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Abnormal T2 relaxation time in the cerebellar vermis of adults sexually abused in childhood: potential role of the vermis in stress-enhanced risk for drug abuse

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Abstract

Recent studies suggest that childhood sexual abuse (CSA) elicits a cascade of neurohumoral events that affect brain development and is also a risk factor for the later development of substance abuse. We hypothesize that the cerebellar vermis may be a key region linking these observations. The vermis has a protracted ontogeny and a high density of glucocorticoid receptors, rendering it highly susceptible to early stress. The vermis modulates dopamine turnover in the accumbens and receives direct dopamine input through fibers with dopamine transporters. To test this hypothesis, steady-state functional magnetic resonance imaging (fMRI) (T2 relaxometry) was performed to assess resting blood flow in the vermis of 24 young adults (18–22 years) selected by screening from a large community sample. Eight subjects had a history of repeated CSA but were unmedicated and not under psychiatric care. Sixteen subjects were age-matched controls who had no personal or family history of Axis I psychiatric disorders. All subjects were screened to exclude known abnormalities affecting brain development, and any history of drug or alcohol abuse. CSA subjects had higher T2 relaxation time (T2-RT) than controls in the vermis but not in cerebral or cerebellar hemispheres. Vermal T2-RT correlated strongly with Limbic System Checklist (LSCL-33) ratings of temporal lobe epilepsy (TLE)-like symptomatology. From 537 prescreened young adults we found that their

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frequency of substance use was associated with a monotonic increase in LSCL-33 ratings and depression scores. Together these findings suggest that early trauma may interfere with the development of the vermis, and produce neuropsychiatric symptoms associated with drug use.

Keywords: Cerebellar vermis; Substance abuse; Child abuse; Sexual abuse; Early stress; fMRI

1. Introduction

Early stress or maltreatment is an important risk factor for the later development of substance abuse (Ellason et al., 1996; Janikowski et al., 1997; Kendler et al., 2000; McClanahan et al., 1999; Najavits et al., 1997; Simpson et al., 1994; Wilsnack et al., 1997). We have spent the last several years pursuing the hypothesis that childhood abuse or neglect induces a cascade of neurohumoral and physiological events that affect brain development (Ito et al., 1993; Ito et al., 1998; Teicher et al. 1993, 1994; Schiffer et al., 1995). Briefly, we found that subjects reporting childhood abuse had markedly increased scores on the Limbic System Checklist-33 (LSCL-33), which was devised to ascertain the frequency of occurrence of symptoms suggestive of temporal lobe epilepsy (TLE) (Teicher et al., 1993). Childhood abuse was associated with a two-fold increased incidence of clinically significant electroencephalographic (EEG) abnormalities, which were restricted to the left hemisphere (Ito et al., 1993). Abused children had highly abnormal measures of left hemisphere EEG coherence, suggesting deficient cortical maturation and differentiation (Ito et al., 1998; Teicher et al., 1997). Bremner et al. (1997) and Stein (1997) found that women with posttraumatic stress disorder (PTSD) who were abused in childhood had a smaller left, but not right, hippocampus. Abuse was also associated with prominent thinning of the middle portion of the corpus callosum, affecting males more than females (DeBellis et al., 1999; Teicher et al., 1997). These anatomic anomalies may contribute to the psychiatric syndromes reported to occur with increased frequency in childhood trauma survivors (Teicher et al., 1994; Teicher, 2000).

Preclinical studies have experimentally established the enduring effects of early experience on brain development and have elucidated potential mechanisms and key target areas. One major finding has been the discovery that excessive levels of glucocorticoids, or stress, damage brain regions with high densities of glucocorticoid receptors, such as the hippocampus (e.g. Sapolsky et al., 1988; McEwen, 1999).

A brain region that should also be extraordinarily sensitive to the effects of early maltreatment is the cerebellar vermis. Like the hippocampus, the vermis has a protracted period of postnatal ontogeny and may produce granule cells postnatally (Altman and Bayer, 1997). The vermis also has the highest density of glucocorticoid receptors during development, exceeding that of the hippocampus (Lawson et al., 1992; Pavlik and Buresova, 1984; Sanchez et al., 2000) and may be particularly vulnerable to the effects of stress hormones (Schapiro, 1971; Ferguson and Holson, 1999).

Our interest in the cerebellar vermis stems from the work of Harlow (Harlow et

al., 1965) on the deleterious effects of maternal separation and early isolation. Mason and Berkson (1975) showed that swinging wire primate surrogates greatly diminished the degree of psychopathology (aggression, self-stimulation) seen in adults as a result of these adverse early experiences. Prescott (1980) suggested that both proprioceptive and vestibular stimulation was protective, and Berman (1997) found that lesions of the vermis, which receives major input from the vestibular system, eliminated aggressive behavior. Heath (1972) found that primates reared in this manner had epileptiform EEG patterns in their fastigial nuclei, which project from the vermis to the limbic system and modulate seizure susceptibility (Heath, 1977; Cooper and Upton, 1985; Maiti and Snider, 1975; Strain et al., 1979).

The purpose of this study was to ascertain whether there were alterations in blood flow in the cerebellar vermis in a carefully selected group of young adults with a history of repeated sexual abuse using a novel functional magnetic resonance imaging (fMRI) procedure (T2 relaxometry) to derive steady state blood flow measures (Teicher et al., 2000) that correlate strongly with cerebral blood volume (CBV) as determined by Dynamic Susceptibility Contrast MRI (Anderson et al., 2000b). T2 Relaxometry (T2-RT) provides an indirect assessment of changes in steady-state blood flow as a result of magnetic susceptibility effects due to regional changes in deoxyhemoglobin concentration. This is known as the blood oxygenation level dependent (BOLD) effect or BOLD effect. In contrast to standard BOLD techniques that use background subtraction to detect acute task-dependent blood flow changes, T2-RT can be used to assess long-term steady-state blood flow changes, which may occur with chronic drug adminstration or as a response to environmental stressors. For example, during a typical fMRI experiment, the acute BOLD signal response to enhanced neuronal activity is due, in large part, to a mismatch between blood flow and oxygen extraction which does not persist under steady-state conditions (Punwani et al., 1998). Instead, regional blood flow is regulated to appropriately match perfusion with ongoing metabolic demand (Buxton et al., 1998), and deoxyhemoglobin concentration becomes constant between regions in the steady-state. Therefore, regions with greater continuous activity would be perfused at a greater rate, and these regions would receive, over time, a greater volume of blood and a greater number of deoxyhemoglobin molecules per volume of tissue. Conversely, with longterm decreases in the activity of a region, there should be a lessening of the paramagnetic properties of the region, which would be detectable as an increased T2 relaxation time.

There are compelling reasons to hypothesize that the vermis plays a role in modulating response to addictive drugs. The vermis, through its fastigial projections to the ventral tegmental area and locus coeruleus, exerts strong effects on the turnover of dopamine and norepinephrine in the caudate and nucleus accumbens (Albert et al., 1985; Nieoullon et al., 1978; Snider et al., 1976; Snider and Snider, 1977; Tellerman et al., 1979). There are also important afferent and efferent pathways between the vermis and the hypothalamus (Dietrichs and Haines, 1986; Supple, 1993). The vermis receives direct monoamine projections from the midbrain (Ikai et al., 1992; Steindler, 1981; Kerr and Bishop, 1991) and has dopamine receptors (Khan et al., 2000) and transporters (Melchitzsky and Lewis, 2000). The vermis is affected by stimulants,

cocaine and ethanol (Cavanagh et al., 1997). Methylphenidate exerts robust effects on blood flow in these regions (Schweitzer et al., 2000; Anderson et al., 2000a). The putative anti-addictive agent, ibogaine, exerts profound effects on the vermis (O'Hearn and Molliver, 1993) and induces transient ataxia (Anderson, 1998). Attentional deficit, hyperactivity disorder (ADHD) is a serious risk factor for development of substance abuse (Schubiner et al., 2000; Wilens et al., 1998), and the most consistent anatomical finding in ADHD is reduced vermal size (Berquin et al., 1998; Castellanos et al., 2001). Hence, it is plausible that the cerebellar vermis may be affected by early stress, and that it may be a component of a neural circuit modulating risk for substance abuse.

The purpose of this study was to ascertain whether there were alterations in blood flow in the cerebellar vermis in a carefully selected group of young adults with a history of repeated sexual abuse. Further, we sought to determine whether there were meaningful associations between the degree of vermal blood flow and certain categories of psychiatric symptoms. Finally, we sought to examine the relevance of these associations by ascertaining whether these psychiatric symptoms were associated with substance use in a large sample of college students.

2. Methods

2.1. Subjects

Twenty-four young right-handed adults (7M/17F, 18–22 years) participated, including 16 (6M/10F) healthy normal controls, and eight (1M/7F) subjects with a history of at least three episodes of forced sexual contact prior to age 16 that were accompanied by threats of harm and feelings of terror. Subjects were recruited by advertisement from local universities and the community and not from psychiatric sources. Potential subjects completed a detailed package of instruments and forms that elicited reports of medical history, birth history, exposure to traumatic events, current psychiatric symptoms, substance use and alcohol use, and family psychiatric history. Factors that excluded participation were: (1) history of known neurological disease or insult; (2) history of maternal substance abuse or viral infection during pregnancy; (3) any complications affecting their mother's pregnancy or delivery; (4) verified seizure disorders; (5) head injury that resulted in more than momentary loss of consciousness or skull fracture; and (6) substance or alcohol abuse (excluding caffeine or nicotine use). Controls had no history of exposure to any form of trauma, and no personal or family (first degree relatives) history of DSM-IV axis-I psychiatric disorders. Sexually-abused subjects were excluded if they had any physical abuse above the shoulders, or any exposure to physical abuse resulting in injury that should have required medical attention, or were exposed to other forms of trauma (e.g. near drowning, witnessing violence, motor vehicle accidents). Subjects recruited for fMRI evaluation underwent a battery of evaluations including structured diagnostic interview (SCID), trauma interview (Herman et al., 1989), and ratings of depression and anxiety using Hamilton scales (HAM-D, HAM-A). Urine toxic screens (Triage) and

alcohol breath tests were administered at each visit. All procedures were carried out with the adequate understanding and written consent of the subjects.

As part of the recruitment process, detailed rating booklets were completed by 537 young adults (169M/368F). Data were analyzed to ascertain whether there was a relationship between LSCL-33 scores, Dissociative Experience Scale (DES; Bernstein and Putnam, 1986) scores, and Symptom Questionnaire (Kellner, 1987) ratings of depression, anxiety, somatization and anger–hostility, along with self-reported rates of substance use and alcohol use (0/Never–3/Daily). The LSCL-33 consists of four subscales (somatic, sensory, automatisms, mnemonic) and has high test–retest reliability (r=0.92). LSCL-33 scores correlate significantly with the DES (r=0.81) and the somatization and psychoticism subscales of the Hopkins Symptom Checklist-90 (r=0.65, 0.57 respectively). LSCL-33 scores have been found to be low in normal adults (_10) and elevated in patients with documented TLE (range 23–60). They were included as a putative index of the effect of early abuse on electrical irritability within the limbic system.

2.2. Procedures

In this study we utilized a novel functional magnetic resonance imaging (fMRI) procedure (T2 relaxometry) to derive steady state blood flow measures (Teicher et al., 2000) that correlate strongly with cerebral blood volume (CBV) as determined by Dynamic Susceptibility Contrast MRI (Anderson et al., 2000b). On a separate day, each subject underwent fMRI (1.5-T GE Signa Scanner with Advanced NMR Systems echo planar coil) to assess basal T2-RT in regions of interest (ROI) for the cerebellar vermis, cerebellar hemispheres, anterior temporal lobe, and entire left and right cerebral hemispheres (Fig. 1). This was accomplished by collecting a series of 32 'TE-stepped' echo-planar images in 10 axial slices under resting conditions. A regional decay curve was generated from median pixel intensity within the ROI at each value of TE examined to calculate true T2-relaxation time following motion correction (Maas et al., 1997).

2.3. Statistics

Data were analyzed using ANOVA, which was covaried to test and adjust for differences in the gender composition of the two groups. Significant differences were confirmed by ANOVA analysis of the female subsample (10 controls, seven abused) to verify that any significant difference were not an artifact of unequal gender ratios.

3. Results

As expected, recruited young adults with a history of repeated childhood sexual abuse (CSA) had substantially higher symptom scores than healthy controls in several domains. These included a 2.1-fold elevation in LSCL-33 scores (F(1,21)=8.62, P_0.008), a 3.6-fold elevation in DES scores (F(1,21)=10.6, P_0.003), and a 2.4-

Fig. 1. (Box A) An orthogonal illustration of the region of the midline cerebellum from which two to three axial T2RT slices were acquired in young adults (parallel horizontal lines in the upper right sagittal image indicate approximate locations). To the left of the sagittal image is a depiction of region of interest (ROI) sampling areas for the temporal lobes and cerebellar hemispheres overlaid on a T1-weighted axial slice. (Box B) Maps of calculated T2 relaxation times with representative ROIs for the cerebellar hemispheres (C), cerebral hemispheres (H), cerebellar vermis (V) and temporal lobes (T).

fold elevation in HAM-D scores (F(1,19)=5.3, P_0.04). Some of the abused subjects had abnormally high scores on the LSCL-33 and DES. All of the HAM-D score were within the normal adult range (*8) and five of eight subjects had no diagnosable Axis I psychiatric disorder, and only one subject had posttraumatic stress disorder (PTSD).

Highly significant differences in T2-RT were found in the cerebellar vermis of abused subjects versus controls ($F(1,21)=13.01$, *P*_0.002). Comparable results emerged when the analysis was limited to female subjects (Controls: 94.55±1.08, Abused: 99.64±1.29, $F(1,15)=9.22$, *P*_0.008). No differences were found between groups in any of the other regions of interest (Table 1).

As shown in Fig. 2, there was a significant relationship between T2-RT in the cerebellar vermis and LSCL-33 ratings for both abused patients (*r*=_0.714, *P*_0.05) and controls (*r*=_0.677, *P*_0.004). Higher LSCL-33 scores were associated with lower T2-RT measures in both groups, suggesting increased blood volume. Abused subjects had a higher intercept (103.43±1.80 vs. 98.07±1.41, $t(22)=5.29$, *P*_0.0003)

Table 1
Regional T2-RT measures (mean±SEM)

	Controls	Abused	*F*(1,21)	Probability
Vermis	93.90±0.82	99.16±1.18	13.01	0.004
Right hemisphere	89.23±1.95	87.30±2.79	0.31	ns
Left hemisphere	89.24±2.02	87.29±2.89	0.59	ns
Right temporal lobe	95.96±1.93	95.14±2.76	0.81	ns
Left temporal lobe	98.87±2.50	97.29±3.57	0.72	ns
Right cerebellum	89.92±0.76	90.27±1.09	0.76	ns
Left cerebellum	89.74±0.60	89.55±0.85	0.86	ns

Fig. 2. Association between T2-RT and ratings on the limbic system checklist (LSCL-33) for sexual abuse subjects (males, filled square; females, empty squares) and normal controls (males, filled circles; females, empty circles). There is a substantial inverse linear correlation between the incidence of temporal lobe seizure phenomenon as indexed by increasing LSCL-33 score and T2-RT. Higher LSCL-33 scores in both controls and abuse subjects were associated with increased blood volume in the vermis, although abuse subjects as a group had significantly higher scores.

and appeared to have a more shallow slope (_0.157±0.06 vs _0.349±0.101), though this difference was not significant ($t(22)=0.77$, *P*_0.4). LSCL-33 did not correlate with T2-RT in any other region. DES scores and HAM-A scores did not correlate with T2-RT in any of the regions measured. HAM-D scores correlated positively with right and left hemisphere T2-RT measures in controls, and inversely with right and left cerebellar T2-RT measures in abused subjects.

From the 537 completed screening booklets we sought to ascertain if there was an association between frequency of substance use and elevations in LSCL-33 scores and other rating scales. Fig. 3 summarizes the association between frequency of substance use and self-report ratings of psychiatric symptomatology that showed a significant relationship. Data were corrected by ANCOVA for presence of absence of sexual abuse. LSCL-33 scores showed a highly significant monotonic relationship with substance use ($F(3,512)=4.14$, *P*_0.007), depression ($F(3,518)=4.02$, *P*_0.008) and anger–hostility ($F(3,518)=3.21$, *P*_0.03). DES scores also varied with frequency of substance use ($F(3,539)=3.31$, *P*_0.02). LSCL-33 scores were 57–74% higher in subjects exposed to physical abuse, sexual abuse, or domestic violence (all *P*'s_10_14). Depression scores were 36–60% higher in abused subjects (all *P*'s_0.00001). LSCL-33 scores were elevated to a comparable degree in subjects who were sexually abused by unrelated individuals (60% increase, *n*=97, *P*_10_9) or by family members (71% increase, *n*=26, *P*_0.000002).

Fig. 3. The association between frequency of substance use and self-reported ratings of psychiatric symptomatology in 537 college students based on their substance use history. College students who frequently use illicit drugs have higher levels of depression, irritability, DES and LSCL-33 scores, after controlling for sexual abuse history, supporting the association of vermal pathology with substance abuse. Rating scales include LSCL-33 (filled circles), DES (empty circles), Anger–Hostility (empty square), Depression (filled triangles). **P*_0.03; ***P*_0.02; ****P*_0.008; *****P*_0.007.

4. Discussion

Elevated T2-RT measures are associated with decreased blood volume and neuronal activity (Anderson et al., 2000a,b; Teicher et al., 2000). Elevated T2-RT in the cerebellar vermis of young adults with CSA suggests that early abuse may produce a functional deficit in the cerebellar vermis leading to diminished blood volume, which may be a consequence of reduced neuronal activity. T2-RT decreased with greater LSCL-33 scores, suggesting that symptoms of limbic irritability were associated with an increase in vermal blood volume and neuronal activation. This may represent a compensatory effort by the vermis to control the irritability, as studies have shown that vermal stimulation quells electrical excitability within the limbic system (Cooper and Upton, 1985; Heath, 1977; Snider and Maiti, 1975; Strain et al., 1979).

These findings support the hypothesis that the functional activity of the cerebellar vermis may be affected by exposure to repetitive sexual abuse. However, at this juncture it is premature to claim causality, as the association is correlational. It is also conceivable that enhanced vermal T2-RT may be a risk factor for sexual abuse, or that this abnormality runs in families and is associated with an increased rate of abusive behavior on the part of family members. We know, however, that LSCL-33 scores were elevated to a similar extent in subjects abused inside or outside the family, and 4/8 of the scanned abused subjects were molested by unrelated individuals. This suggests that the association of abuse with elevated LSCL-33 scores and abnormal vermal T2-RT, may not be an artifact of shared heredity. It should also be noted that all but one of the abused subjects were female. Hence, further studies are required in order to generalize these findings to sexually-abused males.

This study was specifically designed to examine the neurobiological effects of childhood sexual abuse (CSA) on young adults. This study differed dramatically from prior investigations as we recruited subjects from the general population and did not require the presence of any psychiatric symptoms. In contrast, recent imaging investigations by Bremner et al. (1997), Stein (1997) and DeBellis et al. (1999) examined the consequences of CSA in highly symptomatic individuals who met current diagnostic criteria for PTSD or dissociative identity disorder. These studies are likely to overestimate the impact of CSA as most abused individuals fail to develop PTSD (Ackerman et al., 1998; Fierman et al., 1993) and relatively few subjects remain actively symptomatic into adulthood. Hence, previous studies focused only on the most vulnerable and seriously affected subgroup. Our aim was to assess the impact of exposure to a potentially traumatic degree of sexual abuse, but to include in the study the more resilient individuals who experienced severe trauma but who maintained or regained relative psychiatric health. As described, entry into the study required three or more episodes of forced sexual contact accompanied by threats of harm to self or others and feelings of fear or terror prior to age 16. Hence, all subjects had to have experienced a level of sexual abuse that would meet DSM-IV criteria for a traumatic event. To our knowledge this is the first study to examine the biological consequences of sexual abuse in a non-clinical sample, in which most subjects were free, at present, from significant psychiatric difficulties.

This study also differs from prior studies due to our focus on a narrow young adult age-range. This is the youngest range we could study without mandated abuse reporting requirements that largely preclude voluntary recruitment of individuals not already known to protective services. It is however close enough to childhood for individuals to have detailed recall. Further, subjects are young enough to have enabled us to recruit a sample that was exposed to no other forms of trauma and who had no history of alcohol or substance abuse. In fact, most subjects were entirely abstinent.

One potential criticism of the study is the use of retrospective self-reports of CSA. It is impossible to know the underlying bias or factual validity of their reports. However, research to date suggests that there is a significant bias to underreport episodes of abuse. For instance, Williams (1994) conducted a follow-up study of 129 children evaluated in an emergency room with documented sexual abuse. When Williams contacted the children 17 years later he found that a substantial number (38%) either failed to recall the episode or consciously denied it, though many recalled other instances. Bifulco et al. (1997) examined concordance of 89 sibling pairs residing in the same household regarding presence or absence of sexual abuse. Percent agreement among siblings was 89%, suggesting that sisters that had shared the experience of sexual abuse had a high degree of corroboration.

The question also arises regarding the bias of subjects with a history of CSA who choose to participate in research studies. Do only the most symptomatic patients volunteer (e.g. Pope and Hudson, 1995)? Edwards et al. (2001) had a unique opportunity to assess these issues as part of the Adverse Childhood Experience (ACE) study. In this study by the Centers for Disease Control, a questionnaire requesting sensitive information on childhood experiences was sent to 13,494 adult HMO members who had already completed standardized health histories that included information about psychosocial well-being and a history of rape or molestation (i.e., CSA). Overall, 5.9% of all HMO patients had answered affirmatively to CSA. Among respondents to the questionnaire, the prevalence of CSA was 6.1%, while in the nonrespondent group it was 5.4%. The adjusted odds ratio indicated a slight bias for persons with a history of CSA to respond. The strength of the relationship between CSA and both psychosocial well-being and health outcomes in adulthood was remarkably similar for respondents and nonrespondents to the ACE questionnaire. Where there were minor differences between the two groups, they tended to be slightly *lower* among respondents. Non-respondents who reported CSA were substantially more likely to report experiencing current depression and high stress, and to have a higher prevalence of job and family problems. There were no differences in current health or smoking behavior. No evidence of upward bias was found. Rather, they concluded that if any selection bias existed it would likely result in an underestimation of the psychosocial consequences of childhood abuse (Edwards et al., 2001).

While underreporting may be the larger statistical concern, it is also the case that some individuals fabricate abusive experiences. Sometimes this is for secondary gain; at other times it may occur in response to suggestions from a misguided therapist. No subjects were recruited who were endeavoring to derive any secondary gain from their experience. They also were not in a position to fabricate a sexual trauma history

to gain entrance to the study because subjects were unaware of the entry requirements until after they were screened and selected. Further, subjects who did not have persistent memories of the trauma were excluded. Hence, there were no subjects in the study with 'repressed' or 'recovered' memories. No subject had memories 'come to light' during the course of treatment. Thus, although it is not possible to know the veracity of their self-report there were no reasons to doubt their honesty or their recall. The observation that self-reported exposure to CSA is associated with elevated T2-RT in such a carefully screened non-psychiatric community sample provides some of the most compelling data to date on the association between early stress and brain development.

Overall, studies on the effects of early stress, glucocorticoid receptor development, cerebellar neuroanatomy and neuropharmacology led to the novel hypothesis that early stress exerts deleterious effects on the development of the cerbellar vermis, which may, in turn, increase the risk for substance abuse. Steady-state fMRI provides preliminary evidence that repeated sexual abuse is associated with prominent alterations in the paramagnetic properties of the vermis. These findings fit with a growing body of research indicating that the cerebellum may play a much greater role in mental health than hitherto realized (Schmahmann, 2000).

5. Note added in proof

As this report went to press, Rilling et al. (2001) published observations of a correlation between plasma cortisol concentrations and enhanced neural activity, measured with [18F]-fluorodeoxyglucose PET, in the vermis of juvenile rhesus monkeys who experienced greater maternal aggression.

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