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Preliminary Evidence for White Matter Tract Abnormalities in Young Adults Exposed to Parental Verbal Abuse

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Abstract

Background—Psychiatric sequelae of exposure to parental verbal abuse (PVA) appears to be comparable to that of non-familial sexual abuse and witnessing domestic violence. Diffusion Tensor Imaging (DTI) was used to ascertain whether PVA was associated with abnormalities in brain white matter (WM) tract integrity.

Method—1271 healthy young adults were screened for exposure to childhood adversity. DTI was collected on 16 unmedicated subjects with history of high-level exposure to PVA but no other form of maltreatment (4M/12F, mean age 21.9±2.4 yrs), and 16 healthy controls (5M/11F, 21.0±1.6 yrs). Group differences in fractional anisotropy (FA), covaried by parental education and income, were assessed using Tract-Based Spatial Statistics (TBSS), and correlated with symptom ratings and verbal IQ.

Results—Three WM tract regions had significantly reduced FA: (1) arcuate fasciculus in left superior temporal gyrus, (2) cingulum bundle by the posterior tail of the left hippocampus, and (3) the left body of the fornix. FA in these areas were strongly associated with average PVA scores ($r_s = -0.701$, $P < 0.001$; $r_s = -0.801$, $P < 0.001$; $r_s = 0.524$, $P = 0.002$, respectively), and levels of maternal verbal abuse. Across groups FA in region 1 correlated with verbal IQ ($r_s = 0.411$, $P = 0.024$) and verbal comprehension index ($r_s = 0.437$, $P = 0.016$). FA in region 2 was inversely associated with ratings of depression ($r_s = -0.504$), dissociation ($r_s = -0.373$) and 'limbic irritability' ($r_s = -0.602$). FA in region 3 was inversely correlated with ratings of somatization ($r_s = -0.389$) and anxiety ($r_s = -0.311$).

Conclusions—Exposure to PVA may be associated with alteration in the integrity of neural pathways with implications for language development and psychopathology.

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Introduction

Psychiatry is entering an exciting phase of synthesis in our understanding of the interplay between biology and early experience in the genesis of psychiatric disorders. Genetic studies have identified polymorphisms that interact with exposure to adverse childhood experiences to enhance risk for psychopathology (1,2), and imaging studies have identified brain regions that appear to be vulnerable to the effects of early abuse or stress (3). Childhood sexual abuse (CSA) has come under intense scrutiny as a psychiatric risk factor, though emotional maltreatment may be a more frequent, elusive and insidious problem. Emotional abuse encompasses several forms of childhood maltreatment, such as witnessing domestic violence (WDV) and exposure to verbal aggression (VA) (4). Generally, exposure to VA has received little attention as a specific form of abuse, though we recently reported that young adults exposed to parental verbal abuse (PVA) had elevated symptoms of depression, anxiety, and dissociation. Effect sizes for PVA were comparable to those for WDV or extra-familial CSA (5).

Understanding the importance of emotional abuse is critically important, as parents, physicians, teachers and other individuals responsible for the well-being of children are generally unaware of the potential consequences of exposure to PVA (6,7). Identify neurobiological correlates of exposure to PVA may lead to important changes in parental behavior, and provide a more articulate framework for exploring the relationship between psychopathology and parenting.

To assess the potential consequences of PVA we conducted a diffusion tensor imaging (DTI) analysis of white matter (WM) tract integrity in young adults with and without high-level exposure to PVA. Abnormalities in the corpus callosum, the brain's most extensive WM tract, have been observed with conventional imaging in children and adolescents exposed to physical abuse (PA), CSA or neglect (10-13). We recently found that corpus callosum size was most significantly altered by CSA that occurred at 9-10 years of age (14). DTI, which analyzes the restricted diffusion of water molecules, provides a more detailed assessment of fiber tracts than conventional MRI (15), and has emerged as a powerful new technique for studying the role of neural connectivity in health and disease (15).

A priori, we hypothesized that exposure to PVA would affect the integrity of left hemisphere pathways involved with processing language, as well as fiber tracts involved in emotional regulation. We now report the first evidence of a potential deleterious effect of ridicule, humiliation and disdain on brain connectivity.

Methods and Materials

Participants and Screening

The McLean Hospital Institutional Review Board approved all procedures. The purpose and meaning of this study was explained to subjects, who provided written informed consent. To be eligible, subjects had to be between 18-25 years of age, right-handed, unmedicated, with a self-reported history of exposure to PVA, but to no other form of early stress or trauma, or healthy controls without such exposure. Subjects were excluded who had a history of CSA, WDV, parental loss, neglect, or significant PA, as well as exposure to war, gang violence, motor vehicle accidents, near drowning, fires, natural disasters or animal attacks. Subjects were also required to be free from any neurological disease or insult, including any degree of head trauma resulting in loss of consciousness. Subjects were excluded with a history of premature birth or birth complications; a history of being shaken in infancy or childhood, maternal substance abuse during pregnancy; or medical disorders that could affect brain development. Subjects selected had no more than minimal history of substance use or alcohol use, and tested negative for drugs and alcohol on each visit.

Potential subjects responded to advertisements with the title “Memories of Childhood”, were briefly screened by phone for age, handedness and medication status, and then completed an online assessment instrument with 2342 entry fields that provide a vast array of information regarding childhood history, development, and symptomatology. Degree of exposure to PVA was assessed using the verbal abuse scale (VAS) (5). Subjects with high-level exposure to PVA were required to have a mean parental VAS score ≥ 40 , which corresponds to weekly – monthly exposure to various forms of criticism, scolding, ridicule or yelling and screaming, or a maximal parent VAS score (either mother or father) ≥ 50 . This degree of exposure to PVA occurred in 16.7% of online respondents with no history of CSA, PA or WDV. Control subjects had no exposure to PVA, and no history of DSM-IV Axis-I psychiatric disorders on structured diagnostic interview (16).

From 1,271 respondents who completed online evaluations, 31 subjects exposed to PVA and 31 potential controls were invited to the laboratory for detailed interviews. High quality DTI scans, free from motion artifacts, were collected on 16 subjects with PVA (4M/12F, mean age 21.9 ± 2.4 yrs) and 16 healthy controls (5M/11F, 21.0 ± 1.6 yrs), who met our rigorous inclusion and exclusion criteria (Table I). PVA subjects had average parental VAS scores of 42 ± 9 and maximal parental VAS scores of 66 ± 12 , versus 12 ± 7 and 16 ± 7 for controls, respectively. Onset of PVA was at 6.9 ± 3.2 years (range 3–13 years of age). Seven subjects continue to experience PVA. It abated 4.3 ± 1.7 years ago in the remainder. Hence, it has been a chronic stressor, lasting an average of 12.3 ± 4.1 years. Forty-four percent of the PVA subjects had a history of depression, though none currently met full criteria. Three of the PVA subjects had current anxiety disorders (two with generalized anxiety, one with panic and obsessive compulsive disorders), and another had attention-deficit hyperactivity disorder and a history of phobias. PVA subjects and controls did not differ in paternal or maternal education levels (Table I), but differed substantially in perceived financial sufficiency (Mann Whitney U Test = 50, $P=0.002$). Half of the PVA subjects felt they came from families that had less than enough, or much less than enough money to meet their family's needs. None of the controls came from families with a perception of less than enough money, and 62.5% came from families with more than enough, or much more than enough money to meet their family's needs.

Clinical Measures

All subjects were administered structured diagnostic interviews (16) for current and life-time history of DSM-IV Axis I and II psychiatric disorders. History of exposure to VA, and to no other forms of maltreatment, were confirmed using the 100-item semi-structured Traumatic Antecedents Interview (17). Verbal IQ and verbal comprehension Index (VCI) were assessed using the WAIS-III (18). Ratings of dissociation, ‘limbic irritability’, depression and anxiety were obtained using the Dissociative Experience Scale, (19) limbic system checklist–33 (20), and Kellner's Symptom Questionnaire (21), respectively. These measures were selected, *a priori*, as we had previously reported that they were markedly elevated in a separate sample of young adults with a history of exposure to PVA (5).

Magnetic Resonance Imaging

Image Acquisition—MRI examinations were conducted at the Brain Imaging Center at McLean Hospital. The head was stabilized with cushions and tape before scanning to help minimize movement. Multiple diffusion-weighted images (DWIs), with 12 encoding directions and an additional T2-weighted scan, were acquired using a 3T Siemens Trio scanner with standard single shot, spin echo, echo planar acquisition sequence with eddy current balanced diffusion weighting gradient pulses to reduce distortion (22). Scan parameters were: $b=1000$ sec/mm², TE/TR=81msec/5sec; matrix=128×128 on 220mm×220mm FOV; slices 5mm without gap resulting in voxels of $1.71875 \times 1.71875 \times 5$ mm. Four magnitude averages provided sufficient signal-to-noise ratios. Volumetric T1-weighted anatomic reference images were

acquired using an MP-RAGE sequence (TE/TR/TI=2.74ms/2.1s/1/1s; 256×256×128 matrix for 1×1×1.3 mm voxels).

Image Processing and Analysis—DTI preprocessing, including skull stripping using the Brain Extraction Tool (BET) and Eddy current correction, were performed using the FMRIB Software Library (FSL, Oxford, U.K.). A diffusion tensor model was fit to each voxel to create fractional anisotropy (FA) images. The TBSS tool in FSL was used to calculate tract-based differences in FA values between the PVA group and controls (see Supplemental Fig. 1). TBSS is a new approach for group difference determination that uses an anatomically-based carefully tuned nonlinear registration procedure to project results onto an alignment-invariant tract representation (the “mean FA skeleton”) for voxelwise analysis of multi-subject diffusion data (23). TBSS computes a group mean FA skeleton, which represents the centers of all fiber bundles that are common to the subjects involved in the study (23). Each subject's aligned FA image was projected onto the skeleton, by filling the skeleton with FA values from the nearest relevant tract center. Group-based skeletonized FA maps were used for statistical analysis, applying a General Linear Model covariate analysis. This analysis adjusted for effects of gender, age, maternal and paternal education, and household finances. The latter three measures were included as separate covariates, as research suggests that measures of income and education may serve as more robust correlates of child development than a composite measure of socioeconomic status (24). Requisite significance level was set, *a priori*, to detect regions of at least 30 consecutive voxels in which uncorrected group differences exceeded a threshold of $P < 0.0005$, to balance risk of type I and type II errors.

Exploratory correlation analyses assessed whether regional differences in FA could potentially account for a significant portion of the variance in pre-specified symptom ratings. Similarly, exploratory correlation analyses were performed for possible associations between FA in identified regions and verbal IQ and VCI on the WAIS-III (18). We hypothesized that exposure to aversive or punishing verbal stimuli may exert a counterproductive effect on the development of language skills, based on the assumption that the development of linguistic skills depends on exposure to engaging and enjoyable aspects of language and communication. The idea that language and cognitive abilities may suffer if the communication is not engaging (flat, monotone, not age-appropriate) is supported by studies that report deficits in language skills and cognitive abilities in children with depressed mothers (25), who tend to communicate with their children in this manner. The idea that exposure to violence can interfere with neurocognitive development is supported by studies reporting significant IQ and reading deficits in children who witnessed domestic violence or were exposed to other forms of aggression (26,27).

Both cases and controls were included in the correlation analyses, as we were interested in assessing potential functional correlates of these delineated WM segments in the general population. Although subjects were dichotomized into PVA and control groups using cutoff scores, all subjects had some degree of exposure, and our selection criteria were completely inclusive regarding degree of exposure. Within the actual sample there was only a 2.5 point gap between lowest mean VAS score for PVA subject and highest VAS score for controls. In short, the entire range of VAS scores was sampled with no significant gap in scores between groups, and the distribution of PVA scores for the entire sample did not depart significantly from a single normal distribution (Kolmogorov-Smirnov Test: $z = 1.022$, $p = 0.247$). Second, most of the subjects in our PVA group would be controls in other studies. Third, fiber tract regions identified by TBSS had FA values that showed a strong rank-order correlation with degree of exposure to PVA, and FA values for the entire sample were well-characterized by single normal distributions. Hence, although we dichotomized subjects, it appears that we were dealing less with a threshold or stair-step effect than with a graded response between exposure to PVA and regional FA. Thus, we approached the correlation analysis from the perspective

of a single population of healthy young adult subjects with different degrees of exposure to PVA, and differing FA values in the identified WM tract segments. Examining correlations in only one group restricts the range of the independent variable and can seriously bias results (28). Spearman rank order correlation was used to assess the degree of relationship between variables, to minimize concerns about homoscedasticity, and the impact of group differences on these associations.

Tract-tracing—Probabilistic tract-tracing was used to help identify the most likely fiber tract (s) passing through WM regions identified by TBSS as differing significantly between groups. These WM areas were projected back from MNI space to individual diffusion space, and used as seeding points to trace fiber tracts that passed through this region in representative subjects. Before probabilistic tracking, Markov Chain Monte Carlo sampling was run to build up distributions of diffusion parameters at each voxel using BEDPOST (Bayesian Estimation of Diffusion Parameters Obtained using Sampling Techniques) (29). Probabilistic tractography was performed using FSL.

Detailed Tractography was then performed in representative PVA and control subjects using MedINRIA (Medical Image Navigation and Research Tool by INRIA; <http://www.sop.inria.fr/asclepios/software/MedINRIA/>) to better localize regions of statistically significant differences (determined by TBSS) along the likely pathways identified by probabilistic tract tracing. Regions of interest were selected on the directionally encoded tensor maps similar to the methods described by Vernooij et al. (30) and Concha et al. (31). Minimum fiber length was set to 5 mm and the smoothness of reconstructed fiber to 20. Other parameters for fiber tracking used MedINRIA default values. Tracking of fibers terminated when FA fell below a threshold of 0.18.

Results

TBSS identified three portions of the FA skeleton with reduced FA that exceeded pre-selected criteria for significance and voxel size. The largest and most significant portion ($F(1,26)=29.12$, $P=0.00001$; voxel size=49; MIN coordinates $x=-44$, $y=-32$, $z=3$; Fig. 1,2) was located in the left superior temporal gyrus and identified by tract tracing as the arcuate fasciculus. FA values in this region, covaried for age, gender, parental education and family financial status, were 22% lower in the PVA group than controls. There was a strong correlation between FA values and average parental VAS score ($r_s=-0.701$, $P<0.001$). Multiple regression analysis indicated that FA values in this region correlated with levels of both maternal ($\beta=-.730$, $p<0.001$) and paternal ($\beta=-.391$, $p=0.002$) VA. FA values in this region were significantly correlated with verbal IQ ($r_s=0.411$, $P=0.024$) and VCI ($r_s=0.437$, $P=0.016$).

FA, in the second region identified, was reduced by 26.2% in the PVA group ($F(1,29)=24.4$, $P<0.0002$; voxel size=30; MIN coordinates $x=-28$, $y=-51$, $z=-1$; Fig. 2,3). This region was located in the left fusiform gyrus by the posterior tail of the hippocampus, and appeared to lie along a portion of the cingulum bundle. FA correlated substantially with average levels of parental VAS ($r_s=-0.801$, $P<0.001$), and correlated with both maternal ($\beta=-.803$, $p<0.001$) and paternal ($\beta=-0.470$, $p<0.001$) VA ratings. Self-report ratings of depression ($r_s=-0.504$, $P=0.004$), dissociation ($r_s=-0.373$, $P<0.05$) and 'limbic irritability' ($r_s=-0.602$, $P<0.001$) were inversely correlated with FA values in this region.

FA in the third region identified, was reduced by 23.8% in the PVA group ($F(1,29)=17.8$, $P<0.0003$; voxel size=37; MIN coordinates $x=-3$, $y=-14$, $z=22$; Fig. 2,4), and was located around the left body of the fornix. FA was not influenced by any of the covariates (all P values >0.5), but correlated with average parental VAS ($r_s=0.524$, $P=0.002$; Fig 7). Multiple regression revealed significant correlations with maternal VAS ($\beta=-0.589$, $p<0.001$) but not

paternal VAS ($\beta=-0.120$, $p>0.4$). Region 3 FA values correlated with self-report ratings of somatization ($r_s=-0.389$, $P=0.03$), and showed a trend level association with anxiety ($r_s=-0.311$, $P=0.09$). Blind manual measures of FA were performed to verify results of TBSS for this small region. Manual fornix FA measures correlated strongly with TBSS ($r = 0.844$, $p < 10^{-8}$). They were reduced by 21.3% in the PVA group ($F(1,29)=10.36$, $p<0.003$), and correlated significantly with maternal VAS ($r_s=-0.357$, $p=0.05$), but not paternal VAS ($r_s=-0.071$, $p>0.6$).

One concern in examining the potential effects of exposure to PVA on fiber tracts is that PVA may be due to parental mental illness, and differences observed may be more a consequence of heredity than exposure. To test this possibility we reexamined the association covarying for history of maternal and paternal mental illness. Scores of zero were given for no history, 1 for a definite history and 0.5 for a possible history. Seventy-five percent of controls indicated that neither parent had a definite or possible history of mental illness versus only 38% of PVA subjects. Group differences remained significant after adjustment: Region 1 ($F(1,24)=19.41$, $P<0.0002$); Region 2 ($F(1,27)=14.14$, $P<0.001$) and Region 3 ($F(1,27)=10.37$, $P=0.003$), suggesting that the association between exposure to PVA and reduced regional FA, was not simply an artifact of parental mental illness. The most significant predictor of PVA was financial insufficiency, which was controlled for in all analyses.

Detailed tractography illustrates the apparent location of statistically significant differences in FA, derived by TBSS, along likely fiber tracts passing through these regions. As seen in Figure 5, fibers passing through Region 1 were arcuate fasciculus fibers projecting between temporal and frontal regions, most specifically the more anterior fibers from the caudal superior temporal cortex passed through the region. Likely fibers passing through Region 2 belonged to the cingulum bundle, and TBSS delineated fibers projecting to the hippocampal region (Fig. 6). Fibers passing through Region 3 were traced in all subjects, and observed to follow the course of the fornix, which connects the hippocampus to the mammillary body and septal nucleus (Fig. 7).

Discussion

This study provides preliminary evidence that exposure to PVA is associated with alteration in the integrity of neural pathways. Region 1 was located in the left superior temporal gyrus, and appeared to consist of long association fibers constituting the arcuate fasciculus. Traditionally, the arcuate fasciculus is known as the fiber tract connecting Wernicke's area in the temporoparietal junction with Broca's area in the inferior frontal gyrus. Recent anatomical studies suggest that the arcuate fasciculus connects caudal superior temporal area 22 with frontal lobe areas 8 and 46, and provides a pathway for the prefrontal cortex to receive and modulate auditory information (32). FA in Region 1 correlated with verbal IQ and VCI. PVA subjects and controls did not differ to a significant degree in verbal IQ or VCI (Table I), suggesting that the effects were relatively subtle. PVA subjects differed from controls in two of seven verbal subtests of the WAIS III: comprehension (which tests ability to deal with abstract social conventions, rules and expressions) and similarities (which tests abstract verbal reasoning). Comprehension subtest scores correlated particularly strongly with reduced FA in region 1 ($r_s=0.606$, $p<0.001$). Breier et al (33) recently reported that comprehension deficits after stroke were specifically associated with lower FA values in the arcuate fasciculus of the left hemisphere.

Region 2 was located in the left fusiform gyrus by the posterior tail of the hippocampus, and appeared to contained fibers from the ventral part of the cingulum bundle. Left-sided reduction in FA through three of four subregions of the cingulum bundle has been observed in patients with post-traumatic stress disorder (34), indicating that this is probably a stress-susceptible

structure. Overall, reduced FA in region 2 was associated with elevated scores of ‘limbic irritability’, dissociation and depression. ‘Limbic irritability’ is a term we have used (5,20) to describe the presence of symptoms often seen in patients with temporal lobe epilepsy, such as paroxysmal somatic disturbances, brief hallucinatory events, visual illusions, automatisms, and dissociative disturbances (35). The cingulum bundle is the most prominent tract of the limbic lobe, and connects the limbic lobe with the neocortex, particularly the cingulate gyrus.

Region 3 was located in the left fornix, and reduced FA in this segment was associated with increased ratings of somatization and anxiety. The septo-hippocampal system, connected together via the fornix, plays a major role in the mediation of anxiety (36). Interestingly, the hippocampus receives serotonin fibers from the midbrain raphe via two pathways: the cingulum bundle (which predominantly innervates dorsal hippocampus), and the fornix (which innervates all portions) (37,38). Hence, two of the fiber tracts with segments of reduced FA in PVA subjects, provide pathways for serotonin fibers to innervate the hippocampus.

Although DTI studies are rapidly increasing our understanding of the effects of disease processes on WM tracts, caution is required in interpreting reductions in FA. The analytical technique employed relies on 1mm resampling of data to determine local maxima of FA values. As such, it is sensitive to structures whose size is small compared to the original EPI image voxel size or to tracts that are adjacent to sharp white/non white matter boundaries and their resultant partial volume effects. This is of potential concern in the analysis of FA values for regions 2 and 3. The left fusiform gyrus is adjacent to the atrium of the lateral ventricle, and the left fornix is a relatively small WM tract situated within the lateral ventricle. TBSS reduces the challenges of alignment in FA images without introducing smoothing, and calculates group FA values using voxels from the center of each subject's tract to minimize inclusion of voxels that border sharp non-white matter boundaries. However, partial volume effects are a MR acquisition problem, limited by signal to noise, and not correctable through analysis. FA values observed in these regions were very similar to previously published FA values for healthy controls (39-41). The particularly low FA values observed in region 2 may arise as consequence of divergent crossing of fibers passing through this region. The significance of the group differences and the strength and appropriateness of the anatomical-functional correlations, suggest that FA differences in these regions represent areas of reduced WM integrity and resultant psychopathological effects. Further confirmation will need to occur through replication in larger samples, and through refinements in resolution (42).

Curiously, TBSS identified group differences in FA along specific portions of fiber tracts, but did not delineate the entire tract. This proclivity to identify segments is a property of the program (seen in the representative image in the TBSS user manual), and is determined to a significant degree by the criteria set for cluster size and significance. However, entire tracts were not delineated in this sample even when significance and cluster size levels were lowered. We suspect that reduced FA is restricted to a fraction of the fibers constituting the tract, and that regions of reduced FA become apparent along segments of the tract where these particular fibers enter or exit the pathway, or when these fibers represent a substantial proportion of the pathway due to the exiting of other fibers. Why PVA is associated with reduced FA is unclear. It is unlikely that PVA directly affects the number of axons, as this is generally established early in childhood. PVA however, may affect axon diameter, microtubular structure, and the proportion of myelinated and unmyelinated fibers that constitute a component of the pathway, as these properties are established later in development (8), and appear susceptible to effects of experience during preadolescent and peripubertal periods (9).

The current study is limited by the modest sample size, and by the rigorous selection criteria. PVA subjects studied were healthier than those previously assessed (5), and had average IQ scores higher than the general population, but comparable to those of college graduates. These

subjects were not representative of individuals typically exposed to emotional maltreatment, who often experience other forms of abuse, and show greater sequelae. Subjects were selected to provide a test of the hypothesis unconfounded (to the greatest degree feasible) by exposure to other forms of early stress, medications, or agents that could affect brain development. Identifying abnormalities in such a select group provides a conservative test of the hypothesis. We suspect that more severely affected individuals would have had more extensive findings, though it may have been harder to attribute their findings to PVA.

Overall, results from this study support a hypothesis that the brain is chiseled in precise ways by exposure to adverse early experience. Analysis of neural connectivity patterns provides preliminary but intriguing evidence that the arcuate fasciculus, cingulum bundle and fornix may be vulnerable to the effects of early stress. Diminished fiber integrity, aberrant crossing patterns, alterations in axonal diameter, or extent of myelination along portions of these pathways may underlie some of the psychiatric (5) and neurocognitive (43) consequences of childhood abuse. Although this is a preliminary study of modest size we characterized young adults who to the best of our knowledge only suffered from parental verbal abuse. Results of this study may have public health implications, raising the possibility that parental criticism, condemnation and ridicule can exert deleterious effects on the developing brain.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Caspi A, McClay J, Moffitt TE, Mill J, Martin J, Craig IW, et al. Role of genotype in the cycle of violence in maltreated children. *Science* 2002;297:851–854. [PubMed: 12161658]
2. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science* 2003;301:386–389. [PubMed: 12869766]
3. Teicher MH, Tomoda A, Andersen SL. Neurobiological consequences of early stress and childhood maltreatment: are results from human and animal studies comparable? *Ann N Y Acad Sci* 2006;1071:313–323. [PubMed: 16891580]
4. Bernstein DP, Ahluvalia T, Pogge D, Handelsman L. Validity of the Childhood Trauma Questionnaire in an adolescent psychiatric population. *J Am Acad Child Adolesc Psychiatry* 1997;36:340–348. [PubMed: 9055514]
5. Teicher MH, Samson JA, Polcari A, McGreenery CE. Sticks, stones, and hurtful words: relative effects of various forms of childhood maltreatment. *Am J Psychiatry* 2006;163:993–1000. [PubMed: 16741199]
6. Manning C, Cheers B. Child abuse notification in a country town. *Child Abuse Negl* 1995;19:387–397. [PubMed: 7606518]
7. Saulsbury FT, Campbell RE. Evaluation of child abuse reporting by physicians. *Am J Dis Child* 1985;139:393–395. [PubMed: 3976630]
8. Keshavan MS, Diwadkar VA, DeBellis M, Dick E, Kotwal R, Rosenberg DR, et al. Development of the corpus callosum in childhood, adolescence and early adulthood. *Life Sci* 2002;70:1909–1922. [PubMed: 12005176]

9. Juraska JM, Kopeck JR. Sex and environmental influences on the size and ultrastructure of the rat corpus callosum. *Brain Res* 1988;450:1–8. [PubMed: 3401704]
10. De Bellis MD, Keshavan MS, Shifflett H, Iyengar S, Beers SR, Hall J, et al. Brain structures in pediatric maltreatment-related posttraumatic stress disorder: a sociodemographically matched study. *Biol Psychiatry* 2002;52:1066–1078. [PubMed: 12460690]
11. De Bellis MD, Keshavan MS, Clark DB, Casey BJ, Giedd JN, Boring AM, et al. Developmental traumatology. Part II: Brain development. *Biol Psychiatry* 1999;45:1271–1284. [PubMed: 10349033]
12. Teicher MH, Dumont NL, Ito Y, Vaituzis C, Giedd JN, Andersen SL. Childhood neglect is associated with reduced corpus callosum area. *Biol Psychiatry* 2004;56:80–85. [PubMed: 15231439]
13. Teicher MH, Ito Y, Glod CA, Andersen SL, Dumont N, Ackerman E. Preliminary evidence for abnormal cortical development in physically and sexually abused children using EEG coherence and MRI. *Annals of the New York Academy of Sciences* 1997;821:160–175. [PubMed: 9238202]
14. Andersen SL, Tomada A, Vincow ES, Valente E, Polcari A, Teicher MH. Preliminary evidence for sensitive periods in the effect of childhood sexual abuse on regional brain development. *Journal of Neuropsychiatry and Clinical Neurosciences*. 2008in press
15. Catani M. Diffusion tensor magnetic resonance imaging tractography in cognitive disorders. *Curr Opin Neurol* 2006;19:599–606. [PubMed: 17102700]
16. First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured clinical interview for DSM-IV axis I disorders - clinician version (SCID-CV). Washington, DC: American Psychiatric Press; 1997.
17. Herman, JL.; Perry, JC.; van der Kolk, BA. Traumatic Antecedents Interview. Boston: The Trauma Center; 1989.
18. Wechsler, D. Wechsler Adult Intelligence Scale-III. New York: The Psychological Corporation; 1997.
19. Bernstein EM, Putnam FW. Development, reliability and validity of a dissociation scale. *J Nerv Ment Dis* 1986;174:727–735. [PubMed: 3783140]
20. Teicher MH, Glod CA, Surrey J, Swett C Jr. Early childhood abuse and limbic system ratings in adult psychiatric outpatients. *Journal of Neuropsychiatry & Clinical Neurosciences* 1993;5:301–306. [PubMed: 8369640]
21. Kellner R. A symptom questionnaire. *Journal of Clinical Psychiatry* 1987;48:268–273. [PubMed: 3597327]
22. Reese TG, Heid O, Weisskoff RM, Wedeen VJ. Reduction of eddy-current-induced distortion in diffusion MRI using a twice-refocused spin echo. *Magn Reson Med* 2003;49:177–182. [PubMed: 12509835]
23. Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage* 2006;31:1487–1505. [PubMed: 16624579]
24. Naka D, Maeshima S, Takehara R, Naka Y, Tsuji N, Imai H, et al. Amnesic syndrome after right temporo-occipital subcortical hemorrhage. *No Shinkei Geka* 1995;23:439–443. [PubMed: 7753325]
25. Sohr-Preston SL, Scaramella LV. Implications of timing of maternal depressive symptoms for early cognitive and language development. *Clin Child Fam Psychol Rev* 2006;9:65–83. [PubMed: 16817009]
26. Koenen KC, Moffitt TE, Caspi A, Taylor A, Purcell S. Domestic violence is associated with environmental suppression of IQ in young children. *Dev Psychopathol* 2003;15:297–311. [PubMed: 12931829]
27. Delaney-Black V, Covington C, Ondersma SJ, Nordstrom-Klee B, Templin T, Ager J, et al. Violence exposure, trauma, and IQ and/or reading deficits among urban children. *Arch Pediatr Adolesc Med* 2002;156:280–285. [PubMed: 11876674]
28. Russo, R. Statistics for the Behavioral Sciences: An Introduction. Psychology Press; 2003.
29. Behrens TE, Woolrich MW, Jenkinson M, Johansen-Berg H, Nunes RG, Clare S, et al. Characterization and propagation of uncertainty in diffusion-weighted MR imaging. *Magn Reson Med* 2003;50:1077–1088. [PubMed: 14587019]
30. Vernooij MW, Smits M, Wielopolski PA, Houston GC, Krestin GP, van der Lugt A. Fiber density asymmetry of the arcuate fasciculus in relation to functional hemispheric language lateralization in

- both right- and left-handed healthy subjects: a combined fMRI and DTI study. *Neuroimage* 2007;35:1064–1076. [PubMed: 17320414]
31. Concha L, Gross DW, Beaulieu C. Diffusion tensor tractography of the limbic system. *AJNR Am J Neuroradiol* 2005;26:2267–2274. [PubMed: 16219832]
 32. Makris N, Kennedy DN, McInerney S, Sorensen AG, Wang R, Caviness VS Jr, et al. Segmentation of subcomponents within the superior longitudinal fascicle in humans: a quantitative, in vivo, DT-MRI study. *Cereb Cortex* 2005;15:854–869. [PubMed: 15590909]
 33. Breier JI, Hasan KM, Zhang W, Men D, Papanicolaou AC. Language dysfunction after stroke and damage to white matter tracts evaluated using diffusion tensor imaging. *AJNR Am J Neuroradiol* 2008;29:483–487. [PubMed: 18039757]
 34. Kim SJ, Jeong DU, Sim ME, Bae SC, Chung A, Kim MJ, et al. Asymmetrically altered integrity of cingulum bundle in posttraumatic stress disorder. *Neuropsychobiology* 2006;54:120–125. [PubMed: 17199097]
 35. Spiers, PA.; Schomer, DL.; Blume, HW.; Mesulam, MM. Temporolimbic epilepsy and behavior. In: Mesulam, MM., editor. *Principles of Behavioral Neurology*. Philadelphia: F.A. Davis; 1985. p. 289–326.
 36. Degroot A, Treit D. Anxiety is functionally segregated within the septo-hippocampal system. *Brain Res* 2004;1001:60–71. [PubMed: 14972654]
 37. Moore RY, Halaris AE. Hippocampal innervation by serotonin neurons of the midbrain raphe in the rat. *J Comp Neurol* 1975;164:171–183. [PubMed: 52660]
 38. Patel TD, Azmitia EC, Zhou FC. Increased 5-HT_{1A} receptor immunoreactivity in the rat hippocampus following 5,7-dihydroxytryptamine lesions in the cingulum bundle and fimbria-fornix. *Behav Brain Res* 1996;73:319–323. [PubMed: 8788527]
 39. Jones DK, Catani M, Pierpaoli C, Reeves SJ, Shergill SS, O'Sullivan M, et al. Age effects on diffusion tensor magnetic resonance imaging tractography measures of frontal cortex connections in schizophrenia. *Hum Brain Mapp* 2006;27:230–238. [PubMed: 16082656]
 40. Shergill SS, Kanaan RA, Chitnis XA, O'Daly O, Jones DK, Frangou S, et al. A diffusion tensor imaging study of fasciculi in schizophrenia. *Am J Psychiatry* 2007;164:467–473. [PubMed: 17329472]
 41. Eluvathingal TJ, Hasan KM, Kramer L, Fletcher JM, Ewing-Cobbs L. Quantitative Diffusion Tensor Tractography of Association and Projection Fibers in Normally Developing Children and Adolescents. *Cereb Cortex*. 2007
 42. Schmahmann JD, Pandya DN, Wang R, Dai G, D'Arceuil HE, de Crespigny AJ, et al. Association fibre pathways of the brain: parallel observations from diffusion spectrum imaging and autoradiography. *Brain* 2007;130:630–653. [PubMed: 17293361]
 43. Navalta CP, Polcari A, Webster DM, Boghossian A, Teicher MH. Effects of childhood sexual abuse on neuropsychological and cognitive function in college women. *J Neuropsychiatry Clin Neurosci* 2006;18:45–53. [PubMed: 16525070]

Figure 1.

Coronal, axial and sagittal location of white matter tract region 1 (shown in red, centered at $x=-44$, $y=-32$, $z=3$) that differed most significantly in fractional anisotropy (FA) between subjects with history of exposure to high levels of parental verbal aggression and healthy controls. Region 1 is located in the left superior temporal gyrus and contains fibers from the arcuate fasciculus. Green shows the mean FA skeleton (which represents the centers of white matter fiber bundles that are common to the subjects involved in this study). The background images are MNI152 templates.

Figure 2.

Scatter plot showing individual differences in fractional anisotropy (FA) between subjects with a history of exposure to high levels of parental verbal aggression and healthy controls in: (A) region 1 (arcuate fasciculus left superior temporal gyrus); (B) region 2 (cingulum bundle in the left fusiform gyrus by the posterior tail of the hippocampus); and (C) region 3 (left fornix by corpus callosum).

Figure 3.

Coronal, axial and sagittal location of white matter tract region 2 (shown in red, centered at $x=-28$, $y=-51$, $z=-1$) that differed significantly in fractional anisotropy (FA) between subjects with history of exposure to high levels of parental verbal aggression and healthy controls. Region 2 is located in the left fusiform gyrus by the posterior tail of the hippocampus and contains fibers from the cingulum bundle. Green shows the mean FA skeleton. The background images are MNI152 templates.

Figure 4.

Coronal, axial and sagittal location of white matter tract region 3 (shown in red, centered at $x=-3$, $y=-14$, $z=22$) that differed significantly in fractional anisotropy (FA) between subjects with history of exposure to high levels of parental verbal aggression and healthy controls. Region 3 contains fibers from the body of the left fornix. Green shows the mean FA skeleton. The background images are MNI152 templates.

Figure 5. Detailed tractography of left arcuate fasciculus fibers in a representative subject color coded by fiber direction. Yellow region marks segment of the pathway delineated by TBSS as having significantly lower FA in subjects with PVA versus controls.

Figure 6. Detailed tractography of left cingulum bundle fibers in a representative subject color coded by fiber direction. Yellow region marks segment of the pathway delineated by TBSS as having significantly lower FA in subjects with PVA versus controls.

Figure 7. Detailed tractography of left fornix fibers in a representative subject color coded by fiber direction. Yellow region marks segment of the pathway delineated by TBSS as having significantly lower FA in subjects with PVA versus controls.

Table I**Subject Characteristics**

Characteristic	PVA Subjects (n = 16)	Healthy Control Subjects (n = 16)	P Value
Age, mean (SD), y	21.9 (2.4)	21.0 (1.6)	.242
Sex, No. M/F	4/12	5/11	.78
VIQ, mean (SD)	121 (13)	129 (11)	.094
PIQ, mean (SD)	120 (11)	116 (9)	.295
FSIQ, mean (SD)	122 (12)	124 (11)	.610
Mother VAS, mean (SD)	56 (24)	14 (9)	.001 [*]
Father VAS, mean (SD)	31 (27)	11 (7)	.015 [*]
Maximal (mother or father) VAS, mean (SD)	66 (12)	16 (7)	.001 [*]
Mother Education, mean (SD), y	15.6 (2.3)	16.3 (2.3)	.399
Father Education, mean (SD), y	16.6 (3.4)	16.7 (3.1)	.914
Perceived Financial Sufficiency	2.7 (1.0)	3.8 (0.7)	.002 [*]

Abbreviations: PVA, Parental Verbal Abuse; VIQ, verbal IQ; PIQ, performance IQ; FSIQ, full-scale IQ; VAS, verbal abuse score.

χ^2 Test. All other *P* values are by *t* test.

^{*} Statistically significant.