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Early Life Stress Predicts Future Conduct Disorder in Adolescents

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Early Life Stress Predicts Future Conduct Disorder in Adolescents

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Abstract

Early Life Stress (ELS) and adversity increase people's risk for developing mental, social, or emotional dysregulation and disorders later in life. The objective of this study was to test whether ELS in adolescents could prospectively predict future conduct disorder. The study additionally tested potential neural mediators of the effect of ELS on future conduct disorder, and specifically targeted the structural connections from the anterior insula and medial prefrontal cortex to the Nucleus Accumbens (NAcc). Data for the project came from the Adolescent Brain Cognitive Development Study (ABCD study), which is a longitudinal multi-site consortium funded by the National Institutes of Health that is collecting the full gamut of biomedical assessments in over 11,000 adolescents. Our findings suggest ELS predicts greater likelihood of conduct disorder two years later, and further, ELS correlates with abnormalities in structural connection between the anterior insula and NAcc. This research identifies early environmental and neural factors that might lead adolescents to develop conduct disorder.

Introduction

Conduct Disorder

Conduct disorder (CD) is a psychiatric disorder characterized by behavior that violates socially accepted norms, including repetitive actions of aggression, impulsivity, inability to follow rules, lack of respect for others, and inability to pay attention (Pisano et al., 2017; American Academy of Child and Adolescent Psychiatry, 2018). This diagnosis is also denoted by limited prosocial emotions which extend into adulthood and can affect healthy relationships and employment (Pisano et al., 2017). Previous research of CD shows evidence of volume reductions in gray matter brain regions of Orbitofrontal, Anterior Cingulate, Insular Cortex, Amygdala and Hippocampus; with a 6% reduction in mean gray matter (Haney-Carson et al., 2015; Huebner et al., 2008; Menks et al., 2017). Adolescents diagnosed with CD display reduced functional connectivity between the Amygdala and Ventromedial PreFrontal Cortex and Orbitofrontal Cortex (Menks et al., 2017). CD is strongly associated with antisocial personality disorder, depression, anxiety, mood disorders and post-traumatic stress disorder; these often present as comorbidities (Delisi et al., 2019). These diagnoses are often attributed from early life stress / adversity, genetic factors, or environmental factors (CDC, 2023). Previous research has positively correlated CD diagnoses with higher early life stress, as well as diagnosed PTSD (Delisi et al., 2019; Afifi et al., 2011).

Early Life Stress

Early life Stress (ELS) is defined as any adverse experience that occurs during childhood or adolescence (Fogelman et al., 2019; Smith et al., 2020; Jamie et al., 2016; Andrew et al., 2018). The adverse experience may be emotional, physical, or mental in nature and cause stress

that profoundly shapes the ongoing development of the brain, which impacts long-term psychological and behavioral health (Smith et al., 2020; Smith et al., 2006). Nearly 65% of children in the United States of America have experienced at least one adverse event, and 12.5% of American children experience more than four (Fogelman et al., 2019). ELS is associated with increased mental health issues, like anxiety and depression, as well as emotional dysregulation, lack of impulse control and increased aggression later in life (Lovallo et al., 2013; Cha et al., 2015). Animal and human studies provide supporting evidence that ELS impairs the development of white matter tracts between the Amygdala, Medial PreFrontal Cortex, Ventral Tegmental Area, Insular Cortex and Hippocampus (Cruciani et al., 2021; Gee et al., 2013; Demers et al., 2019; Herringa et al., 2013; Lupien et al., 2011). In addition, findings indicate elevated exposure to ELS positively correlates with stress reactivity, behavior impulsivity and reduced cognitive control, with impairments of attention, behavior, and emotional regulation (Lovallo et al., 2013; Duckworth et al., 2012)

Nucleus Accumbens

The Nucleus Accumbens (NAcc) is a constituent of the Ventral Striatum and is the central connection between the limbic system and the motor system. The NAcc moderates motivation, pleasure, reward/aversion, impulsivity, fear, and addiction behaviors (Mancall et al., 2011; Mavridis et al., 2011; Nolte, 2009). The reward circuit (mesolimbic pathway) consists of dopaminergic projections from the Ventral Tegmental Area (VTA) to the NAcc, Olfactory Tubercle, and Medial PreFrontal Cortex (Ikemoto, 2007; Volman et al., 2013). The increase in dopaminergic firing and lack of regulation to the NAcc plays a key role in maladaptive coping responses and development of anxiety and depression (Josiah et al., 2021; Fareri & Tottenham, 2016; Härfstrand et al., 1986; Fulford & Marsden, 1998; Goff et al., 2013). Along with

dopaminergic pathways, the NAcc receives glutamatergic inputs from the amygdala, PFC, AIns and Hippocampus; which regulates emotional processing and response, cognitive processes, and inhibits neural responses to reward (Hanson et al., 2021, Ferenczi et al., 2016; Leong et al., 2021). NAcc volumetric abnormalities correlate with increased aggression, possibly affecting impulsivity in adolescents (Cha et al., 2015; Dalley et al., 2007). Studies have reported NAcc hypoactivation with increased adolescent and childhood stress, with abnormal development of NAcc region and reduced white matter myelination that has previously been linked to CD (Goff et al., 2013; van den Oord et al., 2023).

Medial PreFrontal Cortex

The Medial PreFrontal Cortex (MPFC) plays a significant role in cognitive functions related to attention, suppression of reward seeking, memory, inhibitory avoidance, and pain processing (Jobson et al., 2021; Kim et al., 2017; Euston et al., 2012). MPFC glutamatergic white matter projections converge in the NAcc. Past research proposes that the Amygdala, MPFC, and NAcc are all interconnected, responsible for encoding emotional information (Bagot et al., 2015; McGinty & Grace, 2009). Within this circuit, projections from MPFC to NAcc were found to be excited by Amygdala stimulation, affecting the ability to seek larger rewards in rats. This suggests that this circuit is important for reward value and decision making (McGinty & Grace, 2008; Block et al., 2007) Any disturbance between the Amygdala and MPFC afferents to the NAcc could impair cognitive function as well as motivation within learned safety (McGinty & Grace, 2008). PFC has also been shown to indirectly influence the VTA to NAcc dopaminergic tracts through the activation of glutaminergic projections PFC to VTA. The increase of glutamate neurotransmission counteracts excitatory response on DA neurons projecting to the NAcc (Jackson & Moghaddam, 2001; Carr & Sesack, 2000). Previous ELS

research established abnormalities between MPFC to NAcc white matter pathways when investigating higher ELS, finding lower tract integrity which correlated with MPFC resting state glutamatergic levels (Kennedy et al., 2021; Duncan et al., 2015). Prior studies also revealed decreased PFC white and gray matter volumes with increased ELS (Duncan et al., 2015). Adolescents with histories of neglect were shown to have decreased connectivity between dlPFC, MPFC, vlPFC, Insula and Amygdala (Herzberg & Gunnar, 2020). Studies that utilized a seed-based approach identified alterations in functional connectivity between Ventral Striatum-MPFC and associations with social problems (Fareri et al., 2017).

Anterior Insula

The Insular Cortex is a region of gray matter that separates the temporal lobe and inferior parietal cortex; it is often associated with homeostatic and survival functions, as well as emotional processing and arousal (Winn, 2017; Uddin et al., 2018). The Insular Cortex has been studied in the context of predictive cues on whether to avoid or approach a reward stimulus. The NAcc is specifically associated with approach toward positive gain, while the Anterior Insula (AIns) to NAcc connection is associated with aversive signals and decrease in NAcc anticipation of non-gain incentives (Leong et al., 2021; Rogers-Carter et al., 2019). Studies have suggested the structural connection between the AIns and NAcc influences anticipatory reward responses and social stress signals have shown to lead to avoidance (Leong et al., 2021; Rogers-Carter et al., 2019). The AIns projects glutamate to the NAcc when incentive stimulus is presented, especially to reduce risky choices (Leong et al., 2021; Chikama et al., 1997). Animal literature demonstrates high juvenile stress within adolescent rats impacts Insular Cortex development, affecting emotional recognition and changes within conspecific behaviors (Rogers-Carter et al., 2019). This abnormality of white matter structure seems to correlate with reduced striatal

activation to social rewards, reduced insular activation to emotional stimuli and reduced functional connectivity between Insula and Ventral Striatum within rats (Rogers-Carter et al., 2019). Previous literature correlates elevated trauma exposure in adolescence to increases in Insula activity and salience network, with lower reward sensitivity and reduced volume (Marusak et al., 2015; Baker et al., 2013). Lower volume within the Insular Cortex is predicted to negatively affect cognitive functions like regulating interpersonal relationships and understanding social contexts (Baker et al., 2013).

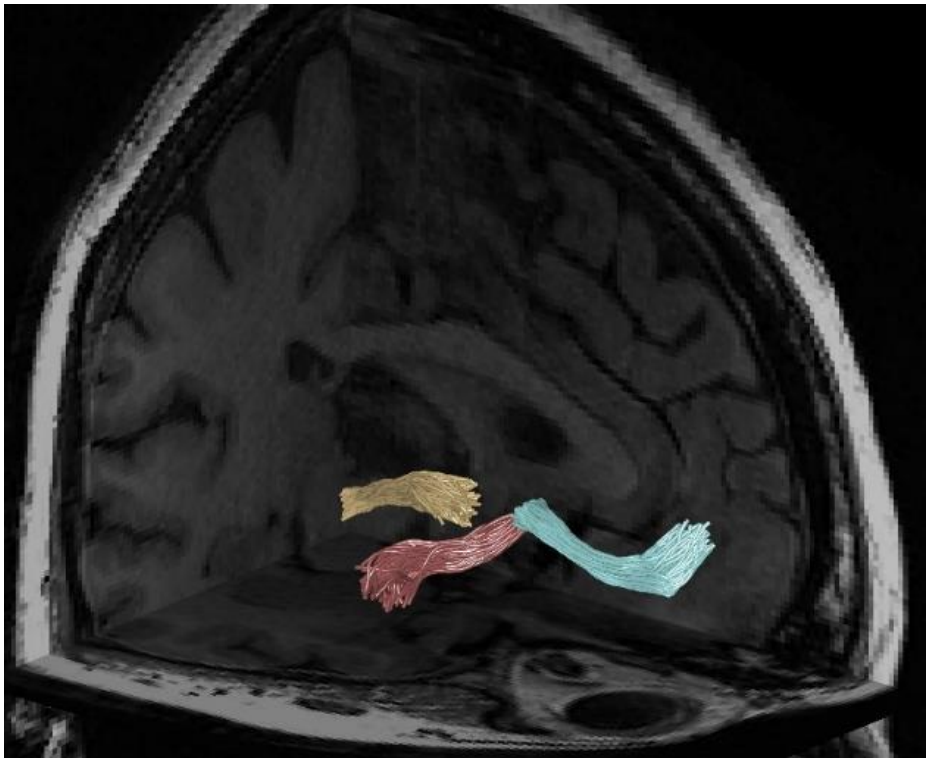

Figure 1: White Matter Tracts, Right Hemisphere. Red = Ains-NAcc. Blue= MPFC-NAcc

The AIns and the MPFC white matter pathways converge monosynaptic and unidirectionally to the NAcc (Leong et al., 2021). These regions play major roles in reward seeking and aversion, which is why the white matter tracts are important to investigate in the context of ELS and CD *(Figure 1).* The goal of this research study is to investigate whether ELS

can predict the later development of CD, while inspecting the structural integrity of white matter tracts between MPFC and AIns to the NAcc. To this end, the Adolescent Brain Cognitive Development (ABCD) longitudinal study was used. White matter tract integrity and structural strength will be evaluated utilizing the diffusion metric of Fractional Anisotropy (FA). With knowledge from prior studies mentioned above, I hypothesize the ABCD participants with higher levels of ELS scores at baseline will experience higher CD score ($t > 60$) at the two year follow up. I also hypothesize participants with higher ELS exhibit reduced FA values in MPFC to NAcc and AIns to NAcc white matter tracts, when compared to lower levels of ELS.

Methods

Participants

The Adolescent Brain Cognitive Development Study (ABCD) is the largest longitudinal study of childhood brain development and health within the United States. The ABCD study was funded by the National Institutes of Health (NIH) and recruited 11,800 children between the ages of 9-10 to record biological, neurological, and behavioral data from adolescence through young adulthood. The present study utilizes 4,788 of these participants for the analysis of ELS. ELS for this study was operationalized using several self-report data sets from ABCD. These sets include youth life events, cyber bullying, and post-traumatic stress, to assess mental, physical, sexual, and social abuse, along with environmental, economic, and familial adversity (yle01, cb01, ptsd01). CD, for the present study, was operationalized using the Child Behavior Checklist (CBCL) and Diagnostic and Statistical Manual of Mental Disorders (DSM-5). This criterion assesses and standardizes behavior and emotional problems, along with defining mental health and neurological conditions. The ABCD study analyzed participant severity of CD via t-scores,

with a score greater than or equal to 60 qualifying as “conduct disorder” and a score below 60 qualifying as “no conduct disorder”. Within this study, 438 participants were categorized as high CD and 4,350 for low CD. Some subjects were eliminated on the basis of motion and demographics, with a subset of excessive head movements within the dMRI scanning to eliminate noise within the data; the final data encompassed participants with brain data from both hemispheres, resulting in 1,877 participants for analysis of AIns-NAcc vs. ELS and 58 participants for MPFC-NAcc vs ELS. This process was repeated with tracts data and CD, resulting in 2,717 participants for AIns-NAcc vs. CD and 72 participants for MPFC-NAcc vs. CD.

Procedures

Preprocessing procedures were performed using the MATLAB mrDiffusion package. During preprocessing, individual subject data analysis identified spherical Volumes of Interest (VOIs) centered on bilateral foci for the NAcc, AIns, and MPFC (Leong et al, 2016). Anatomical landmarks manually defined in the Anterior and Posterior Commissures (AC-PC) and midsagittal plane were used to guide ABCD baseline T-1 weighted images into aligned space for analysis, adjusting for subject movement and distortion. Anatomical VOIs were defined with FreeSurfer software using a binary mask to define AIns-NAcc and MPFC-NAcc white matter fiber bundles, ensuring accuracy in anatomical voxels. Diffusion-weighted image then aligned with T-1 image in AC-PC space. MRtrix software was utilized to perform probabilistic tractography using “constrained spherical deconvolution” fiber tracking to determine orientation and distribution (Leong et al, 2016). Fiber pathways were created by randomly seeding voxels at the start and end of each VOI, for both MPFC-NAcc and AIns-NAcc. Binary mask eliminated fiber outliers outside of the core tract and in gray matter spaces, followed by manual adjustment

trimming in MATLAB. Fibers are reduced to core bundles by eliminating outlier fibers and unlikely pathways based on anatomy. Diffusion index calculation is characterized by mean Fractional Anisotropy (FA) for tracts AIns and MPFC. The mean FA of each node was calculated by the average of the node FA and the spatial distance between fiber and core fiber (Mahalanobis distance). To ensure exclusivity of white matter areas, FA across the middle 50% of the nodes along the pathway was conducted, allowing for FA values for each hemisphere to be available for analysis (Leong et al, 2016).

Results

Logistic regression was performed to investigate if higher ELS (z-score) has prospective predictability for higher CD DSM-5 categorization (t-score). Results revealed significant prospective prediction of CD using ELS z-score, as seen in *Figure 2 ($\beta = .865$, $p < 0.001$).* The interpretation of the log-odds is that for every 1 standard deviation increase in ELS there is a 137% greater risk of future CD.

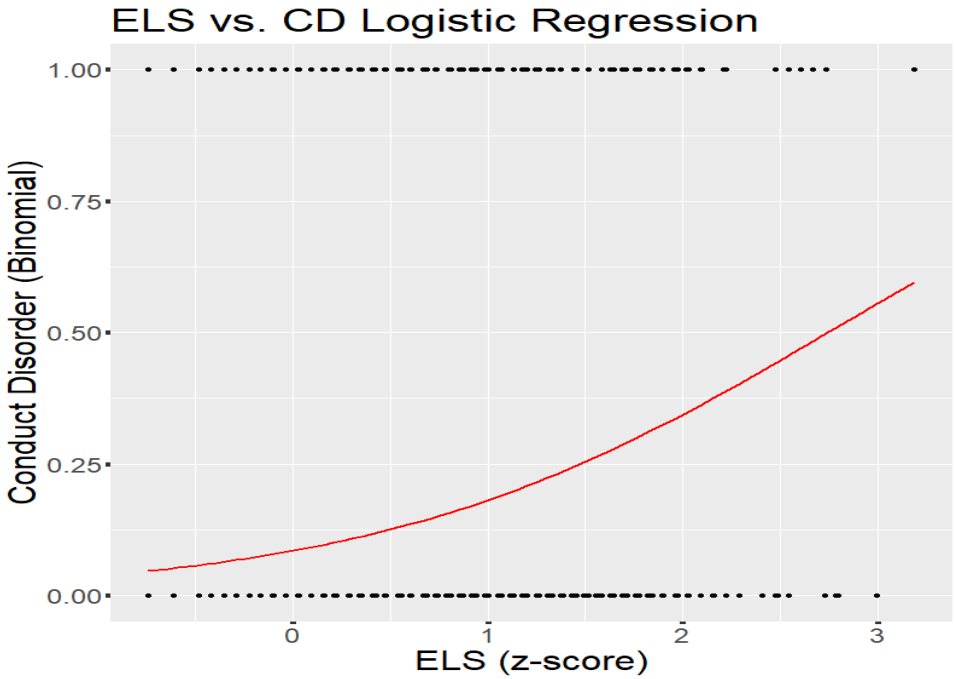

Figure 2: Logistic Regression Model of ELS vs CD ($\beta = 0.865$, $p < 0.001$)

Previous research reveals a disproportionate number of individuals diagnosed with CD identify as African American (Clark, 2006). During the statistical analysis, ethnicity demographics were investigated to determine the proportion of African American participants to other ethnicities. In the no CD group, 13.9% (605 out of 4350) of participants identified as African American; in the CD group, 22.4% (98 out of 438) identified as African American. A chi-squared test was performed to test for significance of this proportion. The results revealed there is a significantly larger proportion of African American adolescents diagnosed with CD within this study (X^2 *(1, N= 98) = 22.77, p < 0.05*). Past studies have shown males to be diagnosed with CD at a higher rate than females. Gender analysis was also conducted to investigate this finding and found that 56.2% of participants with CD were male (246 male out of 438 total). A chi-squared test was conducted to test for significance of sex on CD, revealing trending statistical significance (X^2 *(1, N= 438) = 2.87, p = 0.08*). ELS was significantly predictive of future conduct disorder after controlling for both ethnicity and sex ($\beta = .426$, $p < 0.01$).

Table 1. Ethnicity	Conduct disorder	No conduct disorder
African American	22.4%	13.9%
Alaska Native	0%	0.02%
American Indian	3.2%	3.3%
Asian Indian	0.68%	0.85%
Chinese	1.6%	2.1%
Filipina	0.68%	1.5%
Guamanian	0%	0.05%
Japanese	0%	0.74%
Korean	1.4%	0.8%
Native Hawaiian	0.23%	0.13%
Other Asian	0.23%	0.71%
Other Ethnicity	6.17%	6.85%
Other Pacific Islander	0.46%	0.32%

Table 2. Sex	Conduct Disorder	No Conduct Disorder
Female	43.8%	48.2%
Male	56.2%	51.8%

Probabilistic tractography between MPFC and NAcc revealed no significance between fractional anisotropy of white matter tract and the ELS average z-score (*Table 3*). Statistical analysis could not be completed on MPFC-NAcc vs. CD using a t-test analysis because only 6 participants had DSM-5 level CD; and showed no significant values when linear regression was conducted.

ELS ~ tract	AIns-Nacc tract		MPFC-Nacc tract	
	Left hemisphere	Right hemisphere	Left hemisphere	Right hemisphere
Beginning	t(1872)=1.286, p<1	t(1873)=1.145,p<1	t(56)=-0.497,p<1	t(56)=-0.534,p<1
Middle	**t(1873)=2.241,p<0.05***	t(1873)=0.085,p<1	t(56)=-0.66,p<1	t(56)=0.298,p<1
End	t(1873)=0.379,p<1	t(1873)=1.329,p<1	t(56)=0.539,p<1	t(56)=0.357,p<1

Table 3: ELS:Tract: t-scores for both Anterior Insula and Medial PreFrontal Cortex to Nucleus Accumbens t-scores in relation to ELS, separated by left and right hemispheres.

Probabilistic tractography analysis between AIns to NAcc white matter tract revealed a positive correlation between FA and ELS along the middle 50% of the left hemisphere tract ($t(1887) = 2.588$, $p < 0.01$). These results reveal an increase in FA value with higher ELS z-scores, which is opposite of the hypothesized relationship. To ensure robustness of this finding, regressors of no-interest like motion and interview age were also included within analysis ($t(1885) = 2.267$, $p < 0.05$). Visual inspection of the scatterplot in *Figure 3A* revealed a small subset of outliers (ELS z-scores > 4). To ensure that these outliers were not leveraging our regression, they were removed by instituting a hard ELS cutoff threshold of an ELS z-score of 4. Regressions were conducted without these subjects and maintained significance (without regressors of no-interest: $t(1875) = 2.999$, $p < 0.01$; with regressors of no-interest: $t(1873) =$

2.241, $p < 0.05$); suggesting that the relationship is present even in the absence of outlier scores *(Figure 3B)*. This significance was not found in the right hemisphere.

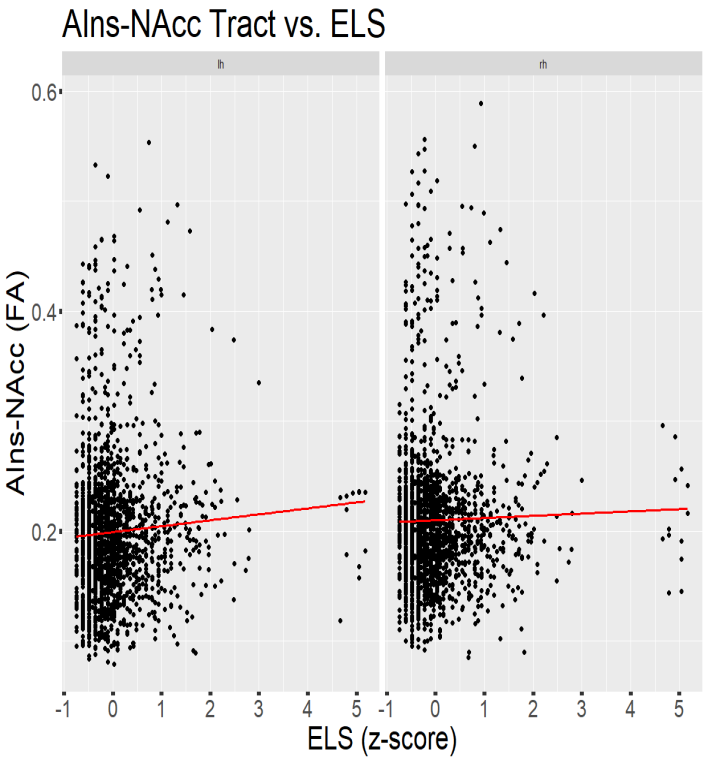

Figure 3A: AIns-NAcc vs ELS: Scatterplot correlating ELS z-score with AIns-Nacc tract.

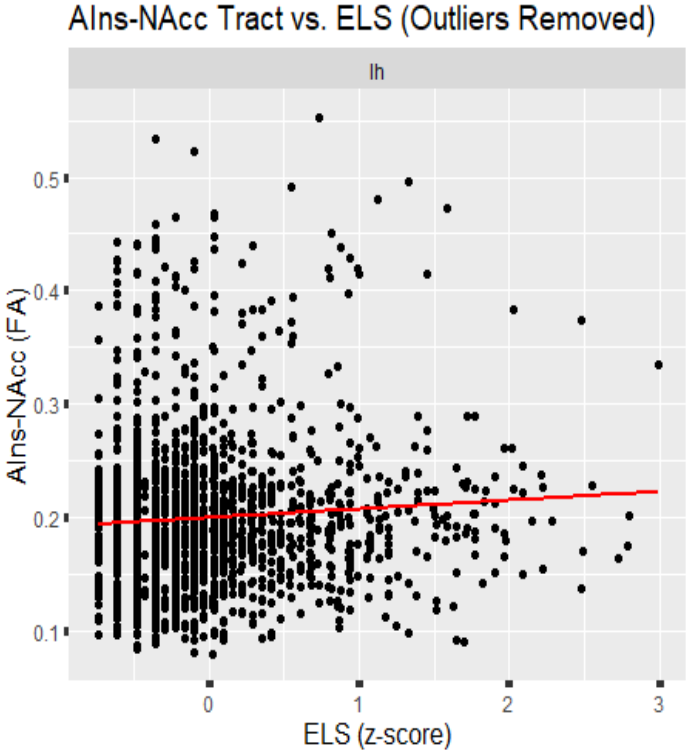

Figure 3B: AIns-NAcc vs ELS (Outliers Removed): Scatterplot correlating ELS z-score with AIns-NAcc tract, removing the ELS outliers to ensure robustness of significant value.

This process was repeated when comparing AIns-Nacc FA values with CD t-score. Analysis revealed significant values, however after further examination of participants, results established no significance between CD and AIns-NAcc tract. A majority of participants scored at the minimum for CD at the regression, resulting in misleading significant results because of a non-normal distribution of t-scores *(Figure 4)*.

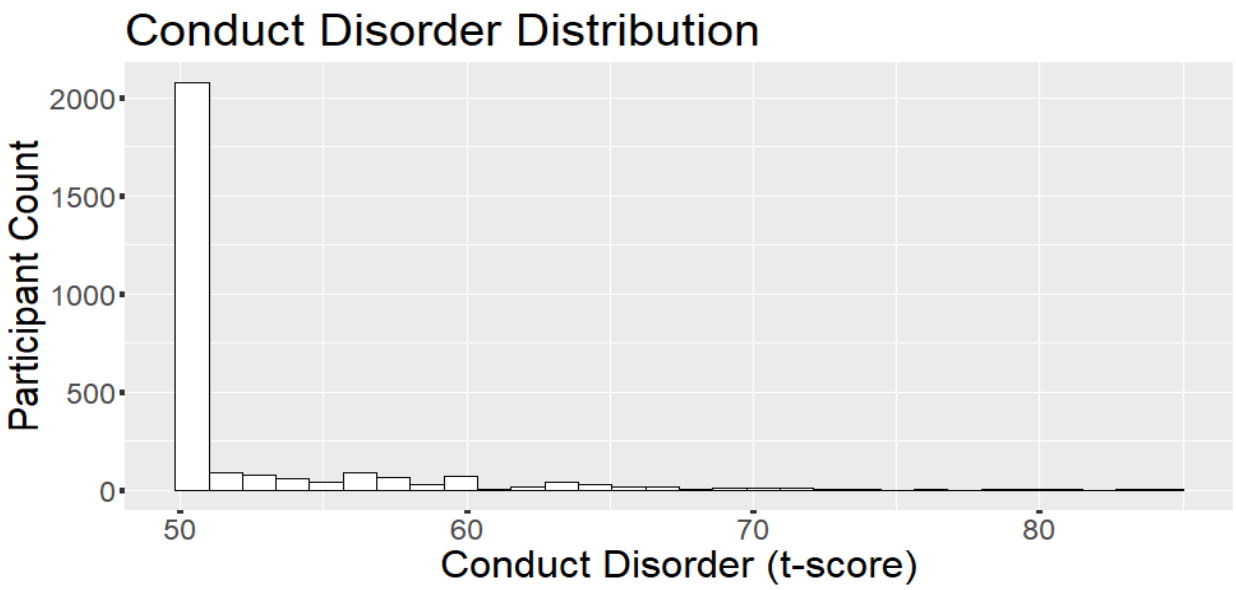

Figure 4: :AIns-NAcc Tract vs CD: Participant distribution of CD t-scores, providing visual of non-normal distribution.

Discussion

This study characterized participants from the ABCD study using an operationalized ELS z-score and a CD DSM-5 t-score to analyze prospective predictability ELS has on CD two year follow-up, in addition to analyzing the structural connections of white matter tracts that run from AIns-NAcc and MPFC-NAcc, measuring for FA metric. The purpose of this study was to investigate the following hypotheses: the operationalized ELS z-score will predict CD in the two-year follow-up; an increase in ELS will result in a reduction of FA between AIns-NAcc and MPFC-NAcc; and a reduction in FA will result in a higher CD t-score. As hypothesized, the operationalized ELS score from baseline data was able to significantly predict CD t-score at the two-year follow-up, utilizing a logistic regression. The logistic regression allows for additional statistical analysis of log(odds), providing a percentage that represents the chances a participant will have DMS-5 CD categorization (t-score $\geq$ 60) after experiencing a significant level of ELS.

This study found participants had a 137% higher risk for developing CD with every increasing standard deviation of ELS z-score.

This prospective predictability of CD is replicated from previous studies, where childhood maltreatment was associated with increased odds of having a diagnosis of CD in both males and females; with the association of prior traumatic events occurring in individuals that have been diagnosed with CD (Afifi et al., 2011; Reebye et al., 2000). Previous ethnographic research expresses African American adolescent males to be disproportionately more likely to be diagnosed with conduct disorder than any other ethnicity or gender, which is replicated within the current study (Clark, 2006). Past research has associated ELS with later diagnosis of CD that is also associated with increased likelihood of PTSD later in life (Reebye et al., 2000). Analysis of probabilistic tractography did reveal significance within higher ELS and increased FA within the middle 50% of the tract, however, in the opposite direction than expected. The positive correlation between increased ELS and higher FA could be because exposure to ELS within adolescence might mature the brain faster with higher cortisol levels (de Souza-Talarico et al., 2011). Previous literature found an increase in Insula activity and salience network, and with that increase in function, could explain the increased FA structural data within this study (Marusak et al., 2015). There was no notable significance when comparing CD to AIns-NAcc FA. Structural data was not significant when comparing ELS to MPFC-NAcc or CD to MPFC-NAcc. Past research conveys abnormalities with MPFC-NAcc white matter pathways in individuals with higher ELS, resulting in lower tract integrity (Kennedy et al., 2021; Duncan et al., 2015). There was insufficient brain data to run any statistical analyses, with only 6 participants with CD t-scores higher than 60. The MPFC-NAcc tract is difficult to track within adolescents because this brain tract is not developed enough, which could be why there is a lack of significance when

investigating ELS and CD within this area. The current study reproduced similar findings from past research, specifically discussing the unilateral significance of the left hemisphere Insula distortion with high ELS (Baker et al., 2013). Animal literature displays abnormal white matter between AIns-NAcc within adolescent rats experiencing stress; similar to findings in this study, however that study concluded reduced functional connectivity, while this study focuses solely on structural connectivity (Rogers-Carter et al., 2019).

This study presented several confounds that could be rectified within future research. First, the ABCD study did not collect specific data for early life stress or adversity, however collected multiple data sets that would be included within ELS. To operationalize ELS for this study, participant responses from youth life events, cyberbullying and the post-traumatic stress disorder data sets were combined; accessing for a broad range of ELS factors such as mental, emotional, physical, and sexual abuse; as well as socioeconomic stressors, violence within childhood, and cyberbullying. This broad operationalization of ELS allows for a margin of error when analyzing how it will relate to CD, simply because it is unknown which type of stressor or adverse event plays the greatest role. Second, this study only utilizes structural brain data, looking at functional data would be interesting to investigate in the future. Along with lacking functional data, the only structural measurement that was investigated within this study is fractional anisotropy. FA is one of many diffusion metrics used to analyze the coherence of tract integrity in brain structures. Another limitation discussed above is the lack of subject data for MPFC-NAcc analysis. This study was unable to run statistical analysis on the correlation between MPFC-NAcc and CD because there were only 6 participants available within the brain data. Along with this limitation, there was no significance correlating MPFC-NAcc and ELS; as mentioned above, this could be because the PFC at 9 years old (participant age group) is not developed and

diffusion MRI might have a challenging time identifying the white matter tract. Utilizing a large data set like the ABCD study has advantages and limitations. The ABCD study is large in quantity, but may limit the quality of usable data, which can limit what analyses that can be executed.

Future studies should investigate specific types of adverse events within adolescence to determine the detrimental factor each plays on the brain's plasticity, as well as the prospective predictability for CD later on. Another direction future research could advance would be to investigate different diffusion MRI metrics, other than FA. Within the ABCD study, four dMRI metrics were provided: fractional anisotropy (FA), axial diffusivity (AD), mean diffusivity (MD), and radial diffusivity (RD) (Mayo et al 2019). Future studies can also investigate other disorder correlations or comorbidities of CD, such as depression, anxiety, ADHD, substance disorder, and psychosis.

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