myslobodsky et al (1995). Surprisingly, the PTSD diagnosis effect was larger in the unexposed than in the exposed twins, for which we can think of no explanation except happenstance, especially considering that the interaction was not significant. Nonetheless, this pattern suggests that vulnerability to PTSD is not mediated directly by the abnormal CSP itself but rather indirectly by some (familial) neurodevelopmental third factor(s), which its presence reflects. Thus, the results of the present study bolster the evidence for nonspecific neurologic vulnerability to PTSD provided by findings of increased neurologic soft signs and histories of neurodevelopmental abnormalities in this disorder (Gurvits et al 1993, 2000, 2002).

Acknowledgments

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References

Fukuzako T, Fukuzako H, Kodama S, Hashiguchi T, Takigawa M. Cavum septum pellucidum in schizophrenia: A magnetic resonance imaging study. Psychiatry Clin Neurosci 1996;50:125–128. [PubMed: 9201757]

Gilbertson MW, Shenton ME, Ciszewski A, Kasai K, Lasko NB, Orr SP, et al. Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. Nat Neurosci 2002;5:1242–1247. [PubMed: 12379862]

Gurvits TV, Gilbertson MW, Lasko NB, Tarhan AS, Simeon D, Macklin ML, et al. Neurologic soft signs in chronic post-traumatic stress disorder. Arch Gen Psychiatry 2000;57:181–186. [PubMed: 10665621]

Gurvits TV, Lasko NB, Repak AL, Metzger LJ, Orr SP, Pitman RK. Performance on visuospatial copying tasks in individuals with chronic post-traumatic stress disorder. Psychiatry Res 2002;112:263–268. [PubMed: 12450636]

Gurvits TV, Lasko NB, Schachter SC, Kuhne AA, Orr SP, Pitman RK. Neurological status of Vietnam veterans with chronic post-traumatic stress disorder. J Neuropsychiatry Clin Neurosci 1993;5:183–188. [PubMed: 8508036]

Hagino H, Suzuki M, Kurokawa K, Mori K, Nohara S, Takahashi T, et al. Magnetic resonance imaging study of the cavum septi pellucidi in patients with schizophrenia. Am J Psychiatry 2001;158:1717–1719. [PubMed: 11579008]

Kwon JS, Shenton ME, Hirayasu Y, Salisbury DF, Fischer IA, Dickey CC, et al. MRI study of cavum septi pellucidi in schizophrenia, affective disorder, and schizotypal personality disorder. Am J Psychiatry 1998;155:509–515. [PubMed: 9545997]

Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. Biometrika 1986;73:13–22.

Little, RC.; Milliken, GA.; Stroup, WW.; Wolfinger, RD. SAS System for Mixed Models. Cary, NC: SAS Institute Inc; 1996.

Myslobodsky MS, Glicksohn J, Singer J, Stern M, Bar-Ziv J, Friedland N, et al. Changes of brain anatomy in patients with posttraumatic stress disorder: A pilot magnetic resonance imaging study. Psychiatry Res 1995;58:259–264. [PubMed: 8570781]

Nopoulos P, Swayze V, Flaum M, Ehrhardt JC, Yuh WTC, Andreasen NC. Cavum septi pellucidi in normals and patients with schizophrenia as detected by magnetic resonance imaging. Biol Psychiatry 1997;41:1102–1108. [PubMed: 9146821]

Orr SP, Metzger LJ, Lasko NB, Macklin ML, Hu FB, Shalev AY, et al. Physiologic responses to sudden, loud tones in monozygotic twins discordant for combat exposure: Association with PTSD. Arch Gen Psychiatry 2003;60:283–288. [PubMed: 12622661]

Rajarethinam R, Miedler J, DeQuardo J, Smet CI, Brunberg J, Kirbat R, et al. Prevalence of cavum septum pellucidum in schizophrenia studied with MRI. Schizophr Res 2001;48:201–205. [PubMed: 11295373]

Rakic P, Yakovlev PI. Development of corpus callosum and cavum septi in man. J Comp Neurol 1968;132:355–362.

Sarwar M. The septum pellucidum: Normal and abnormal. AJNR Am J Neuroradiol 1989;10:989–1005. [PubMed: 2505543]

Shaw CM, Alvord EC. Cavum septi pellucidi et vergae: Their normal and pathological state. Brain 1969;92:213–224. [PubMed: 5774029]

Weathers FW, Keane TM, Davidson JR. Clinician-Administered PTSD Scale: A review of the first ten years of research. Depress Anxiety 2001;13:132–156. [PubMed: 11387733]

Table 1

Group Mean (SD) Demographic, Psychometric, and Cavum Septum Pellucidum Data

	PTSD[a] (Ex *n* = 20) (Ux *n* = 23)	Non-PTSD[a] (Ex *n* = 23) (Ux *n* = 24)	Mixed Model Analyses[b]		
	Mean (SD)	Mean (SD)	PTSD Diagnosis[a]	Combat Exposure	Interaction
Age					
Exposed	52.3 (3.3)	51.8 (2.3)	$t = .5$	$t = 1.0$	$t = 1.1$
Unexposed	52.7 (3.2)	51.8 (2.3)	$p = .48$	$p = .32$	$p = .27$
Education[c]					
Exposed	13.5 (2.5)	14.7 (2.4)	$t = 2.1$	$t = .3$	$t = 1.0$
Unexposed	13.8 (3.2)	14.5 (2.5)	$p = .16$	$p = .58$	$p = .34$
CAPS Score					
Exposed	73.3 (16.4)	6.4 (7.5)	$t = 25.1$		
Unexposed[d]	72.3 (16.1)	6.8 (7.6)	$p < .0001$		
Whole Brain Volume (mL)					
Exposed	1241 (118)	1258 (106)	$t = 00$	$t = .50$	$t = 1.9$
Unexposed	1257 (116)	1247 (110)	$p = .85$	$p = .94$	$p = .07$
	n (%)	*n* (%)			
Abnormal CSP[e]					
Exposed	5 (25%)	4 (17%)	$\chi^2 = 2.8$	$\chi^2 = .5$	$\chi^2 = .5$
Unexposed	9 (39%)	4 (17%)	$p = .09$	$p = .48$	$p = .49$

Ex, combat-exposed; Ux, combat-unexposed; PTSD, posttraumatic stress disorder; CAPS, Clinician-Administered PTSD Scale; CSP, cavum septum pellucidum.

[a] Combat-related PTSD diagnostic status of the combat-exposed twin.

[b] All *p* values are two-sided.

[c] Grades completed.

[d] Combat-exposed brother's score.

[e] Of approximate length ≥5.6 mm.