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Volume of cerebellar vermis in monozygotic twins discordant for combat exposure: Lack of relationship to post-traumatic stress disorder

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Abstract

Several functional neuroimaging studies have implicated the cerebellar vermis in post-traumatic stress disorder (PTSD), but there have been no structural neuroimaging studies of this brain structure in PTSD. We utilized magnetic resonance imaging (MRI) with manual tracing to quantify the volumes of three divisions of the mid-sagittal vermis, and their total, within an identical, co-twin control design that employed Vietnam veterans discordant for combat exposure in Vietnam. Each structure's volume was significantly correlated between twins, indicating a partial familial determination: for anterior superior vermis, $r=0.73$; for posterior superior vermis, $r=0.47$; for inferior posterior vermis, $r=0.51$; and for total vermis, $r=0.57$. There were no significant differences between the PTSD and non-PTSD veterans for any vermis volume, and no significant main effects or interactions when their non-combat-exposed co-twins were added to the analyses. Thus, the results do not support the structural abnormality of cerebellar vermis in combat-related PTSD.
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1. Introduction

The cerebellar vermis, sometimes called the "limbic cerebellum," plays a role in the control of affective behaviors and in the coordination of fear-related somatic and autonomic conditioned responses (Ghelarducci and Sebastiani, 1997). A review of functional neuroimaging

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studies of emotion conducted by Reiman (1997) suggests that the vermis participates in the elaboration of normal and pathological forms of anxiety.

Several studies have implicated altered function of the vermis in the pathophysiology of post-traumatic stress disorder (PTSD). Using positron emission tomography in combat veterans with PTSD from recent wars, Pissiota et al. (2002) found greater regional cerebral blood flow (rCBF) during the presentation of combat vs. neutral sounds in the vermis, as well as in the amygdala and periaqueductal gray matter. Anderson et al. (2002) utilized steady-state functional magnetic resonance imaging (fMRI) to assess resting blood flow in the vermis of subjects with repeated childhood sexual abuse and age-matched controls. Abused subjects had higher T2 relaxation times, indicative of diminished rCBF, than did controls in the vermis, but not in the cerebral or cerebellar hemispheres. According to the authors, these findings suggest that early trauma may interfere with the development of the vermis, and, in turn, inadequate vermis function may fail to contain temporal lobe epilepsy-like psychiatric symptoms found in abused persons. Using single proton emission computed tomography (SPECT), Bonne et al. (2003) found a positive association between regional cerebral blood flow in midline cerebellum and PTSD symptoms.

Teicher et al. (2003) have suggested that the cerebellar vermis should be particularly vulnerable to stress because it has the highest density of glucocorticoid receptors during development, exceeding even those in the hippocampus. There has, however, been very little structural neuroimaging investigation of the vermis in PTSD. In one morphometric study of various brain regions of interest, which did not focus on the vermis, Fennema-Notestine et al. (2002) did not find volumetric differences between victims of intimate partner violence with PTSD and victims without PTSD or normal control subjects in cerebellar gray or white matter regions of interest on structural MRI.

In a recent review, Hull (2002) noted that hippocampal volumetric reduction is the most replicated morphometric finding in PTSD. In a group of monozygotic twins discordant for combat exposure in Vietnam, we also found that combat veterans with PSTD had smaller hippocampi compared to combat veterans without PSTD. This diminished hippocampal volume was shared by the non-combat-exposed, identical co-twins of the combat veterans with PSTD, suggesting that it represents a vulnerability factor for PTSD rather than an acquired PTSD sign (Gilbertson et al., 2002). In the present study, we measured the volume of the cerebellar vermis, divided into three parts, in the same twin subjects as in that study, in order to test the hypothesis that this structure is also reduced in PTSD. Furthermore, should this have turned out to be the case, we planned to use the vermis volumes in the non-combat-exposed co-twins to clarify the origin of the hypothesized vermis volume reduction.

2. Materials and methods

2.1. 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 non-combat traumatic events, presence of other mental disorders, and substance use, have been presented in detail elsewhere (Gilbertson et al., 2002; Orr et al., 2003).

As previously noted (Gilbertson et al., 2002), subects were excluded if they met DSM-IV criteria for a psychotic/affective disorder or non-combat-related PTSD. Due to the high comorbidity of major depression and substance use disorders with PTSD, these disorders did not represent exclusion criteria. History of major neurologic disorder or significant abnormality discovered upon MRI scan during the course of the study which could impact volumetric measurements, e.g., tumor, resulted in exclusion of two subjects; the affected individuals were provided with this information and arrangements made for appropriate clinical transfer of MRI reports. Three subjects were unable to complete MRI due to claustrophobic reactions, and one subject due to a cardiac condition. Two MRI scans were not segmented for volumetric measurement due to excessive movement artifact.

The same MRI scans that were used to quantify hippocampal volume in the study of Gilbertson et al. (2002) were used to quantify cerebellar vermis volume here. That is, the subjects in the present study are the same as those in that report, with a few exceptions. Whereas the Gilbertson et al. study's data analysis approach (analysis of variance) discarded both members of a twin pair if data were missing from one of its members, the mixed model statistical technique used in the present study allowed for the inclusion of data from singletons (i.e., subjects whose twin's data were missing). Additionally, a few subjects

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