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The Relationship Between Child Adversity, Anxiety Symptoms and  
White Matter Integrity

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## Abstract

Chronic activation of the stress response during childhood has been proposed to cause long-term maladaptive changes to the structure of stress response systems, resulting in chronic mental illness. This study helps us to understand how maltreatment in children is associated with differences in white matter integrity and how these factors relate to anxiety symptoms in children. Using Diffusional Kurtosis Imaging data, we examined 106 participants, aged 7-16. Approximately half of the participants were recruited through the Department for Children and Families, and had experienced at least one out-of-home placement following a verified instance of abuse or neglect. Associations between white matter integrity, environmental stressors, and anxiety symptoms were assessed. This study found that specific anxiety symptoms associated with Post-Traumatic Stress Disorder were associated with FA reductions. In addition, levels of general adversity and intrafamilial violence were both associated with Fractional Anisotropy reductions. Understanding the mechanisms by which early adversity is linked to long-term psychiatric outcomes is the first step in designing interventions for this vulnerable population.

Stress, for some, is a state of mind that ebbs and flows depending on the day and situation. However, for children who have been traumatized, chronic and/or extreme stress may contribute to the development of psychopathology. According to the United States Department of Health and Human Services (2012), 1 in 5 children, either currently or at some point in their lives will have a debilitating mental disorder. It is also estimated that 5% of adolescents have met the criteria for Post-Traumatic Stress Disorder (PTSD) and 1 in 4 adolescents will experience Anxiety. Certain environmental effects like trauma/stress, family life, diet, exercise, and peer group can all contribute to a child's neuropsychiatric health. For PTSD and anxiety, however, we may see a stronger correlation between traumatic experience and severity of symptoms (Mancini, Ameringen & MacMillan, 1995; MacMillan et al. 2001). Green et al. (2010) estimated that maltreatment in children was the cause of 45% of the population attributable risk for childhood onset mental disorders. Although trauma is associated with neuropsychiatric complaints in children, most research in the field has been conducted on adults.

### **Literature Review**

Adolescence is a period of time when the brain experiences many structural changes in both gray and white matter regions. Typically, gray matter development increases in volume during childhood, reaches a peak during adolescence, and then proceeds to decline into adulthood (Giedd et al., [1999](#)). On the other hand, white matter tends to increase between childhood and adolescence, and eventually stabilizes in adulthood. (Giedd et al., [1999](#); Tamnes et al., [2009](#)) Efficient communication between disparate grey matter regions is highly dependent on the integrity, or composition, of white matter. Diffusion Kurtosis Imaging (DKI) allows us to visualize water movement within axons, which helps to characterize axonal microstructure. We use Fractional Anisotropy (FA) as a measurement for white matter integrity. FA is thereby

sensitive to axonal size, density, degree of myelination, and organization of white matter. Voxels containing water that moves primarily along the principal diffusion direction, rather than the transverse direction, have higher levels of FA (Ladouceur, Peper, Crone & Dahl, 2011).

A stressful environment can lead to disruptions in white matter formation, thereby leading to psychopathology. Specifically, it is hypothesized that maltreatment induces a chain of stress-mediated effects on both hormones and neurotransmitters, which may affect programming of the glucocorticoid, noradrenergic, and vasopressin oxytocin stress responses (Anderson, Teicher, Polcari & Renshaw, 2002). This may disrupt the capability of brain regions related to these functions, such as the hippocampus, amygdala, neocortex, cerebellum, and white matter tracts (Teicher et al., 2002).

When a child has been maltreated, this only increases the risk of producing long-lasting cognitive, behavioral, and social dysfunction. According to the CDC (2015), childhood maltreatment includes all types of abuse and neglect of a child by a parent, caregiver, or a person in a custodial role. This includes physical, sexual, and emotional abuse as well as neglect. Early life adversity has been thought to alter the brain, and it is believed that psychopathology emerges from these alterations (National Scientific Council on the Developing Child, 2005). Another school of thought lies in the idea that the brain adapts to a stressful environment, and it is only when there is a mismatch between the stressful environment and subsequent environments that psychopathology occurs (Teicher, 2000, 2002; Teicher et al., 2003). Both hypotheses may contribute to the phenomena we see in the brain following maltreatment.

### **Potential Mechanisms**

Evidence shows that the amygdala and hippocampus, which are both implicated in the stress response system are affected by maltreatment. In adults, those with a history of

maltreatment generally have smaller hippocampi than those who were not maltreated (Cohen et al., 2006). The amygdala and hippocampus have high densities of glucocorticoid receptors (implicated with stress hormones released during a stress response), which supports the idea that brain regions most affected by maltreatment are those with many glucocorticoid receptors, or that have some degree of postnatal neurogenesis, leaving them vulnerable to the environment (Morimoto et al., 1996; Suslow et al., 2013; Teicher et al., 2003).

Since white matter is the primary focus of the current study, it is important to mention the potential epigenetic mechanisms underlying white matter changes in the brain after exposure to trauma. Epigenetics refers to chemical modifications to the genome caused by environmental factors. These changes can alter how one's genes are expressed, and thereby the structure of the brain. The TPPP gene, which is involved with neural circuitry development, is implicated in the mechanism for psychopathology and white matter disruptions (Weder et al., 2014). Depending on how this gene is methylated epigenetically, we may see a biologically plausible mechanism by which stress can affect white matter.

### **White Matter**

While there are many brain regions affected by childhood maltreatment, this current study examines white matter integrity in particular. A study by De Bellis et al. (2002) found a 5.9% reduction in white matter volume in maltreated children. During adolescence, many of the connections from the amygdala to the prefrontal cortex (involved in inhibition and regulation of behavior) are developing, amongst many other areas of white matter (Gabard-Durnam et al., 2014). As such, the adolescent brain is extremely vulnerable to depression and other mental illnesses during this period of time. A study by Huang, Gundapeunedi, & Rao (2012) found that children with a history of maltreatment who later went on to develop major depressive

disorder had lower white matter integrity in the superior longitudinal fasciculi and the right cingulum-hippocampal projection. In addition, those who had developed substance-use disorder also had less white matter integrity in similar areas. Here we see evidence for the idea that white matter integrity is correlated with both psychiatric illness and maltreatment.

The idea that some types of abuse, like intrafamilial, are worse than others when it comes to white matter integrity has yet to be fully investigated. Intrafamilial violence may be particularly toxic, as it activates the fear response system involving the amygdala and the hippocampus, which were mentioned previously as including high amounts of glucocorticoid receptors. In children who had suffered from verbal abuse, there have been observed reductions in the arcuate fasciculus, the left body of the fornix, and the cingulum bundle, which are major projections of white matter (Choi et al., 2010). The arcuate fasciculus is involved with human language, and diminished fractional anisotropy measures were associated with lower verbal IQ scores. The reduced integrity of the cingulum bundle and fornix were correlated with depressive and dissociative symptoms. Furthermore, maltreatment does not have to be considered abuse for it to change a child's mental outcome. Parental verbal aggression during childhood has implications for future wellbeing. Those who had experienced verbal aggression from their parents were more likely to score higher on depression, anxiety, and anger-hostility measures (Polcari, Rabi, Bolger & Teicher, 2014). Any amount of stress can have effects on the development of the brain and psychopathology. The current study performs novel regressions using a full range of trauma and anxiety scores. This allows for us to capture the effects of the entire spectrum of adversity.

A large portion of research in this field lies in studying adults who were maltreated as children. A study by Peng et al. (2013) investigated 40 depressive patients aged 18-45 who had

either experienced childhood neglect or had not, as well as 20 healthy controls without depression. Those with depression who had experienced neglect had significantly decreased densities of white matter in the parietal lobe, whereas those with depression, but without childhood neglect showed decreased densities in extra nuclear white matter compared to the healthy controls. Similarly, Zhu et al. (2011) found that in young adults with major depressive disorder, cortical-subcortical white matter showed a reduction in integrity compared to healthy controls. Another study looked at adults aged 20-24 who had witnessed domestic violence as children. They found that the degree of reduction in white matter in the left lateral occipital lobe correlated with the length of exposure to the violence between the ages of 7 and 13 years old (Choi, Jeong, Polcari, Rohan & Teicher, 2012). Here we see further evidence for reductions in white matter integrity in adult brains correlated with maltreatment during childhood.

There are significantly fewer studies where the participants are actually children or adolescents. One of these studies looked at prefrontal cortical white matter integrity in children with maltreatment-related Post-Traumatic Stress Disorder. In comparison to healthy controls, the affected children showed a reduction in this white matter (De Bellis et al., 2002). According to Jackowski et al (2008), children with PTSD who had been maltreated had a reduction in the volume of corpus callosum white matter, particularly areas involved with processing emotional stimuli as well as certain memory functions. These findings are similar to those of a study by De Bellis et al. (2002), which noted a reduction in superior temporal gyrus white matter in children with PTSD who had been maltreated compared to healthy controls. Most current research in white matter and development lies in PTSD- related areas, but there are still discrepancies in the specific fiber tracts affected. The current study will be one of the first to examine whole brain effects of maltreatment and psychopathology proximal to traumatic events.

Current research in this field focuses largely on the adult brain that is fully formed. This is important to understanding how dysfunctional behaviors and brain areas correlate. However, it does not necessarily explain what occurs during development to cause these white matter decreases in brain regions that are vital to emotion and behavior regulation. It also does not explain the age at which we start seeing the effects of trauma in terms of white matter changes. We know that maltreatment in children can lead to adverse behavioral effects during childhood, adolescence, and into adulthood (MacMillan et al., 2001; Rossiter et al., 2015). We also see a decrease in fiber tracts in the brain of those with diagnosed mental disorders that have been previously maltreated. What we do not know is what is occurring at ages 7-16 to the developing brains that have gone through, or are currently going through large amounts of stress in comparison to lower stressed children. This study aims to investigate how trauma is affecting this population given a wide range of phenotypic presentations of trauma, anxiety and PTSD.

Although childhood trauma is associated with a range of psychopathology, including depression and substance abuse disorders, it is beyond the scope of this study to attempt to map the relationship between trauma, white matter, and specific outcomes. PTSD and anxiety will be studied primarily, as there has been strong evidence for PTSD or anxiety disorders in adults who have experienced childhood trauma, as well as the role of white matter in symptom expression. We hypothesize that as phenotypic psychopathology increases, we expect a decrease in white matter integrity, or FA in brain. Furthermore, as adversity increases, we expect to see decreases in FA. Although we are conducting whole brain analyses, we predict effects to be observed in the corpus callosum and anterior white matter tracts connecting subcortical structures with the frontal lobes.

## Methods

### Participants

There were 106 children (57 female) recruited from both the local community and the Vermont Department of Child Services (DCF). The participants ranged from seven to sixteen years of age at the time of scanning. Each participant had varying levels of trauma, anxiety, and PTSD scores. All participants recruited from DCF were seen within 6 months of their out-of-home placement.

### Phenotypic Assessment

**Patient-Reported Measurement Information System Anxiety (PROMIS):** The PROMIS requires participants to indicate on a 5-point Likert scale the extent to which they have experienced each of seven symptoms related to anxiety in the past two weeks, with one indicating “never occurs” and five “always” (Cella et al., 2010). Three participants did not complete the PROMIS for Anxiety.

**Post Traumatic Stress Disorder- Reaction Index (PTSD-RI).** The PTSD-RI requires participants to indicate on a 4-point Likert scale the extent to which they have experienced each of 22 symptoms related to PTSD in the past month, where zero indicates “experienced never” while four is “experienced almost daily.” This is usually administered after a significant trauma (Steinburg et al., 2004). The PTSD-RI was only administered to those participants with a category A trauma. Therefore, twenty participants did not complete the PTSD-RI.

**Yale-Vermont Adversity in Children Scale (Y-VACS).** The Y-VACS requires participants to indicate the severity and frequency of the instance of certain traumatic events that have taken place in their lives. It was designed by the Principal Investigators of this project based on the ACES (Adverse Childhood Experience Score) in order to better capture the

frequency and severity of adverse events. Frequency is indicated by a 3- point Likert scale, where zero is “Never” and two is “More than once.” Severity is also indicated by a 3-point Likert scale, where one is “Mild or suspected” and three is “Severe.” These events are categorized into either intrafamilial or extrafamilial trauma. The Y-VACS is a multi-informant battery in which the child reports on their own experiences (Y-VACS self-report); a parent or guardian reports on the child’s experiences (Y-VACS parent-report); and a trained clinician integrates information from the Y-VACS self-report, Y-VACS parent-report, clinical interview, and DCF case history to complete the Y-VACS clinician-report. The current study used scores from the Y-VACS clinician-report.

Participants completed the PROMIS, PTSD-RI, and Y-VACS self-report at a summer camp designed to enhance research acquisition and incent study involvement. The three measures were a subset of a broader assessment battery. Prior to attending the camp, the child’s parent or legal guardian provided informed consent and the child provided assent to participate. Following the camp, those children who were eligible to participate in the MRI subproject were contacted; prior to completing the MRI assessment, the child’s parent or legal guardian provided informed consent and the child provided assent to participate.

### **Neuroimaging Measures**

**Image acquisition.** Data were acquired at the University of Vermont MRI Center for Biomedical Imaging, which is equipped with a Philips Achieva 3 Tesla scanner. Diffusion-weighted images were acquired using a single shot, spin-echo, echo-planar image (EPI) sequence of 60 contiguous transverse slices of 2.0 mm thickness (TR = 13,000 msec, TE = 87 msec, field of view [FOV] = 240 mm, voxel size =  $2 \cdot 2 \cdot 2$  mm<sup>3</sup>). We acquired diffusion weighted b values

(1000 and 2000 s/mm<sup>2</sup>) in 30 uniformly distributed, noncollinear directions and six additional images with no diffusion weighting.

**Image Processing.** DKI Diffusion weighted images corrected for movement artifacts and eddy-current-induced distortions using the FSL tool EDDY were passed to the diffusion kurtosis estimator (DKE) (Tabesh, Jensen, Ardekani & Helpert, 2011). DKE models tensor estimation using a linearly constrained linear least squares model, in which the constraints ensure physically and/or biologically plausible tensor estimates. Each participant's FA statistics were pre-processed and aligned to the FMRIB52\_FA standard space image (1 mm isotropic) using nonlinear registration in FSL tool tract based spatial statistics (Smith et al., 2006). This was done to standardize the overall shape of the brain. Each participant's standard space FA was projected onto a group-mean FA skeleton (thresholded at FA = 0.2). Voxel-wise between group comparison of skeletonized FA maps was implemented in Randomise (Winkler et al., 2014). Family-wise error was maintained at  $p < 0.05$  using threshold-free cluster enhancement, with 5,000 permutations (Smith & Nichols, 2009).

Four analyses were performed. The first related anxiety measures to FA across 82 participants, as participants who scored a zero or who did not complete the PROMIS were removed. The next analysis related PTSD-RI to FA across 78 subjects, as participants who scored a zero or who did not complete the PTSD-RI were removed. For trauma scores, there were two assessments: one compared 103 participants based on their overall Y-VACS scores, while the other assessed intrafamilial violence scores in the 77 participants who reported intrafamilial violence. This included physical and sexual abuse as well as exposure to domestic violence. Age, sex and handedness were included as covariates in all group level.

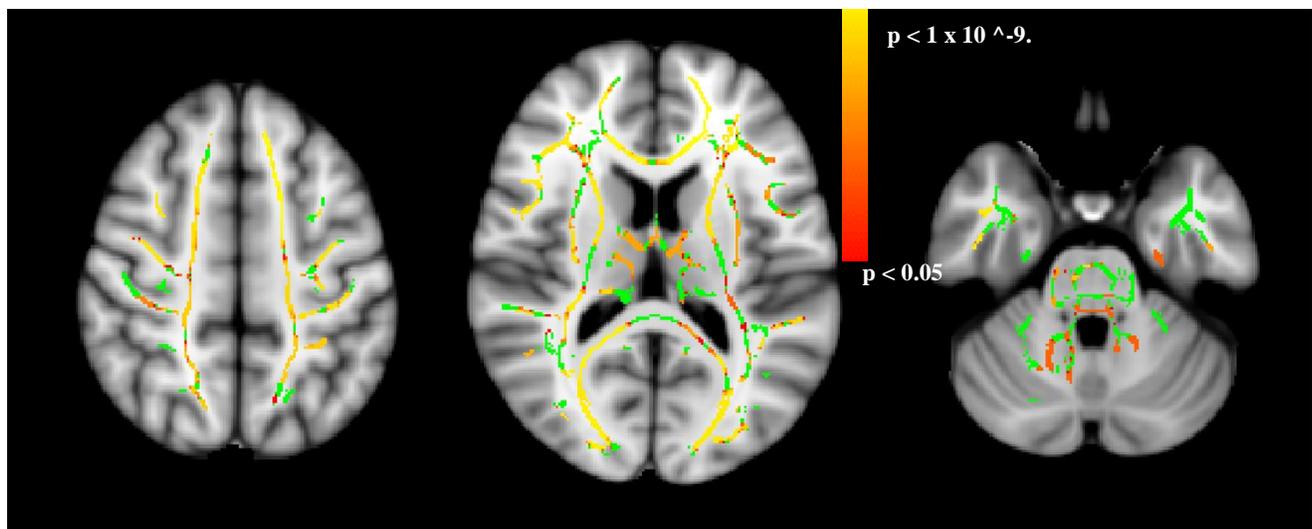
## Results

### PROMIS Anxiety

Whole-brain, voxelwise analysis revealed no regions at which there was a significant association between FA and anxiety symptoms as assessed by the PROMIS.

### PTSD-RI

Whole-brain, voxelwise analysis revealed a large cluster of voxels showing a significant negative association between symptoms of PTSD (assessed by PTSD-RI) and FA ( $r = -.524$ ,  $p < 0.001$ ) (see Figure 1). As PTSD-RI scores increased, FA decreased. These findings were widespread throughout the brain. In order to assess regional variation in effects, we conducted post-hoc tests within specific tracts previously shown to be relevant for childhood adversity and for anxiety symptoms, which were implicated as significant in the whole brain results. Results are contained in Table 1.



**Figure 1:** Tract-based spatial statistics analyses of group means within the white matter skeleton mask (thresholded at 0.2, green voxels) identified one cluster in which fractional anisotropy was significantly elevated in children with elevated PTSD-RI scores compared to those with lower scores. From left to right, axial slices are taken from  $z = 50$ ,  $z = 14$ ,  $z = -30$ . Red-yellow corresponds to low-high significance. Images are presented in the radiological view where the right hemisphere appears on the left of the image, presented in MNI152 standard space.

Table 1. Correlations between FA and PTSD symptoms within specific tracts

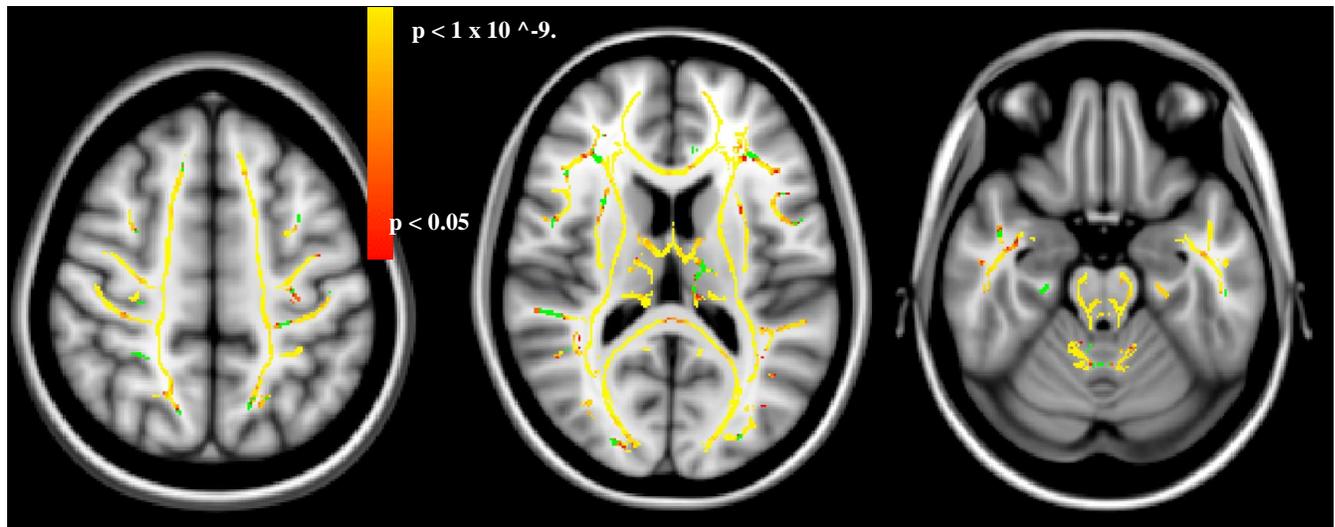
Tract (hemisphere)	R	p <sup>1</sup>
Genu of Corpus Callosum	-.505	$p = 1.2 \times 10^{-5}$
Body of Corpus Callosum	-.463	$p = 5.7 \times 10^{-5}$
Splenium of Corpus Callosum	-.420	$p = 1.29 \times 10^{-4}$
Anterior Corona Radiata (R)	-.481	$p = 3.2 \times 10^{-5}$
Anterior Corona Radiata (L)	-.487	$p = 3.0 \times 10^{-5}$
Uncinate Fasciculus (R)	-.549	$p = 1.39 \times 10^{-7}$
Uncinate Fasciculus (L)	-.440	$P = 1.12 \times 10^{-4}$

<sup>1</sup>Reported p values are corrected for multiple comparisons using a modified Bonferroni procedure

The interaction between Age and PTSD- RI was not significantly associated with FA in any region.

### Total V-YACS

Whole-brain voxelwise analysis revealed a large cluster of voxels at which total Y-VACS scores had a significant association with FA ( $r = -.657$ ,  $p < 0.001$ ) (see Figure 2). As V-YACS scores increased, FA decreased. These findings were widespread throughout the entire brain.



**Figure 2:** Tract-based spatial statistics analyses of group means within the white matter skeleton mask (thresholded at 0.2, green voxels) identified one cluster in which fractional anisotropy was significantly elevated in children with elevated overall Y-VACS scores compared to those with lower scores. From left to right, axial slices are taken from  $z = 50$ ,  $z = 14$ ,  $z = -22$ . Red-yellow corresponds to low-high significance. Images are presented in the radiological view where the right hemisphere appears on the left of the image, presented in MNI152 standard space.

In order to assess regional variation in effects, we conducted post-hoc tests within specific tracts previously shown to be relevant for childhood adversity and for anxiety symptoms, which were implicated as significant in the whole brain results. Results are contained in Table 2.

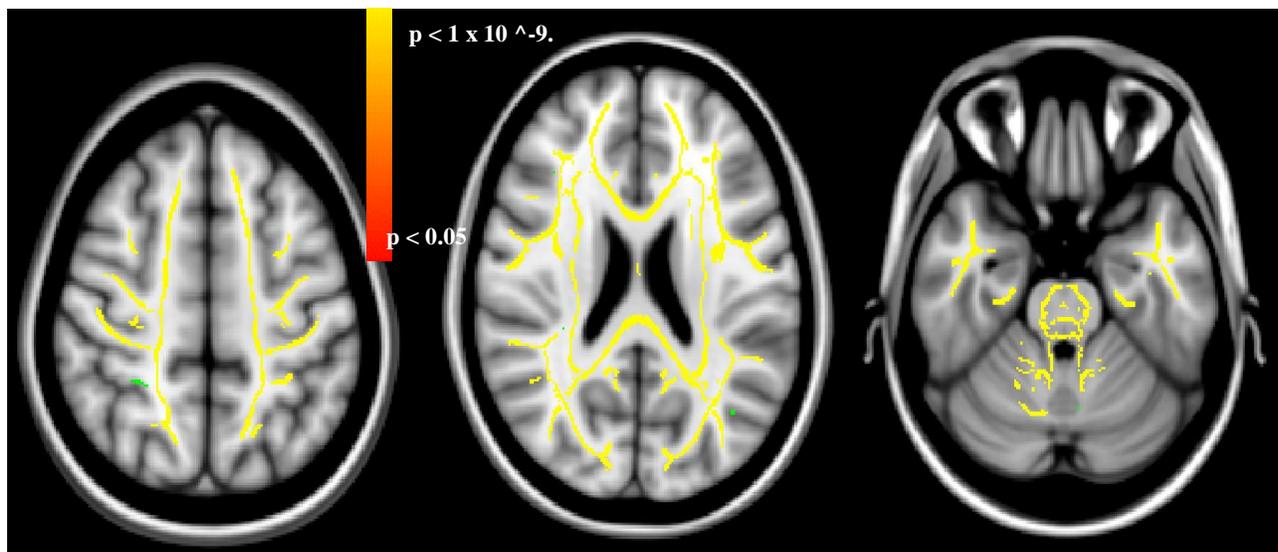
Table 2. Correlations between FA and Total Y-VACS within specific tracts

Tract (hemisphere)	R	$p^1$
Genu of Corpus Callosum	-.252	$p = .028$
Body of Corpus Callosum	-.219	$p = .029$
Splenium of Corpus Callosum	-.204	$p = .041$
Anterior Corona Radiata (R)	-.221	$p = .081$
Anterior Corona Radiata (L)	-.257	$p = .054$
Uncinate Fasciculus (R)	-.194	$p = .106$
Uncinate Fasciculus (L)	-.178	$P = .077$

<sup>1</sup>Reported p values are corrected for multiple comparisons using a modified Bonferroni procedure

### Intrafamilial Violence Y-VACS

Whole-brain, voxelwise analysis revealed a direct relationship between Intrafamilial violence and FA that approached, but did not reach, significance (the most significant voxel was in the left Uncinate Fasciculus,  $p < .17$ ). The interaction between intrafamilial violence Y-VACS scores and age, however, was significantly associated with FA ( $F_{24,34} = 11.098$ ,  $p < .001$ ) in a large cluster that included much of the white matter of the brain (see Figure 3). Post-hoc Linear Mixed Effects analyses conducted in SPSS revealed that this effect was the result of a trend for an increase in FA with age and a decrease in FA as intrafamilial violence increased.



**Figure 3:** Tract-based spatial statistics analyses of group means within the white matter skeleton mask (thresholded at 0.2, green voxels) identified one cluster in which fractional anisotropy was significantly elevated in children with elevated intrafamilial violence Y-VACS scores compared to those with lower scores interacting with age. From left to right, axial slices are taken from  $z = 54$ ,  $z = 22$ ,  $z = -26$ . Significant clusters have been thickened using the FMRIB Software Library “tbss\_fill” tool for visualization (red-yellow corresponding to low-high significance). Images are presented in the radiological view where the right hemisphere appears on the left of the image, presented in MNI152 standard space.

In order to assess regional variation in effects, we conducted post-hoc tests within specific tracts previously shown to be relevant for childhood adversity and for anxiety symptoms, which were implicated as significant in the whole brain results. Results are contained in Table 3.

Table 3. Relationship between FA and the interaction between Age and Intrafamilial Violence within specific tracts.

Tract (hemisphere)	F <sub>24,34</sub>	p <sup>1</sup>
Genu of Corpus Callosum	5.879	p = .000086
Body of Corpus Callosum	7.227	p = .000015
Splenium of Corpus Callosum	4.666	p = .000332
Anterior Corona Radiata (R)	7.121	p = 000024
Anterior Corona Radiata (L)	7.762	p = .000018
Uncinate Fasciculus (R)	7.143	p = .00003
Uncinate Fasciculus (L)	25.746	P = 3.60 x 10 <sup>-12</sup>

. <sup>1</sup>Reported p values are corrected for multiple comparisons using a modified Bonferroni procedure

### Discussion

In the present study, we examined the relationships between anxiety, PTSD, trauma and white matter integrity in the brain. Using DKI, we demonstrated that there were widespread regions throughout the brain at which elevated PTSD scores and total adversity scores were associated with reductions in FA. In addition, there was a significant reduction of FA seen as intrafamilial violence scores increased interacting with age. We found no significant effects of anxiety on FA. These findings support previous literature showing white matter reductions related to increases in PTSD levels in areas of the corpus callosum and fiber tracts connecting the amygdala with the frontal cortex. However, the findings also show whole-brain effects, which are not usually seen in adulthood.

One hypothesis for why we see whole-brain effects is that during early adolescence, white matter is developing rapidly and much of the pruning and fine-tuning of the tracts is in the process of occurring. Studies focusing on adult brains mainly report specific brain regions

affected, such as the corpus callosum. Perhaps, maltreatment during adolescence causes an overall decrease in white matter integrity, but as time progresses recovery can occur leaving only the areas most susceptible to stress affected in adulthood. A potential future direction of this study would be to reassess white matter integrity in approximately ten years, once the brain is fully formed. While the PTSD and Intrafamilial violence analyses produced effects that covered most of the brain, the total Y-VACS produced effects that were only significant in the corpus callosum after correcting for multiple comparisons. The corpus callosum is implicated in trauma while the Uncinate and Anterior Corona Radiata are implicated in the emotion/stress network. Perhaps the lack of an effect in the emotion/stress network for overall Y-VACS was mediated by protective factors that were not assessed in the current study. Another explanation could be intrafamilial violence is a particularly extreme form of adversity, so the effects are exaggerated relative to some of the other adverse events included in the Y-VACS (e.g. bullying, chronic illness or death of a family member). These findings support the fact that different types of abuse affect the brain at varying levels. Another future study could assess extrafamilial stressors or less violent stressors like neglect and verbal abuse, and how they differ from intrafamilial violence scores.

In regards to protective factors or resilience, it would appear that white matter may be extremely plastic, and the changes seen due to maltreatment may not always be the same. A study by Galinowski et al. (2015) reported an increase in FA in segments of the corpus callosum in subjects who were at low risk of developing a mental disorder despite experiencing high levels of stress. It was unclear whether the elevated FA was a pre-existing characteristic that offered protection, or whether the children with increased FA had protective factors in their environment that either reduced FA degradation or allowed for FA recovery. Furthermore, they observed a

linear trend that corpus callosum FA was greater in resilient subjects than in controls. While white matter FA can vary depending on protective and genetic factors, it is also thought that white matter abnormalities can correct themselves given a better environment.

The Bucharest Early Intervention Project looked at orphans who were being raised in institutional care. Institutionalized care has been associated with many forms of psychopathology, as the ratio of caregivers to children and caregiver investment in children is low (McCall et al., 2012). This study was unique due to its within-subject design, where they looked at children before and after placement into high-quality foster care. They found that those placed in foster care had recovered white matter volume so that there was no difference between them and the never institutionalized controls (Sheridan et al., 2012). The reversibility of white matter volumes is a major finding, as future studies may be able to pinpoint which variables can provide the highest amount of protection.

As previously mentioned, both epigenetics and genetic are implicated in the mechanisms by which early life stress increases risk for psychopathology, and may help us to understand the very complex mechanisms behind why some children are more resilient than others. A study by Kaufman et al. (2004) observed that the quality and availability of social supports was found to moderate the risk for depression correlated with a history of maltreatment. In addition, they noted that the presence of the short allele of the serotonin transporter gene promoter polymorphism confers a vulnerability to depression only in those who had been exposed to high levels of stress. This study highlights the complexity of both genetic and environmental factors in their relationship to the development of psychopathology. Similar mechanisms may be occurring related to risk for anxiety or PTSD. A limitation of the current study involves the fact that we did not include protective environmental or genetic measures in our analysis, which may

have explained why we did not see significant results in the anxiety analysis. Methylation of the TPPP gene previously mentioned has been correlated with increased depression scores in adolescents (Weder et al., 2014). Since the TPPP gene is implicated in neural circuitry development, future directions of the current study could compare those with a methylation of this gene to those without, and how they relate to white matter discrepancies and a range of psychopathologies.

Another factor that may account for differences in white matter is sex. Exposure to childhood maltreatment is associated with a two-fold greater reduction in the corpus callosum area in males compared to females (De Bllis & Keshavan, 2003; Teicher et al., 1997). In addition, corpus callosum area is more susceptible to neglect in males and to sexual abuse in females (Teicher et al., 2004). This may have to do with periods of sensitization, where the brain is most malleable to change. In males, this period may be earlier, as neglect is most harmful during infancy and childhood. In females, exposure to sexual abuse increases with age (Teicher & Parigger, 2015). The relationship between sex, type of abuse, and time of maltreatment is very complex, and should be taken into account when analyzing the neurobiological effects of maltreatment. In the current study, besides setting sex as a covariate, we did not delve further into sex differences, which may have been a limitation.

Age was used as a covariate in the current study but the relationship between age and puberty is not precisely linear. Puberty is a period of time when the body and mind go through many emotional, physical, and psychological changes. An increase in white matter integrity throughout the brain is seen during puberty as various hormones are circulating throughout the body. A study by Asato et al. (2010) found that white matter tracts (including the uncinate fasciculus, corpus callosum, anterior thalamic radiation) were not fully developed until post-

puberty. This indicates that pubertal maturation may be implicated in the development of these tracts. If puberty is a time when white matter integrity increases, it is important to note that types of adversity have been associated with elicit earlier onset of puberty and therefore we may see increases in white matter density in children exposed to adversity relative to age-matched peers. A study by Romans, Martin, Gendall & Herbison (2003) found that low socio-economic status, absence of a father, and childhood physical and sexual abuse were correlated with an earlier menarche in a sample of New Zealand women. A limitation to the current study is that pubertal development was not included in the analysis, but may be relevant to understanding cortical development in children, especially when attempting to understand effects of trauma.

Overall, the relationship between type of adversity, psychopathology, duration and age at which adversity occurred, presence of protective factors, sex, pubertal development, and neurobiological changes is complex. The current study has given a snapshot into some neurobiological changes in white matter that affect children suffering from PTSD-like symptoms and those who have experienced varying levels of adversity. This study was unique in that it assessed children close to the time of adversity, which allowed us to see the immediate effects of trauma on the brain. In this study, we aimed to mirror our analyses with how psychopathology presents in individuals. Using regression techniques rather than t-tests allowed us to understand an entire spectrum of symptoms and severity as opposed to just two groups. Future studies assessing all types of genetic and environmental factors will be vital to understanding the complex puzzle of how our environment changes our behavior. With more comprehensive knowledge of these systems, clinicians and psychiatrists will be able to better target interventions and treatments for children and adults suffering from mental illness.

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