UNDERSTANDING THE NEUROBIOLOGICAL CORRELATES OF PARENT-CHILD INTERACTIONS IN PSYCHOPATHOLOGY: THE ROLE OF CAREGIVER MENTAL HEALTH

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TABLE OF CONTENTS

ABSTRACT

In the last twenty years, the United States has seen a two to three-fold increase in mental health disorders in children and adolescents, and youth whose parents have psychopathology are more likely to have mental health disorders themselves. While there has been previous research on behavioral links of parent and child psychopathology, little is understood about the neurobehavioral links and the mechanisms responsible for such linkage. In this dissertation, I have added beneficial research that helps inform future psychiatric work. My dissertation will address several critical knowledge gaps in the field of parent-child interactions, neurodevelopment, and risk for psychopathology in youth. My first aim addresses how parent symptoms and behaviors are related to child brain-symptom networks. I sought to understand if positive parenting may mitigate the risk of parental psychopathology on child symptoms. My second aim extends my first aim's work into a more applied task involving parent to child emotional learning. Fear extinction is a well validated and applicable behavioral mechanism and can be disrupted in PTSD and anxiety disorders. Here, I examined whether synchrony is a potential mechanism underlying vicarious fear extinction learning and if this is related to parent symptoms, parent-child relationships, or any other aspects of parent-child interactions. These results provide potential targets for parents that experience mental health symptoms to help mitigate potential intergenerational transmission of mental illness. Understanding healthy and unhealthy transmission of information between parents and children is important for prevention and treatment of families with mental health disorders.

INTRODUCTION

In the last twenty years, the United States has seen a two to three-fold increase in mental health disorders in children and adolescents [1]. In 2021, the U.S. Surgeon General issued an advisory on youth mental health and called for a coordinated response to this crisis [2]. It is imperative that research prioritize children and families that are disproportionally affected by the COVID-19 pandemic, especially those who were already vulnerable to mental health disorders.

Children whose parents have psychopathology are also more likely to have mental health disorders and worse later life outcomes [3,4]. Despite the abundance of behavioral evidence that parents' interactions with their children affect children's behavioral outcomes, little is understood about the neurobehavioral links between parent and child psychopathology and the mechanisms responsible for such linkage. While genetic inheritance leads to some risk (anywhere from .2 to .6 inheritability) it does not account for environmental factors, like parent psychopathology, that can interact with and influence child psychopathology [5–7]. Behaviorally, children must learn basic functional processes directly from their caregivers to survive and thrive, and a combination of parental and child psychopathology may disrupt the transmission of healthy learned behaviors [8,9]. This transmission is likely to affect biological metrics like brain function and peripheral nervous system responses like autonomic reactivity [10,11]. However, it is unclear how healthy or disrupted transmission is instantiated biologically, which has limited the development of novel prevention and treatment strategies for at risk families.

Because the persistence of traumatic stress reactions has major consequences on biological health, therapies such as Trauma-Focused Cognitive Behavioral Therapy (TF-CBT) critically rely on parental coaching to model appropriate fear responses to help children recover from trauma [12,13]. A major knowledge gap in such therapies, however, is how the presence of parental

psychopathology and its corresponding parenting behaviors may impact a child's biological function and recovery from illness. A previous study has found that caregiver behavior predicted child externalizing and internalizing symptoms in follow-up during trauma-focused CBT [14]. Another study found that maternal depression mediates the relationship between CBT and child PTSD symptoms over time insofar as lower maternal depression helps decrease child PTSD symptoms through CBT in the future [15]. While there is behavioral evidence for parent's effect on child symptom expression in therapy, little is known about the biological mechanisms that underly this process.

Intergenerational Mental Health

Rodent Models

Animal studies have given insights into the impact of maternal stress in utero and postnatally on offspring's neural development [1]. Prenatally, mothers who have been exposed to stress, a common precipitant of psychopathology, have pups that have impaired cognition, increased cytokines, and altered DNA methylation which have been linked to many mental health disorders [16–18]. Repeated maternal separation is also associated with lifelong epigenetic changes in the hippocampus and decreased ability to cope during stressful experiences [19]. Early life stress in addition to maternal separation causes similar deficits in development of emotional systems, which may lead to other anxiety-like phenotypes later in life [20]. Conversely, increased quality of maternal care can promote negative feedback to the hypothalamic-pituitary-adrenal (HPA) stress axis in offspring, resulting in reduced anxiety-like behaviors [21].

Fear learning is imperative for healthy functioning in human and non-human animals and is generally first learned through parent-infant interactions or through genetic heritability. Impairments in fear learning and safety learning (or extinction) are hallmarks of disorders like

PTSD, anxiety, and ADHD [22–24]. For example in rodents, pups still show fear responses to smells that their father was conditioned to but that the pups were never shown, indicating that epigenetic changes in fear can be passed down to future generations [25]. Further, when mothers modeled fear behaviors, pups showed increased amygdala activity when not actively going through fear acquisition, demonstrating how observation can change brain function even without personal experience of a stimulus [10]. Parenting and stress throughout the parents' lifetime can have biologically relevant outcomes in rodent models. Therefore, it is important to think about the biological implications, in addition to the behavioral symptoms, of this stress and behaviors on human children as well.

Genetic Heritability

Overall, genetic heritability accounts for between 17 and 29 percent of variance in psychiatric disorders and many of these disorders share common genetic variation [7]. At the top end of the spectrum, bipolar disorder and schizophrenia, are about equal as likely to be influenced by genetic and environmental factors [26]. Transmission of anxiety symptoms, however, has been found to be more likely to reflect a model of environmental transmission compared to genetic transmission which was almost non-existent [5]. While genetic inheritance is responsible for some variation, it is likely that environmental modeling, either from family or peers, of anxiety and other neuroticism behaviors is a more likely driver of anxiety symptoms in children and adolescents.

Human Behavioral Studies

Intergenerational mental health is highly correlated within the United States and sits around .6 which other countries sit between .2 and .6 [27]. While the role that parents play in child psychopathology has been established, little specificity has been identified in terms of which parent symptoms may account for the largest effects. Most studies to date have separately

examined parent general psychopathology, anxiety, or aggression symptoms and the corresponding symptom in their children [4,28,29]. For example, maternal depression pre- and postnatally is related to increased internalizing symptoms in childhood [30]. Children also tend to endorse more behavior problems and depressive symptoms when mothers have more adverse childhood experiences [31]. Past or present anxiety symptoms in adults further lead to increased risk for anxiety presentation in related youth [32]. It is likely that anxiety and depression symptoms, because of the their tendency to be externally presenting, will be the most influential as they are easily modeled from parent to child [30,33].

While these studies importantly support the hypothesis that parent mental health can be transmitted to youth, they have limited scope as they usually focus on just one aspect of parent mental health, such as anxiety or depressive symptoms, and very few have additionally looked at parenting behaviors as well as parent mental health in relation to child mental health. Only one study [30] previously mentioned the mediating effect of parenting behavior and its role in child psychopathology, few studies have looked at both and their consequences on behavioral outputs as well as how this is related to neural functioning. To expand on this literature, it is imperative to understand which symptoms, cross-domain, and parenting behaviors are most influential on child psychopathology and neural health and therefore are the highest yield targets for interventions.

Human Imaging Studies

Neurobiology studies have also given insights into how intergenerational mental health can affect the central nervous system. [34,35]. Prior work has identified three brain networks, the default mode (DMN) , control (CTL), and salience (SN) as potential targets that are related to psychopathology [34,36–38]. These networks are important for self-referential thinking, executive function, and emotion regulation which are generally dysregulated in many psychopathological

disorders [37]. In rhesus monkeys, there is evidence of a strong connection between prefrontal-limbic-midbrain circuitry and heritability of anxious behavior [39]. In the human brain, parental anxiety is related to increased fear learning and stronger medial prefrontal-amygdala connectivity in offspring indicating a hyperactive response to fear [40]. Structurally, depression in mothers significantly predicted cortical thickness in the fusiform cortex for their daughters, regardless of diagnosis in the offspring [41]. Together, these findings lend evidence for transgenerational effects of mental health on the child's brain function and structure. However, these studies lack parent-child interactions and behaviors, and how these shape neural outcomes.

Parenting Theories

Attachment Theory

One of the oldest and most useful theories in child development is the concept of Attachment Theory. Attachment Theory was first proposed by John Bowlby and explains the psychobiological need for infants to seek contact with caregivers for comfort during vulnerability or fear [42]. Available, sensitive, and responsive parenting allows the child the ability to feel security and create positive associations with themselves and others [43]. Lack of reliable parenting is related to a higher likelihood of difficulties with emotional regulation and relationship issues later in life. In more recent years, Mary Ainsworth used this theory to examine the parent-child relationship and parenting behaviors more generally [44]. Her observations included secure, insecure-avoidance, insecure-resistant, and insecure-disorganized attachments. Numerous twin studies have found evidence for environmental factors being the most influential for attachment style compared to genetic heritability, indicating the importance of parent-child attachment on behavioral mechanisms [45–47].

While originally created for a parent-infant bond, research over the last 30 years have used attachment theory to explain parent-adolescent relationships and how they affect youth emotional development and mental health outcomes [48]. Generally, studies have linked increases in attachment insecurity to greater externalizing and to a lesser extent greater internalizing symptoms in youth [49,50]. A large review found that attachment insecurity was widespread among several mental disorders including schizophrenia, depression, anxiety, and PTSD [51]. It is also important to highlight the protective effects of secure attachment. Secure attachment can help protect positive moods from threatening contexts and is a predictor of high resilience to psychopathology [52,53]. It is therefore important to study both positive and negative aspects of attachment and parent-child relationships to understand behavioral transmission of psychopathology.

Parenting Styles Theory

Parenting Styles Theory, which gained influence concurrent with attachment theory, describes three parenting approaches: authoritative, authoritarian, and permissive [54]. In more recent years, it was reconceptualized as two dimensions: responsiveness and warmth, and high demandingness, which gives the child safety but also provides boundaries [55]. This work also gave way to a fourth parenting style, neglectful. Descriptions of the four parenting styles can be found in Figure 1. Authoritative style of parenting has been noted as the most positive across many cultures and ages, with some exceptions for ethnic minorities or families that reside in dangerous situations [55]. Overall, authoritative parenting is related to better school grades, less psychopathology in youth, and more prosocial behavior [56–58].

Figure 1. Overview of Parenting Styles

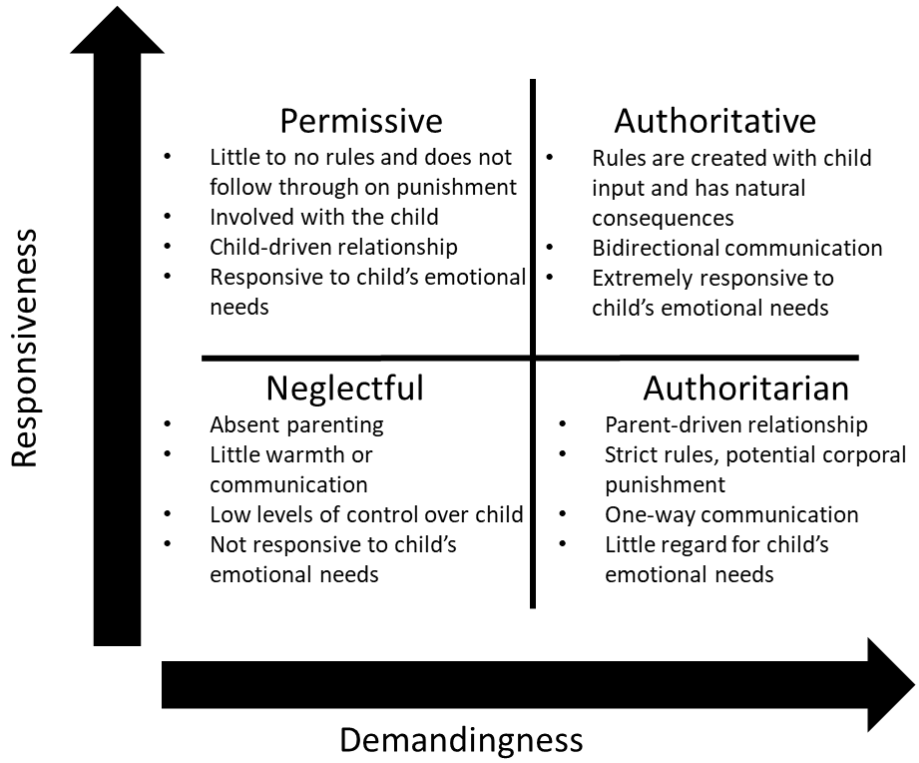

Figure 1. Descriptor of the four main parenting styles.

One important debate I want to highlight in this work is if parental "monitoring" is considered beneficial to child development and can be thought of as in the high demandingness category. Parental monitoring in most contexts refers to parental knowledge of the child and their activities [59]. In western countries, parental monitoring is usually associated with youth's willingness to share details about their lives and is not describing parent snooping or over-solicitation of adolescents out-of-home behaviors and events and therefore can be seen as an indicator of family health and connectedness [55]. In the context of my work, I will view parental monitoring as a positive parenting behavior, not a controlling or intrusive one.

Transactional Model of Parent-Adolescent Relationship

A more recent model of parent-child interactions is the Transactional Model of Parent-Adolescent Relationships theorized by Sameroff and Mackenzie [60]. This theory models a

bidirectional and reciprocal influence of the child and the context of their lives, including the relationship with their parents and family and how they all can influence each other. This is in slight contrast to Attachment Theory, as it focuses more on the continuous back and forth relationship with the child, instead of a parent-only effect on child outcomes.

For example, Fitzgerald and colleagues found that adolescents' perception of the mother-child relationship, not the mothers' perception, mediates the effect of maternal childhood abuse and the child's own anxiety and depression symptoms [61]. Further, adolescents' internalizing symptoms have a reciprocal association with relationship quality with their mother, continuing a cycle of psychopathology [62]. These studies provide evidence that adolescents can be involved in their own symptom output and are contributors to parent-child relationship quality. It is imperative to use this information to look at all aspects of parent-child interactions including relationship, parent psychopathology, and child psychopathology to create more targets for interventions.

Parenting on the Child Brain

Parenting and parent-child relationships and their effect on the child neurodevelopment are some of the most understudied aspects of child development. As seen in previous sections, parenting research has been conducted since the early 1970's; however, how parenting affects the child's brain has only recently started to be researched. Results so far indicate that the impacts of positive parental behavior can be related to children's neural connectivity and network functioning. For example, one study found that parental acceptance moderated the relationship between neighborhood disadvantage and resting state functional connectivity between the ventral attention/visual networks and the default mode networks, denoting that parents can be protective from factors out of their control like neighborhood disadvantage [34]. The ventral attention and visual attention networks are important for identifying and orienting to salient stimuli while the default

mode network is important for self-referential thinking, possibly indicating that positive parenting buffers effects of disadvantage and allows youth to have higher emotional regulation, cognition, and attention [34,37,63]. Positive maternal behavior also is associated with lower activation in the dorsal later prefrontal cortex (PFC) and left parietal cortex and decreased connectivity between the default mode and control networks, which may indicate better task switching, especially for emotional salience stimuli [36,64]. These studies put positive parenting anchored in the default mode and control network nodes that are important for task switching and emotional control.

The effects of negative parenting are also correlated to children's brain function and structure. For example, maternal hostility was associated with more negative amygdala connectivity to frontal and parietal regions when responding to stimuli like sad faces, which has been previously shown to be indicative of less emotion regulation [36,65]. Higher perceived parental dysfunction was related to lower within-default mode connectivity, which may signify an impaired ability to relate to others experiences [66]. Structurally, parental hostility was related to reduced longitudinal cortical thickness in males in the middle frontal and fusiform cortices, which are likely to affect emotional and cognitive functioning [67]. Suffren and colleagues also found significantly smaller gray matter volumes in the prefrontal cortex and amygdala, regions important for emotional processing and control, for youth with higher levels of harsh parenting compared to youth with low levels [68]. Nodes for negative parenting are more related to default mode and salience canonical networks and are related to emotional processing.

After review of this work and parenting theories, it is important to understand the bidirectional and integrative relationship parents have with their children. How children are treated by their parents and the child's view of that treatment can both influence the child's biological functioning. It is crucial to investigate how parenting-child relationships and parenting behaviors

interact with parent-child psychopathology to help facilitate treatment of youth with psychiatric disorders.

Review of Vicarious Extinction Learning

Biological and Behavioral Correlates of Social and Fear Transmission

Children's ability to learn emotional content from their parents and caregivers is one of the most important pieces of child development [69]. Specifically, youth must learn the value of information and its potential effects on their health and safety to live a healthy life [70]. At the most basic level, animals, including humans, use aspects of Pavlovian and operant conditioning to learn cultural, social, and fear-based information. For the purposes of this dissertation, I will be focusing on fear and emotion-based transmission of parent-child dyads.

It is important for children to pay special attention to their caregiver's facial expression and body language to attune correctly to social-affective stimuli [71]. For example, infants and toddlers learn fear and avoidance through their mother's fearful facial expressions [72,73]. In viewing their parent's face, researchers saw increased autonomic reactivity which is indicative of emotion self-regulation and ability to effortfully control their responses to stress [71,74].

When learning fear, adults showed increased amygdala and parietal activation in both the left and right hemispheres which coincided with increased skin conductance responses [9,75]. While there have been studies in adults, few studies have looked at the neurobiological correlates of children's social and fear learning. The biological effects of learning and unlearning fear in youth are important indicators for children's ability to appropriately deal with fear and stress as well as an indicator of parent-child functioning.

Neurobiological Correlates of Fear Extinction

Fear extinction learning has been widely used to understand fear-related disorders like PTSD in adults, but with less study in children [22,23]. Previous studies in humans, with support from rodent models, have indicated alterations in fear learning like enhanced acquisition and impaired extinction in those with anxiety disorders (for a review see Milad et al., 2014). While fear learning may be enhanced in youth with trauma, fear extinction or extinction recall may also be disrupted [76]. Therefore, it is important to study fear extinction and recall, in addition to acquisition, to fully understand the impact of differential fear learning on psychopathology in youth.

Childhood PTSD is currently theorized as a disorder characterized as a disruption in fear extinction; however, only a few studies have tested this hypothesis [76–78]. The fear extinction network consists of nodes in the amygdala, hippocampus, and medial prefrontal regions [79]. Marusak et al. (2021) found that trauma exposure led to increased activity in the dorsal anterior cingulate cortex and the lateral anterior insula during extinction recall, both important regions in the salience network. One study focusing on adversity in adolescents observed that experience of threat interacted with age to predict physiological response, insofar as more threat led to decreased physiological response over time [77]. Fear learning behaviors can also be affected by parental psychopathology. Children of anxious mothers had increased skin conductance responses during extinction and children of depressed mothers showed decreased responses during acquisition [80]. Here, it is important to understand both the child's own psychopathology and the parents as both can affect their fear learning.

Vicarious Extinction Learning

Of particular salience for youth, altered fear learning may partly be due to youth's difficulty to learn fear and safety by observation, or vicarious learning, as this learning has been shown to

influence a child's normal fear development [81]. Vicarious fear learning, or vicarious extinction learning, in parent-child dyads is a well-documented behavioral process and may be more effective than classic Pavlovian fear extinction; however, this process but has received little neuroscientific attention [82,83]. During fear acquisition, one study found that anxious children had increased reactivity to fear acquisition, demonstrating that psychopathology may influence vicarious fear learning [84]. Reactivity to vicarious fear extinction also changes over development. Skversky-Blocq and colleagues found that children had higher physiological reactivity during acquisition, and adolescents were inclined to over-generalize their fear [85].

Our preliminary work in in pediatric PTSD has shown promising results in PTSD-specific impairments of fear extinction learning [86]. Overall, we saw youth with PTSD have increased physiological reactivity during vicarious extinction compared to typically developing youth (Figure 2B). We also found that PTSD symptoms were positively related to reactivity during recall (Figure 2C). Together, this indicates that there may be disruptions in learning fear from their caregivers that specifically arises from trauma exposure or trauma diagnosis insofar as youth with PTSD are not able to learn safety cues. More detailed information on this study can be found in Appendix C.

Figure 2. Parent-Child Vicarious Extinction Results

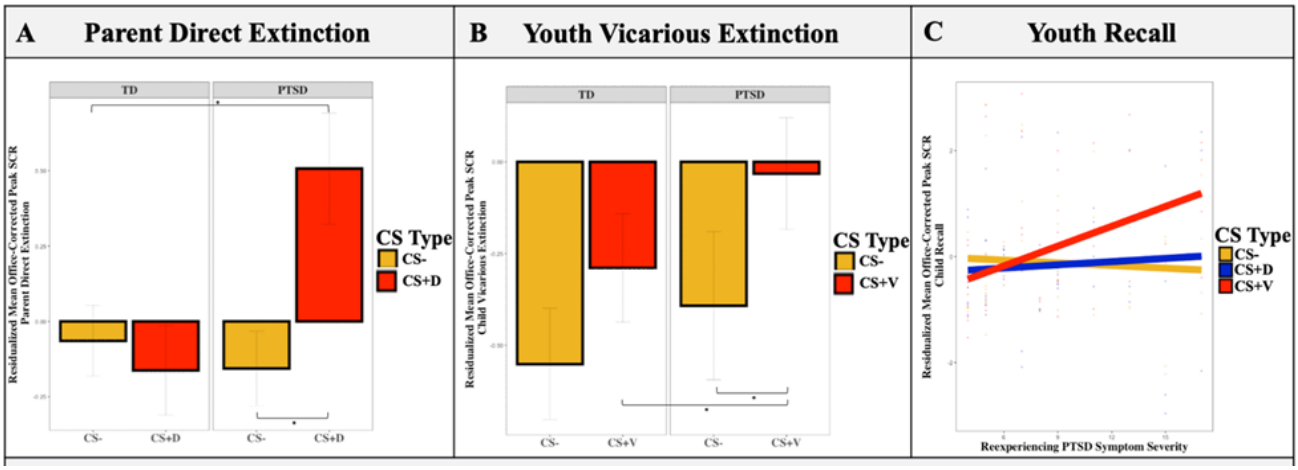

Figure 2. A. Parents that had a child with PTSD showed higher reactivity to the CS+D compared to the CS- after extinction, but the parents with typically developing children did not and this difference was also significant. B. Children with PTSD had higher reactivity to the CS+V compared to typically developing youth. C. Increased PTSD severity was related to increasing SCR reactivity during recall for the child only to the CS+V, but not the CS+D or CS-.

Biological Synchrony

Synchrony is the bidirectional coupling of two separate systems so that their behavior, feelings, or biological responses are correlated in time [87]. For parent- child dyads, synchrony is a critical method of learnt emotion regulation in children and a way to foster healthy attachments [88]. Thus far, most parent-child synchrony analyses have been in infants and toddlers and used words or behaviors to assess attachment or regulation [88]. However, an increasing number of studies have started to investigate more biological metrics of synchrony. Physiological synchrony, a subset of biological synchrony, uses peripheral nervous system methods like respiratory sinus arrhythmia, skin conductance response (SCR), or cortisol activity to evaluate the degree to which caregivers and their children are coupled [89]. Physiological synchrony has been shown to change with age development as well as task demands and parent psychopathology [90]. In tasks that require learning, greater synchrony in a learning phase was associated with greater threat learning as observed with SCR [11]. Because caregivers serve as a key source of information for youth, understanding how they transmit information about fear and safety cues is imperative. Further, fear and safety cue

understanding and learning is a behavior that potentially impact fear disorders such as PTSD [69]. Parent-child synchrony may represent an empirical way to measure transmission of safety and extinction cues rather than relying on self-reports [87].

Conclusions

It is clear more than ever that children and adolescent's mental health in the United States is in danger. An ongoing pandemic, increasing wealth inequality, climate change, and other factors contribute to a traumatic landscape to grow up in. It is therefore imperative to continue to fund research that focuses on the mental health and well-being of children and families. It further is important to understand the neurobiological mechanisms and consequences of intergenerational mental health and potential transmission of symptoms between caregivers and children. This could potentially help therapeutics, in conjunction with medication, to redirect children back on a healthy biological trajectory.

It is difficult for parents to control every variable in their child's life; however, giving parents targets to focus on is useful for their own development as parents, and for therapists to help work on with parents. Parenting is a skill that continues to develop throughout the child's life and should be seen as such. Especially when parents themselves have psychopathology, it is important to mitigate potential transmission to the child. In future work in children with psychiatric disorders, parenting factors should be included to fully understand biological and symptom outputs.

In this dissertation, I have added beneficial research that I hope will help inform future psychiatric work. My dissertation addresses several critical knowledge gaps in the field of parent-child interaction, neurodevelopment, and risk for psychopathology in youth. First, it is currently unknown whether and how unique parent symptoms relate to child brain connectivity, and further

how this relationship is connected to behavioral outcomes. This knowledge is important for developing and applying new and effective therapeutic interventions for children and their families. Parents and caregivers are integral to creating a safe and healthy environment for their children, and it is unclear to what extent certain parental phenotypes, other than genetic relation, can affect children's emotional development. For example, it may be that certain symptoms, like anxiety or aggression, are more detrimental to child functioning and recovery than others. Secondly, it important to utilize this knowledge, i.e., symptoms or behaviors that affect the child, to ask specific questions about parent-child interactions. Specifically, how dyad relationships and modeling behaviors can contribute to persistence, protection, or to children's ability to navigate the world in a healthy way. If these nuances are parses apart, future therapies may benefit from this knowledge to incorporate into their practice.

My first research aim addressed how parent symptoms and behaviors are related to child symptom-brain connectivity networks. This work directly asked if parent symptoms are related to child neural networks underlying symptom expression, and if their parenting behaviors mediate some of this relationship. Most research on parent-child interactions relate general presentation of parent psychopathology or other interactions like parenting style to child diagnoses, but few have looked at specific parental symptoms and their relationship to brain connectivity or child symptoms [4].

My second aim extended my first aim's work into a more applied task involving parent to child emotional learning. Fear extinction is a well validated and applicable behavioral mechanism and can be disrupted in PTSD and anxiety disorders [91,92]. Here, I examined whether synchrony is a potential mechanism underlying vicarious fear extinction learning and if this is related to parent symptoms, parent-child relationships, or any other aspects of parent-child interactions. My work

has begun to reveal how parent psychopathology may contribute to real-life behavioral consequences like fear learning. Again, this is relevant for therapies looking to help children and their parents remit from stress and anxiety disorders. Understanding healthy and unhealthy transmission of information between parents and children is important for prevention and treatment of families with mental health disorders.

CHAPTER 1

Parent Behaviors Mediate the Effect of Parent Psychopathology on Child Brain-Symptom Networks in the Adolescent Brain Cognitive Development Study

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Abstract

Children are more likely to have mental illness if their parent also suffers from psychopathology. Notably, positive parenting may mitigate the risk of intergenerational transmission of psychopathology. However, a knowledge gap in the literature is how the presence of parental psychopathology and parenting behaviors impact child psychopathology and its neural underpinnings. I utilized the baseline cohort of the Adolescent Brain Cognitive Development Study (n=7210, Female=3658, ages 9-11 years) to derive brain-symptom networks using sparse canonical correlation analysis with the Child Behavior Checklist and resting-state fMRI. I then correlated parent psychopathology symptoms and parental behaviors with child brain-symptom networks. Lastly, I used the significant correlations to understand if parent behaviors mediated the effect of parent psychopathology on child brain connectivity. I observed three brain-symptom networks related to externalizing, internalizing, and neurodevelopmental symptoms. These corresponded to differences in connectivity between the Default Mode-Salience/Ventral Attention, Default Mode-Control, and Visual-Visual canonical networks. I further detected aspects of parental psychopathology, including personal strength, withdrawal, and rule breaking symptoms to be related to child brain connectivity. Lastly, I found that parental acceptance and monitoring mediated the relationship between parent psychopathology and child brain connectivity in both internalizing and externalizing networks. The current study suggests that parental acceptance and parental monitoring can mitigate potentially detrimental effects of parental symptoms on child brain connectivity and corresponding child symptoms. Altogether, these results provide a framework for future research and potential targets for parents that experience mental health symptoms to help mitigate potential intergenerational transmission of mental illness.

Introduction

Children of parents with psychopathology are more likely to have mental health disorders and poor outcomes through adulthood [3,4]. Despite an abundance of behavioral evidence that parents' interactions with their children affect children's behavioral outcomes, little is understood about the neurobehavioral links between parent and child psychopathology and the mechanisms responsible for such linkage. While genetic inheritance leads to some risk, it does not account for all the potential ways parent psychopathology can interact with and influence child psychopathology [6].

Although numerous genetic consortium studies characterize the genetic heritability of psychopathology, environmental factors appear to be just as important in utero and post-natally [93–95]. Notably, studies across animals and humans show that certain parent behaviors are highly related to presentation of psychopathology traits in offspring [95,96]. For example, increasing evidence suggests that both positive family environments and positive parenting can have potential protective effects on the brain [34,38]. Critically, however, the neurobiological mechanisms linking parent mental illness, parenting behavior, and children's risk for, resilience to, and recovery from psychopathology remains poorly understood. Such knowledge has important implications for both prevention and intervention approaches to mitigate risk for child psychopathology in the presence of parental symptoms.

To our knowledge, very few studies have investigated if and how unique parent symptoms relate to functional brain connectivity in children, and further whether this relationship may be mediated by malleable parental behaviors [34,35]. Prior work has identified three brain networks, the default mode (DMN) , control (CTL), and salience (SN) networks as potential targets that are related to parenting [34,36–38]. These networks are important for self-referential thinking, executive

function, and emotion regulation – each of which are generally dysregulated in many psychiatric disorders [37]. Positive parenting behaviors and strategies have been shown to mitigate some irregularities in these networks' functioning, indicating that these regions are affected by parenting [34,36,97].

Previous work using the Philadelphia Neurodevelopmental Cohort (PNC; n=663, ages 8–22) utilized a data-driven approach to characterize how child clinical symptoms relate to functional brain connectivity [98]. Four significant brain-symptom networks were identified in youth, each mapping onto four different domains of psychopathology: mood, psychosis, fear, and externalizing symptoms. Each symptom domain exhibited both unique and shared connectivity patterns within canonical brain networks. Briefly, the mood dimension predicted increased connectivity in the ventral attention and salience networks, the fear dimension correlated with greater frontoparietal within-network connectivity, and scores for the externalizing dimension linked to reduced connectivity in the default mode network and the frontoparietal network. While this study was critical in identifying the existence of functional brain-symptom networks within a developmental sample, no subsequent work has investigated how these networks may be influenced by other external environmental factors.

Theoretically, it may be that parent symptoms and parenting behaviors are directly related to the development of child brain-symptom networks. Though research has investigated the interactions between child mental health diagnoses and parent psychopathology or parenting styles, most rely on singular aspects of parent psychopathology, like anxiety or depression, but few studies have attempted to clarify mechanisms linking specific domains of parent symptoms and brain connectivity or child symptoms [4]. Previous work within large adolescent datasets suggests that parent internalizing symptoms, like anxiety and depression, and parent aggression

are the most strongly related to child symptoms [4,99]. These specific symptoms and behaviors are plausible as being highly influential to their child, as they are more easily modeled to children, perhaps in comparison to some other symptoms like intrusive thoughts which have less outward presentation [4]. For example, parent anxiety is linked to increased anxious parenting styles [28], while parenting practices and child anxiety symptoms exert an interactive effect on underlying brain regions (amygdala volume and rostral anterior cingulate cortex) [68]. Such differences in brain structure may explain potential resilience to anxiety disorders, further illustrating that parenting behavior may interact with symptomology to change neural structure, and potentially, neural function.

Furthermore, if some parenting symptoms are related to maladaptive parenting styles and youth psychopathology, the inverse may also be true. Authoritative parenting, or high responsiveness and high control, is generally linked to positive outcomes including resilience, self-esteem, and academic achievement in youth (albeit with some cultural differences; for a review, see Kuppens & Ceulemans, 2019). However, it remains unknown how these and other parenting behaviors moderate the relationship between parent symptoms and child brain-symptom networks.

The current study first aimed to use a data-driven approach to replicate and expand on previously identified brain-symptom networks within a large, nationally representative sample of adolescents [98], followed by an investigation into whether parenting symptoms and behaviors are related to child brain-symptom networks. For the brain-symptom networks, I anticipated findings similar to those recently observed in the PNC cohort. Next, I expected to see an influence of more heavily modeled parent symptoms on child brain-symptom networks, including parental anxiety and aggression. Specifically, I predicted that increased negative parent symptoms would be related to increased connectivity within internalizing brain-symptom networks and decreased connectivity

within externalizing brain-symptom networks. Finally, I anticipated parental acceptance and monitoring, which generally fall within the authoritative parenting domain, to mitigate the effect of parental symptoms on child brain connectivity.

Methods and Materials

Sample

Clinical and neuroimaging data for the current study were pulled from the Adolescent Brain and Cognitive Development (ABCD) study, a nationally representative sample of adolescents between the ages of 9 and 11 recruited from 21 different sites across the United States in order to reflect national sociodemographic characteristics [101]. All participants from the baseline wave of the ABCD study were eligible for this study, resulting in a total available sample of 11,875 youths. The sample was chosen due to the size and breadth of available reports on both parent and child symptoms and behaviors, with the final sample for this analysis being 7,210. Prior to study enrollment, all parent participants provided informed consent and all study procedures were approved by each University's Institutional Review Board. Details on demographics can be found in Table 1.

Table 1. Demographic information of ABCD cohort used.

Basic Demographic Variables		
N		7210
Child Biological Sex		F = 3658 ; M = 3552
Child Age in Months		119.52 (7.49)
Parent Gender		F = 6404 ; M = 799 ; Non-Conforming/Other: 7
Parent Age in Years		40.22 (6.67)
Race	African-American/Black	959
	American Indian/Native American	34
	Asian	480
	Two or More	870
	White	4867
Ethnicity	Hispanic or Latino	1329
	Not Hispanic Latino	5789
	Not Provided	88
Parent Education Level	Some High School or Below	340
	High School Degree/GED	679
	Some College	1708
	College Degree	2171

	Graduate Degree	1904

Table 1. Demographic information of ABCD cohort used. Parent gender information in Non-conforming/Other included gender queer, non-conforming, and those who did not want to respond.

Psychopathology and Behavioral Measures

The Child Behavior Checklist (CBCL) was used as the primary psychiatric symptom instrument for youth and includes 11 symptom domains including externalizing, internalizing, and total problems [102]. This is a validated parent-report instrument designed to assess current and lifetime history of psychopathology in children and adolescents based on DSM-5 criteria. I decided to use the CBCL rather than the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS) report due to the similarity between the CBCL and the parent symptom data, making comparisons between parent and child psychopathology more interpretable, and the extreme amount of missing data due to the skip logic inherent to the KSADS instrument. For the CBCL, I removed 13 questions that were endorsed less than 1%. These can be found in the Appendix A.

Parent psychopathology symptoms were assessed using the Adult Self Report (ASR) questionnaire on the main caregiver [102]. The ASR offers eight syndrome scales as well as an internalizing, externalizing, and totally psychopathology score. To assess parent behavioral factors for the mediation analyses, I used the acceptance subscale from the Child Report of Parent Behavior Inventory, Parental Monitoring Scale, and Family Conflict subscale of the Family Environment Scale [104–106] .

fMRI Acquisition and Processing

All functional and structural MRI data (N=11,875) was acquired on 3T scanners over 21 different sites across the country. Details can be found in Appendix A.

Symptom-Network Sparse Canonical Correlation Analysis

To understand symptom specific brain networks of child psychopathology, I used the unsupervised machine learning algorithm sparse canonical correlation analysis (sCCA) [107]. sCCA

and subsequent methodology is summarized in Figure 3. Briefly, sCCA is a multivariate tool that is able to find relationships between many variables and two (or more) separate datasets that do not have a particular directionality [107], such as neuroimaging and behavioral data. sCCA works by finding dimensions that share variance across the different datasets. In other words, it analyzes the linear connection between the variable sets based on the Pearson's correlation between reduced dimensions of the original variable sets. It finds high correlations within the symptom data, as well as between brain regions and then correlates those together to find the most optimal patterns. The output of this is canonical variates of functional connectivity that will have specific combinations of symptoms. I then conducted permutation testing to assess significance of canonical variates using a scree plot and applied a False Discovery Rate correction. More information can be found in Appendix A.

Figure 3. sCCA and Mediation Analysis Pipeline

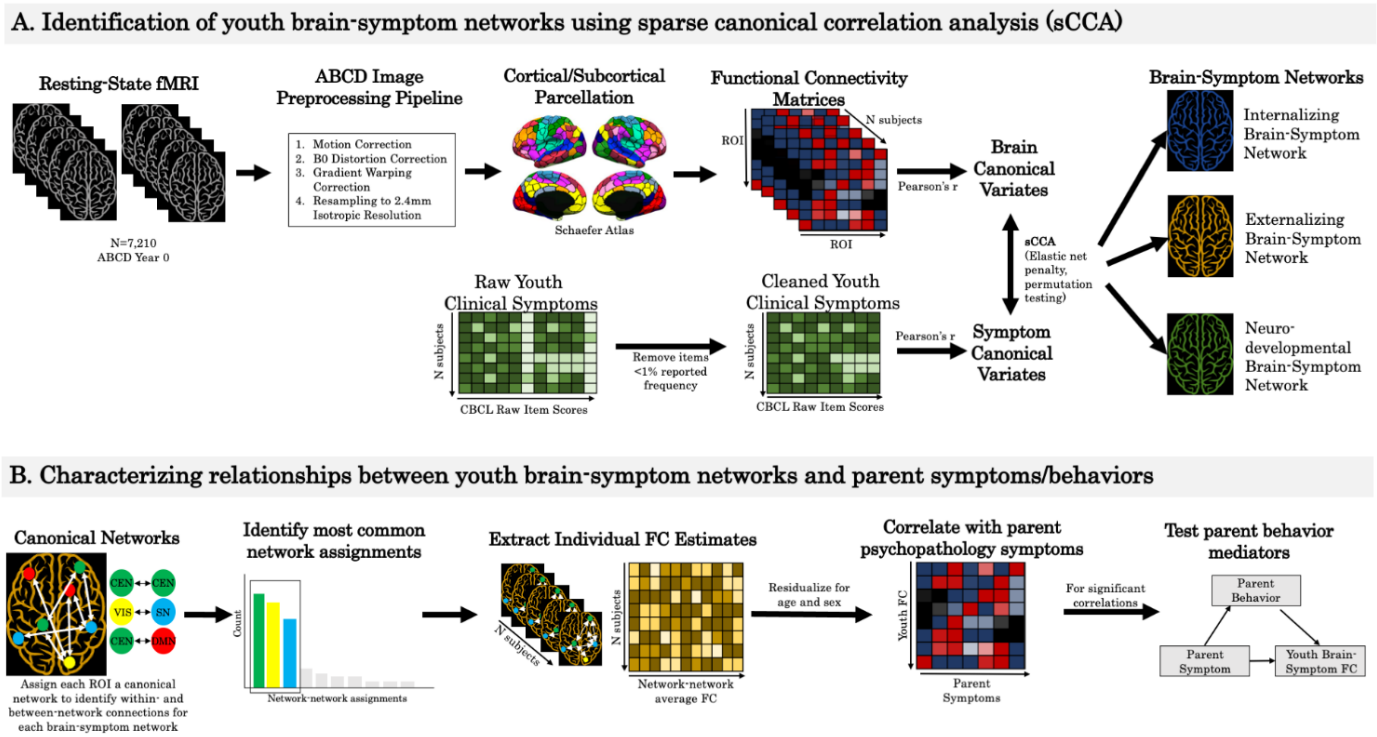

Figure 3. Description of methods. A. First, I used the ABCD preprocessed resting-state functional connectivity and used that to make connectivity matrices. Simultaneously, I used cleaned versions of youth clinical symptoms to create variates. The sCCA algorithm used a Pearson correlation to create orthogonal brain-symptom networks. B. I then identified the most common canonical network assignments to extract individual functional connectivity estimates for each person. I then correlated parent symptoms and behaviors and used the significant variables to test our mediation analyses.

Correlation and Mediation Analyses

For the mediation analyses, the sample was 7,209 due to a missing parent report score. For each of the brain regions in significant brain-symptom domains identified above, I assigned them to their canonical networks as defined by the 400-parcel Schaefer cortical and 54-parcel Melbourne subcortical atlases [108,109]. The networks include default mode (DMN), visual (VIS), somatomotor, dorsal attention, ventral attention (VAN), limbic, and frontoparietal (CTL). For this analysis, I used the combined SN and VAN (to be known as VAS) that was used for the Schaefer atlas. This resulted in a series of network-network assignments for each brain-symptom network. Then, a scree plot was utilized to determine which forms of within or between network connectivity were the most common for each brain-symptoms network, where the top networks above the elbow were chosen for subsequent analyses. Then, for each brain-symptom network and network-network assignment, the functional connectivity scores that fell within the network assignment were averaged for each participant. These average network-network connectivity scores were then correlated to each parent symptom domain and parent behavior using Pearson's correlations. Due to the volume of correlations run, multiple comparison correction was implemented using false discovery rate (FDR, α=.05).

For any significant correlations between youth functional connectivity and parent symptoms, exploratory mediation models were run investigating whether any domains of parent behaviors mediated the relationship using the *mediation* package in R [110]. In summary, to test for significant full or partial mediation, I used multiple regression models to estimate the indirect effect with a nonparametric 1000 resample bootstrapping procedure to produce confidence

intervals for the indirect and direct effect. Mediation was supported if the four conditions outlined by Baron & Kenny were true [111].

Results

sCCA Results

Using the sCCA, I identified three significant brain-symptom networks. Overall, each of the three significant networks represented distinctive domains in psychopathology: internalizing (r =.17), externalizing (r= .21), and neurodevelopmental (r=.18) symptoms. The internalizing network consisted of withdrawn, social, and depressive problems; the externalizing network featured aggressive, rule breaking, and attentional problems; and the neurodevelopmental network consisted of somatic problems like coordination, problems with eyes, as well as speech problems. Full description of symptom nodes can be found in Appendix A. The internalizing and externalizing networks are consistent with the bifactor model of psychopathology [112] and were also identified in the previous sCCA in a similar cohort [98]. While I interpreted the neurodevelopmental network as more likely reflective of genetic influences rather than parental modeling, I nevertheless explored its relationship with parent symptoms and behaviors.

Upon identifying the most common canonical network-network assignments within each brain-symptom network separately, I was able to characterize general functional characteristics of each. Here, in the externalizing network, I observed common connectivity between the CTL-DMN, DMN-VAS, DMN-DMN, and VIS-VIS. For the internalizing network, I observed VIS-VIS, DMN-DMN, CTL-DMN, and CTL-CTL as the most commonly related networks. Lastly, for the neurodevelopmental network, I observed CTL-DMN, DMN-VAS, DMN-DMN, and VIS-VIS (Figure 4).

Figure 4. sCCA Brain-Symptom Network Results

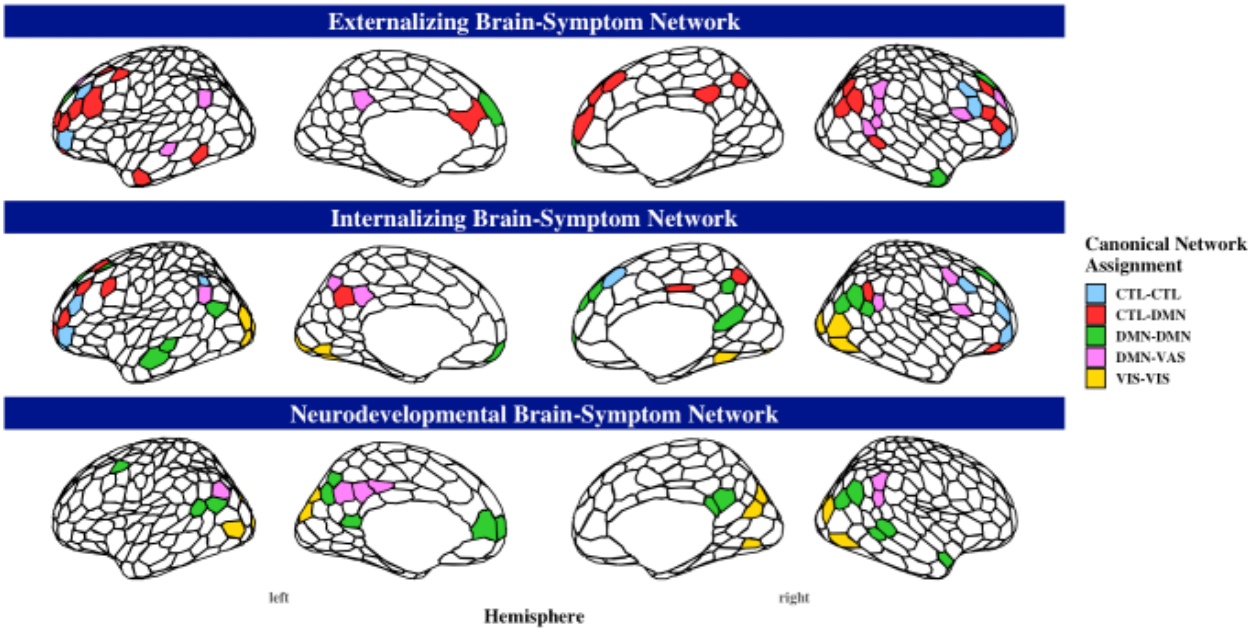

Figure 4. Visual representation of sCCA brain-symptom network results. It represents the top eight most extreme loadings (four positive and found negative) of each brain-symptom network.

Parent Symptoms

Upon characterizing the relationships between average child functional connectivity and parent symptoms, I detected six correlations after FDR correction (Figure 4). Parent personal strength symptoms was negatively related to DMN-VAS connectivity in the externalizing network (R=-.05, p=.01) and positively related to VIS-VIS and DMN-DMN connectivity in the internalizing network (R=.04, p=.021; R=.04, p=.022). Parent withdrawn symptoms were positively related to CTL-DMN connectivity in the externalizing network (R=.04, p=.035). Parent rule breaking symptoms were negatively related to VIS-VIS connectivity in the internalizing network (R=-.04, p=.019). Finally, parent intrusive thought symptoms were negatively related to DMN-VAS connectivity in the neurodevelopmental network (R=-.05, p=.001).

Parent Behaviors

Next, I identified five significant relationships between parent behaviors (parental monitoring, acceptance, family conflict) and average child functional connectivity in each brain-symptom network. Family conflict behaviors was positively related to DMN-DMN connectivity in the externalizing network (R=.03, p=.034). Parental monitoring behaviors was negatively related to DMN-VAS and DMN-CTL connectivity in the externalizing network (R=.04, p=.012; R=.04, p=.012), and positively related to VIS-VIS connectivity in the internalizing network (R=.04, p=.012). Lastly, parental acceptance behaviors were positively related to VIS-VIS connectivity in the internalizing network (R=.04, p=.012). There were no significant correlations of parent behaviors with the neurodevelopmental brain networks.

Mediation Models

Finally, using the parent symptoms and behaviors that were both significantly related to brain connectivity, I tested six models of parenting behaviors mediating the relationship between parent symptoms and child functional connectivity (Table 2).

Table 2. Mediation Results Table

Symptom Network	ROI-ROI	Parent Symptom	Mediator (Parent Behavior)	Effect of IV on Mediator (a)	Unique Effect of Mediator (b)	Indirect Effect (ab)	BC 95% CI	
							Lower	Upper
Externalizing	DMN-VAS	Personal Strength	Parental Monitoring	.017** (.003)	-0.00107* (0.000324)	-1.84e-05**	-3.37e-05	-6.81e-06
	DMN-CTL	Withdrawn Symptoms	Parental Monitoring	-.043** (.006)	-.008* (.003)	3.49e-05**	1.32e-05	-6.15e-05
Internalizing	VN-VN	Personal Strength	Parental Monitoring	.017** (.003)	.002** (.0006)	3.25e-05*	9.89e-05	6.01e-05
			Parental Acceptance	.01** (.002)	.003* (.001)	3.04e-05*	1.05e-05	5.57e-05
		Rule Breaking	Parental Monitoring	-.03488 (.006)	.002* (.0006)	-6.33e-05*	-1.15e-04	-2.15e-05
			Parental Acceptance	-.014** (.004)	.003** (.001)	-4.39e-05*	-8.33e-05	-1.02e-05

Table 2. Mediation analysis results. * p<.05 **p<.001. () is standard error. Bootstrapped 1000 times.95% confidence interval is for the indirect effect (ab). Visual representation can be seen in in Figure 3. Each mediation was significant for a partial mediation.

Here, within the externalizing brain-symptom network, parental monitoring behaviors mediated the relationship between parent personal strength and child DMN-VAS connectivity, and parental monitoring behaviors mediated the relationship between parent withdrawn symptoms and child DMN-CTL connectivity. For the internalizing brain-symptom network, I detected four mediations. First, parental monitoring behaviors mediated the relationship between parent personal strength symptoms and child VIS-VIS connectivity. Second, parental monitoring behaviors mediated the relationship between parent rule breaking symptoms and child VIS -VIS connectivity. Third, parental acceptance behaviors mediated the relationship between parent personal strength and child VIS-VIS connectivity. Lastly, parental acceptance behaviors mediated the relationship between parent rule breaking symptoms and child VIS-VIS connectivity. All mediation models reported were partial mediations. Model results are summarized in Table 2, visualized in Figure 5, and additional details can be found in the Appendix A. I tested reverse models (parent behavior → parent symptoms → network connectivity) which were also significant for partial mediation. These can be found in the Appendix A.

Figure 5. Visual Mediation Results

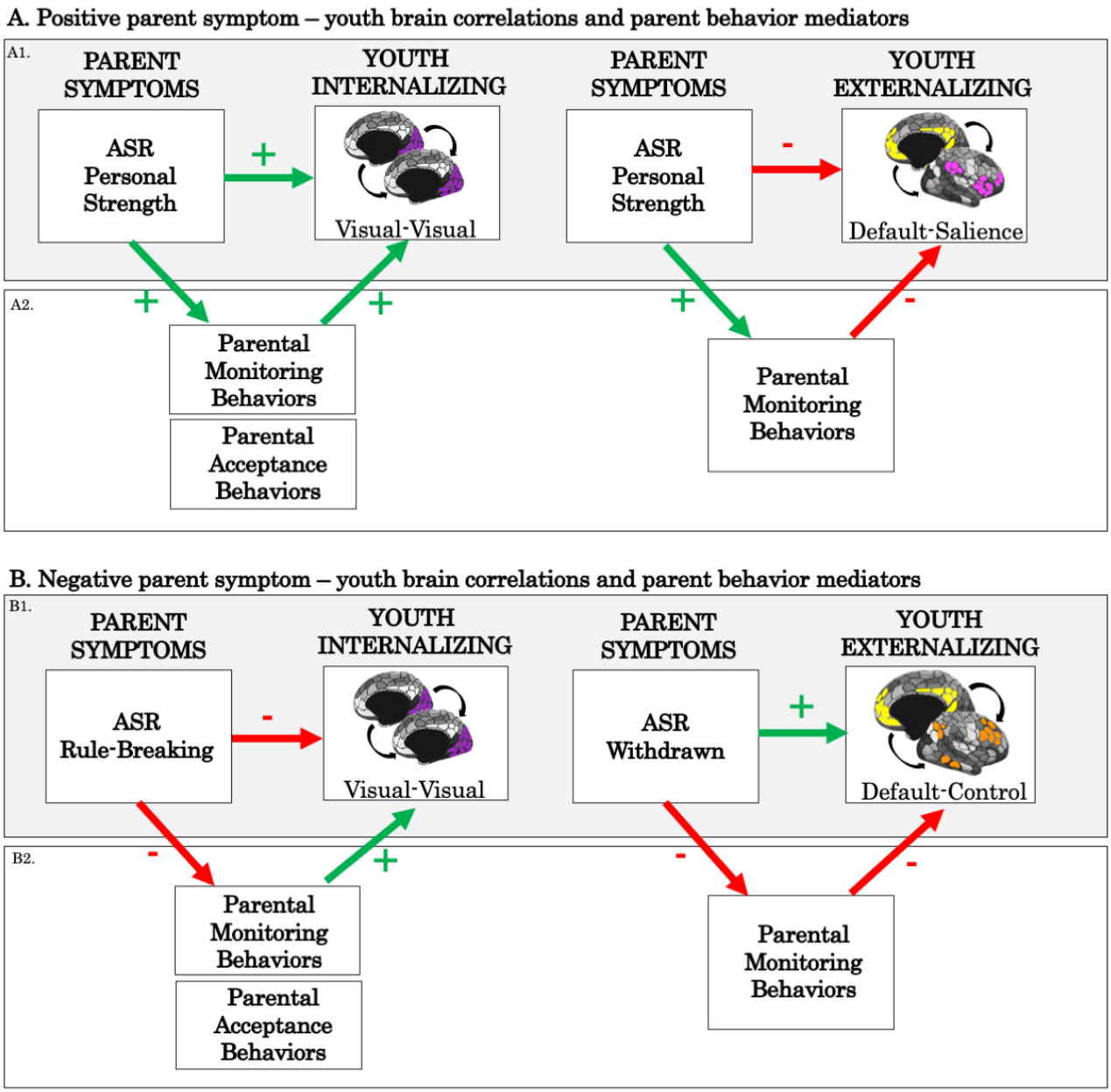

Figure 5. Visual description of the mediation results. A. For the positive parent symptoms, parental monitoring and acceptance significantly mediate the relationship between personal strength and visual-visual and default-salience connectivity. B. For negative parenting symptoms, parental monitoring and acceptance significantly mediate the relationship between parent symptoms and visual-visual and default control network connectivity.

Discussion

In this study, I investigated which specific parent symptoms were related to child brain-symptom networks, and whether active parent behaviors can have mitigating or exacerbating effects on child brain connectivity. First, I observed three brain-symptom networks related to externalizing, internalizing, and neurodevelopmental symptoms. These corresponded to differences in connectivity between the DMN-VAS, DMN-CTL, and VIS-VIS canonical networks. I further detected aspects of parental psychopathology, including personal strength, withdrawn symptoms, and rule breaking symptoms to be related to child brain connectivity. Lastly, I found that two aspects of parenting behaviors, acceptance and monitoring, may mitigate the effects of parent psychopathology on child brain connectivity in both internalizing and externalizing networks. Together, these findings implicate specific parental symptoms that are influential for child brain-symptom network connectivity, as well as targetable parenting behaviors that could mitigate these effects.

The sCCA analysis revealed three significant brain-symptom networks that replicate and expand upon previous work: internalizing, externalizing, and neurodevelopmental. Importantly, due to the CBCL having a good reliability of internalizing and externalizing factors of child psychopathology both within and beyond the ABCD sample [112,113], I were able to identify and replicate the existence of an internalizing and externalizing brain-symptom network. For the internalizing network, similar to the mood and fear networks identified by Xia and colleagues [98], variance in CTL-CTL connectivity was an important component. I also expanded this characterization and identified additional associations with VIS-VIS connectivity. This is in line with increasing evidence for internalizing psychopathology supporting both emotion processing and visual processing regions as candidate substrates [114,115]. I further found congruence with our

externalizing network and the externalizing network previously identified [98]. In both studies, I see variations in CTL-DMN as well as within VIS-VIS connectivity related to externalizing symptoms. I did not detect a psychosis or other thought disorder network, likely due to the age range of ABCD participants (mean age 9.96) as younger than the PNC sample (mean age 15.82) [98,102,116].

Analyses revealed that both positive and negative parental symptoms may influence connectivity in child brain-symptom networks. Within the externalizing brain-symptom network, parent personal strength and withdrawal symptoms are related to differences in DMN-VAS and DMN-CTL networks, respectively, which is consistent with numerous studies implicating these networks in psychopathology (for a review, see Menon, 2011). Additionally, variations in VIS-VIS connectivity in the internalizing brain-symptom network were related to parent personal strength and rule breaking symptoms. Across both brain-symptom networks, I found that parental personal strength, withdrawn, and rule breaking symptoms as the most related to child brain-symptom networks. Similar parent symptom analyses within ABCD have shown that parent withdrawn, and rule-breaking symptoms were both positively related to child psychopathology, child impulsivity, and child cognition [4]. Overall, these symptoms are likely easy for the child to detect based on their own observations of explicitly modeled feelings and accompanying behaviors which may impart greater influence on the development of brain-symptom networks in youth.

When looking more broadly at the make-up of brain networks within the externalizing brain-symptom network, parent personal strength and withdrawn symptoms were related to the canonical DMN, SN, and CTL networks, which are the most commonly implicated networks in psychopathology [37]. I identified that parent personal strength was related to decreased DMN-VAS connectivity, and this parent effect was previously shown in work with pediatric bipolar disorder

and adult PTSD [117,118]. Of note, these patterns may relate to increased segregation, or less connectivity, between DMN-VAS. This atypical pattern is consistent with previous work, where anticorrelated connectivity, or increased segregation of canonical functional networks, is an important marker of normative child neurodevelopment [119]. It has been theorized that excessive DMN-VAS coupling leads to an inability to filter internal processes in order to attend to salient tasks and stimuli [120]. While speculative, it is possible that increased parent personal strength allows the child to understand how to better filter relevant stimuli and experience fewer externalizing symptoms via increased DMN-VAS segregation in the externalizing brain-symptom network. When characterizing impacts of parent withdrawn symptoms, I saw increased symptoms are related to increased DMN-CTL connectivity. Similarly, this is consistent with another study of externalizing symptoms [121]. Here, increased DMN-CTL connectivity may reflect a failure to effectively switch been resting (DMN-driven) and focused (CTL-driven) state, which is commonly identified in externalizing attentional symptoms [121].

For the internalizing brain-symptom network, both personal strength and rule breaking were related to differential VIS-VIS connectivity. Personal strength was related to increased VIS-VIS connectivity while parent rule breaking was related to decreased VIS-VIS connectivity. Few studies have implicated the visual network, including the ventral and dorsal visual processing streams, in psychopathology. Both streams have previously been associated with numerous aspects of emotion, including attention, processing, and reactivity [122–124]. Visual areas have been shown to be anatomically and functionally connected to nodes in the CTL and VAS networks, such as the insula and amygdala [125,126]. Further, increased psychopathology symptoms, or p-factor, have been associated with reduced gray matter in visual association cortex, indicating that visual regions may be implicated in general psychopathology [127]. Our results expand this relationship by identifying

VIS-VIS connectivity to be uniquely associated with internalizing symptoms in early adolescents. I hypothesize that this may result in atypical processing of emotional visual stimuli, a process known to be disrupted in internalizing disorders such as social anxiety disorder [128]. While novel, more targeted brain-behavior studies are warranted to understand how internalizing symptoms are related to VIS-VIS connectivity [129].

After identifying relationships between parent symptoms and child brain-symptom networks, I then sought to characterize the possible mediating effects of parent behaviors on this relationship. Our analyses detected two specific domains of parenting behaviors that are related to child brain-symptom networks: parental monitoring and acceptance. Both parental monitoring and parental acceptance are aspects of authoritative parenting. Authoritative parenting, one of four common parenting styles, is generally considered advantageous in most safe environments [130]. It is characterized by high engagement or responsiveness and high warmth towards the child. Overall, authoritative parenting is related to better school grades, less psychopathology in youth, and more prosocial behavior [56–58]. One study found that parental acceptance, an aspect of warm or positive parenting, moderated the relationship between neighborhood disadvantage and resting state functional connectivity between the VAN and VIS and the DMN [34]. This indicates that positive parenting may mitigate some effects of environmental disadvantage on the child's brain. Our work further capitalizes on this literature by providing additional evidence of parental behaviors mitigating effects of other disadvantages such as parent psychopathology.

Results of the current study indicate that monitoring and acceptance of the child may help diminish the negative effects of parent psychopathology on youth brain-symptom networks or enhance the effects of positive parent symptoms. Within the externalizing brain-symptom network, parental monitoring mediates the relationship between parent personal strength and DMN-VAS

connectivity and the relationship between parent withdrawn symptoms and DMN-CTL connectivity. Overall, this implies that parent personal strength can be enhanced by positive parenting practices like parental monitoring. It also lends evidence to parental monitoring being a protective measure against parental withdrawn symptoms effect on the child's brain. In the internalizing network, I found high levels of parental monitoring and parental acceptance can mitigate the effect of parental rule breaking on within VIS connectivity. Together, these findings suggest that positive parental behaviors may protect the child's brain from potentially detrimental effects of parent psychopathology, linking to potential mechanisms of resilience.

While these analyses help provide insights into parent psychopathology and behavior on child brain-symptom networks, this work is not without limitations. Regarding sCCA methodology, I emphasized ease of interpretability. Here, rather than splitting based on the direction of connectivity, I split the connectivity outputs into their respective canonical networks and used averages of the most common network connections in subsequent analyses, however, other ways of splitting the connectivity could give different results. Additionally, ABCD had a limited assessment of parenting at baseline, obviating finer-grained analyses of parenting behaviors. Furthermore, the child symptoms and parent symptoms were reported by the parents rather than a child. Previous studies have indicated that parent reports of symptoms may be different then a child's report (Khoury et al., 2022), and therefore results should be interpreted within this context. However, it should be noted that in this age group (9–11-year-olds), parent reports may be more reliable than child reports (Nauta et al., 2004). Lastly, our mediation models are conducted on concomitant data points, which limits inference on temporal causality. I further tested the reverse models and found these to also be significant. It is likely that parenting behaviors and psychopathology are mutually influential and therefore are partially responsible for variance

that affects child connectivity. Future studies are warranted to disentangle these concepts using prospective mediation models, instead of a singular time point, to better understand how parent symptoms and behaviors interact to affect brain development over time.

Parenting styles and behaviors can be heavily influenced by uncontrollable factors, such as socioeconomic status and experience of domestic violence, which are factors typically outside of a caregiver's control. With these principles in mind, the current study suggests that parental acceptance and parental monitoring can mitigate potentially detrimental effects of parent mental health symptoms such as rule breaking and withdrawal symptoms on child brain connectivity and corresponding child symptoms. Altogether, these results provide a framework for future research and potential targets for parents that experience mental health symptoms to help mitigate potential intergenerational transmission of mental illness.

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CHAPTER 2

Parent-Child Autonomic Synchrony During Vicarious Extinction Learning

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In Preparation

Abstract

Children learn about threat and safety in their environment in part from their caregivers; this learning process may be disrupted in child psychopathology. This transmission may be seen through biological measures like peripheral nervous system outputs such as skin conductance (SCR). Fear learning deficits have been observed in fear-related disorders like PTSD but have received little study in terms of parent-child learning transmission. In this study, I used a vicarious fear extinction paradigm to examine whether biological synchrony is a potential mechanism by which children learn safety cues from their parents. In this pilot study, 27 dyads (Trauma Exposed n=5) underwent a vicarious fear extinction paradigm. I used cross-recurrence quantification analysis (CRQA) to assess SCR synchrony between parent-child dyads. I then used linear models to examine if biological synchrony is related to vicarious fear extinction and if other demographics were related to synchrony. I found that increased dyad synchrony was related to greater decreases in parent SCR during extinction, an indicator of better extinction learning, but not child SCR during extinction. Additionally, increased parent anxiety is related to decreased dyad synchrony. Collectively, it appears that parents' mental health and parents' ability to successfully learn fear extinction may be related to the biological coupling of dyads. This may be the first key to understanding why youth are able to learn effectively from their parents. While preliminary, this may lead to advancements in future therapies that give applicable and biological targets for parent-child dyadic interventions.

Introduction

Children's ability to learn emotional content from their caregivers is an important aspect of child development [131]. However, the transmission of emotional content may be altered in settings of parent or child psychopathology, as well as trauma, contributing to the emergence and/or persistence of fear-related disorders in youth (e.g. anxiety, PTSD) [132,133]. In a clinical setting, especially for Trauma-Focused Cognitive Behavioral Therapy (TF-CBT) which utilizes dyadic treatment to help youth with trauma disorders, heightened transmission of threat signals from caregiver to child may hinder youth from reducing their symptom load [134]. Thus, it is critical to understand how children vicariously learn from their caregivers to better help treatment of fear-related disorders.

Fear extinction learning has been widely used to understand fear-related disorders like PTSD in adults, but with less study in children [22,23]. Previous studies in humans, with support from rodent models, have indicated alterations in fear learning like enhanced acquisition and impaired extinction in those with anxiety disorders (for a review see Milad et al., 2014). Altered fear learning may partly be due to youths' difficulty to learn fear and safety by observation, or vicarious learning, as this learning has been shown to influence a child's normal fear development [81]. During fear acquisition, one study found that anxious children had increased reactivity to fear acquisition, demonstrating that psychopathology may influence vicarious fear learning [135]. While fear learning may be enhanced in youth with trauma, fear extinction or extinction recall may also be disrupted [136]. Therefore, it is important to study fear extinction and recall, in addition to acquisition, to fully understand the impact of vicarious fear learning on psychopathology in youth.

One mechanism through which vicarious extinction may occur is through parent-child physiological synchrony. Synchrony is the temporally-matched coordination of responses between

two people [137]. For parent-child dyads, synchrony is a critical method of learned emotion regulation in children and a way to foster healthy attachments [88]. Physiological synchrony uses peripheral nervous system methods like skin conductance response (SCR) to evaluate the degree to which dyads are coupled [137]. Youth or parent trauma leads to differences in physiological, or autonomic, synchrony but how these variations affect real-world behaviors like fear learning is still unknown [138,139]. Understanding the biological mechanism behind vicarious learning is crucial for understanding the transmission of fear and safety cues between dyads, especially in those with fear-related disorders like PTSD.

To address these knowledge gaps, these analyses examined physiological synchrony during vicarious extinction learning in youth. During this paradigm, youth went through both direct and vicarious extinction, which included watching their parent undergo direct extinction. The paradigm can be seen in Figure 6.

Figure 6. Behavioral Paradigm for Observational Learning Study

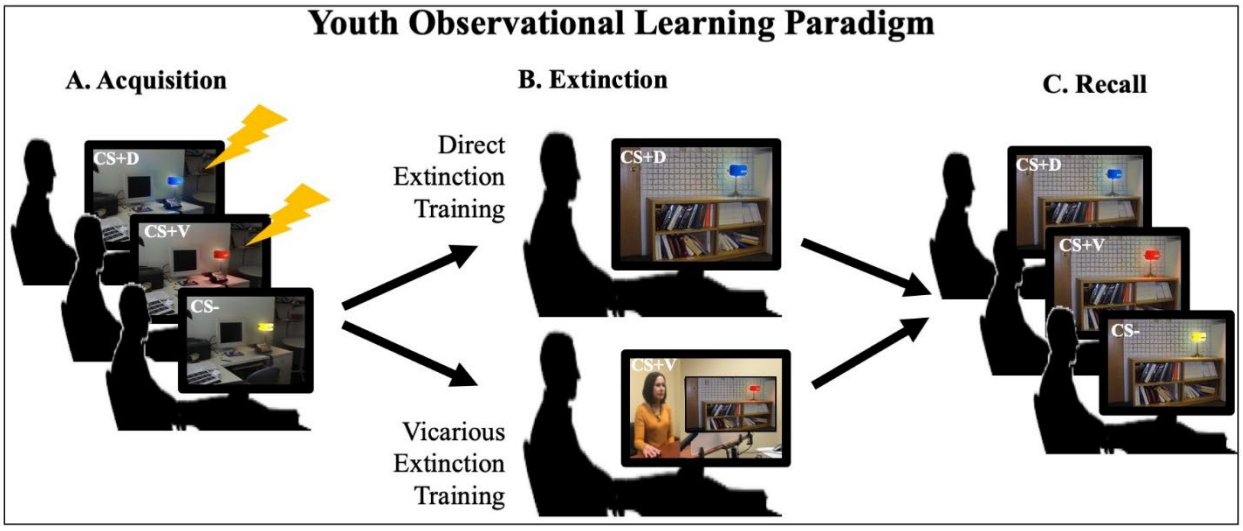

Figure 6. A. Day 1, acquisition of learned fear via electrodermal stimulation. Children will be conditioned to two stimuli. B. Day 2, the child will undergo direct and vicarious extinction. C. Day 3, children will undergo recall.

I used SCR to assess fear learning. SCR is a widely used measure of physiological arousal and is one of the most common biological metrics of fear condition and extinction [140]. In my analyses, I investigated three questions:

1. Is synchrony related to metrics of extinction learning?
2. Do aspects of parenting, parent-child relationships, or parent psychopathology affect synchrony?
3. In preliminary analyses, are there group differences between youth with trauma exposure (TE) versus typically developing (TD) youth? And is this related to extinction learning outcomes?

Preliminary evidence from the paradigm validation study suggests that youth with PTSD have increased SCR during *vicarious* fear learning compared to TD youth (Appendix C). This demonstrates that there maybe be a biological mechanism at play when youth are learning fear and safety cues from their caregivers, and potentially this is disrupted in youth with PTSD. Here, I expanded on this finding to understand if biological synchrony is related to vicarious fear extinction and if so, what in turn can affect synchrony and fear extinction learning. All analyses undertaken in this study were interim, and therefore should not be taken as our final analyses. Final analyses will be completed once data collection has concluded.

For question one, I predicted that greater synchrony would be related to better extinction learning for the parent and the youth. This predicts that greater synchrony would be related to a more negative slope during direct extinction for the parent and vicarious extinction for the child as well as decreased SCR during extinction recall for both parts of the dyad. For question two, I predicted that greater parental bonding and positive parenting behaviors would be related to greater synchrony. I also predicted that greater parent psychopathology symptoms would be related to less

synchrony. For the final question, I predicted that TE dyads would have lower synchrony compared to their typically developing counterparts.

Materials and Methods

In this study, I recruited 27 youth, and one of their parents, with youth ranging from ages 7-17 years. For the exploratory analyses, I recruited an additional five trauma exposed child dyads. Demographics can be found in Table 3. Exclusion criteria for our youth participants included past or present brain injury, unstable or severe medical conditions, substance abuse, acute suicidality, or ongoing abuse. Each parent-child dyad was assessed for past and current psychopathology diagnosis, including PTSD status, using the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) for the youth and PTSD Checklist for the DSM-5 for the parents [103]. Further psychopathology questionnaires for the child included the Mood and Feelings Questionnaire (MFQ) for child depression, the Screen for Child Anxiety-Related Emotional Disorder (SCARED) for child anxiety, the UCLA PTSD Reaction Index (PTSD-RI) for child PTSD symptoms, and the Screening Assessment for Guiding Evaluation-Self-Report for adult depression and anxiety symptoms [141–144].

Table 3. Observational Learning Study Demographics

Basic Demographic Variables		
N		25
Child Biological Sex		F = 16 ; M = 9
Child Age in Months		12.7 (1.28)
Parent Sex		F = 23 ; M = 2
Parent Age in Years		43.9 (4.83)
Race of Child	African-American/Black	0
	American Indian/Native American	0
	Asian	0
	Two or More	0
	White	25
Ethnicity of Child	Hispanic or Latino	0
	Not Hispanic Latino	25
	Not Provided	0
Parent Mental Health Diagnosis	Major Depression	1
	Bipolar/Manic Disorder	2
	Panic Disorder	1
	Social Anxiety Disorder	2
	ADHD	1
	PTSD	1
	Other Psychotic Disorder	1

	N	5
	Sexual Assault	3
Child Trauma Exposure	Emotional Abuse	2
	Physical Abuse	1
	Witnessing Physical Abuse	1

Table 3. Demographic information of Participants. ADHD: Attention Deficit Hyperactive Disorder. PTSD: Post-Traumatic Stress Disorder.

Experimental Design

In the current study, parent-child dyads underwent a three-day vicarious and direct fear learning paradigm. I used an adaptation from Milad and colleagues [145] which is described in detail in Appendix C. Briefly, each dyad completed a fear learning paradigm separately, with the child completing all paradigm phases in an MRI scanner. On day one, both parent and child were conditioned to two colored stimuli (CS+), while the remaining stimulus was left unpaired (CS-). On the second day, both parent and child went through extinction training. During extinction training for the parent, one CS+ was extinguished while the other CS+ was left unextinguished. For the child, both CS+'s were extinguished, one by direct extinction learning (CS+D) and the other vicariously extinguished by watching their parent (CS+V). Day three consisted of extinction recall for the dyads. All three task days were approximately 24 hours apart. For the unconditioned stimulus, I used tactile electrodermal stimulation. Each participant was allowed to manually select their level of stimulation. No participants dropped out due to intolerance of the stimulation. Further discussion of experimental design can be found in Appendix C.

During vicarious learning, psychophysiological metrics including SCR, heart rate (HR), and respiration was measured for each dyad, but for the following analyses, only SCR was used. For both parent and child SCR, each time series was cut from the beginning of the first fixation to the beginning of the last fixation. For the parent, the SCR analyses include a low-pass filter of 1 Hz and down sampling to 8 Hz using Ledalab [146]. For the child, scanner artifacts were filtered out due to multiband, multiecho sequences before low-pass filtering and down sampling [147]. I then detrended each SCR time series and Z-scored for the synchrony analyses.

Statistical Analysis

Statistical analyses were performed in RStudio [148]. For each synchrony analysis, I used cross-recurrence quantification analysis (CRQA) using the R package *crqa* [149]. In brief, CRQA captures recurring properties and patterns of two distinct time series. Increased CRQA metrics, or synchrony, indicate that the two time series, for example, parent-child SCR, resemble each other or mimic each other over time. I followed Pärnamets et al. (2019) parameters for the CRQA analysis. I then picked three metrics (Determinism, Entropy, and Laminarity) that were highly correlated and conducted a Principal Component Analysis with varimax rotation to find a single composite score of synchrony using the *psych* package in R[150]. To test for outliers, I conducted a Grubbs analysis using the *outliers* package in R[151]. I found a significant outlier and excluded that participant from the following analyses.

For the first question, I ran four main linear regressions. I predicted both the CS+ slope of the parent and child during fear extinction from dyad synchrony while controlling for the CS- slope. A negative slope over time for the CS+ would indicate more fear extinction learning. I controlled for the CS- to account for general drift of SCR responses over time as well as child age and sex. I then tested if synchrony was related to the first four trials of parent and child CS+ recall while controlling for the CS- as well as child sex and age. To then test if this was also true behaviorally, I ran linear mixed effect models predicting child and parent expectancy during recall from an interaction of synchrony and CS type. For the second question, I tested if any demographic information was related to synchrony as sensitivity analyses. I tested if child age, child sex, parent age, same vs different sex dyads, parent depression, and parent anxiety were related to synchrony. Then I ran correlation on the parent and child APQ, parenting styles, and parental bonding questionnaires with synchrony with a false discovery rate correction. For the last exploratory

question, I ran a linear regression on group differences between the trauma exposed and typically developing youth to predict synchrony. Then I interacted group with the independent variable to predict the outcomes in questions one and two using linear regressions.

For reporting, I will be reporting any results that are less than .1 due to the interim nature of these analyses. Further, all correlations in question two were FDR corrected across all correlations, not within, as these analyses had a high number of comparisons.

Results

Is synchrony related to metrics of extinction learning?

First, I wanted to understand if synchrony was related to real-time patterns and outcomes of extinction learning. To do this, I ran the four linear regressions found in the statistical analysis section. I found that synchrony significantly and inversely predicted slope of parent SCR responses during extinction as hypothesized (b=-.24, t(20)=-3.35, p=.003, Figure 7).

Figure 7. Visual model of Synchrony Predicting Slope of CS+ During Parent Extinction

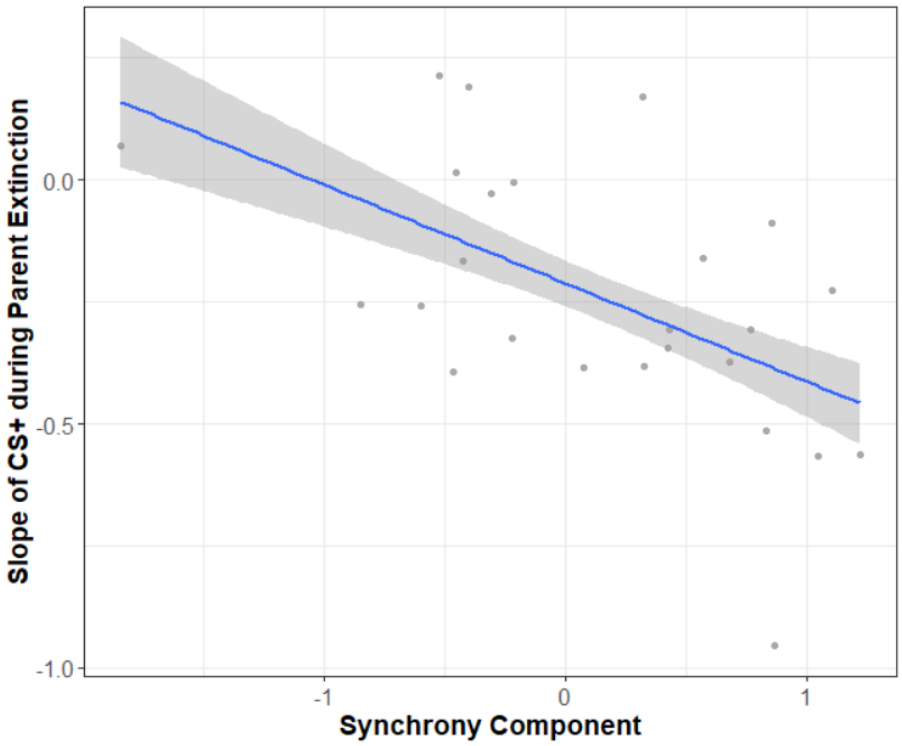

Figure 7. Higher synchrony predicts a more negative slope of the CS+ during parent extinction.

However, synchrony did not predict child SCR slope during vicarious learning. For recall, I found that synchrony did not predict parent or child average SCR during recall ($p>.05$).

It may be possible that due to scanner noise and that children have a more difficult time learning and therefore have a more blunted autonomic response to conditioned fear [152]. Accordingly, I also tested whether synchrony predicted behavioral expectancy of fear. Therefore, I conducted a linear mixed effect model predicting child and parent expectancy during recall from an interaction of synchrony and CS type but found no significant interaction.

Do aspects of parenting, parent-child relationships, or parent psychopathology affect synchrony?

I then wanted to test if demographic information was related to synchrony as sensitivity analyses. Only two, same- vs different-sex dyads and parent anxiety, were marginally significant. Generally, same-sex dyads had higher synchrony than opposite-sex dyads ($b=.55$, $t(24)=1.94$,

p=.064, Figure 8A). I also found that higher parent anxiety is related to lower synchrony (b=-.10, t(20) =-1.92, p=.069, Figure 8B). All other analyses were nonsignificant (p>.05).

Figure 8. Parent Demographics Predict Synchrony

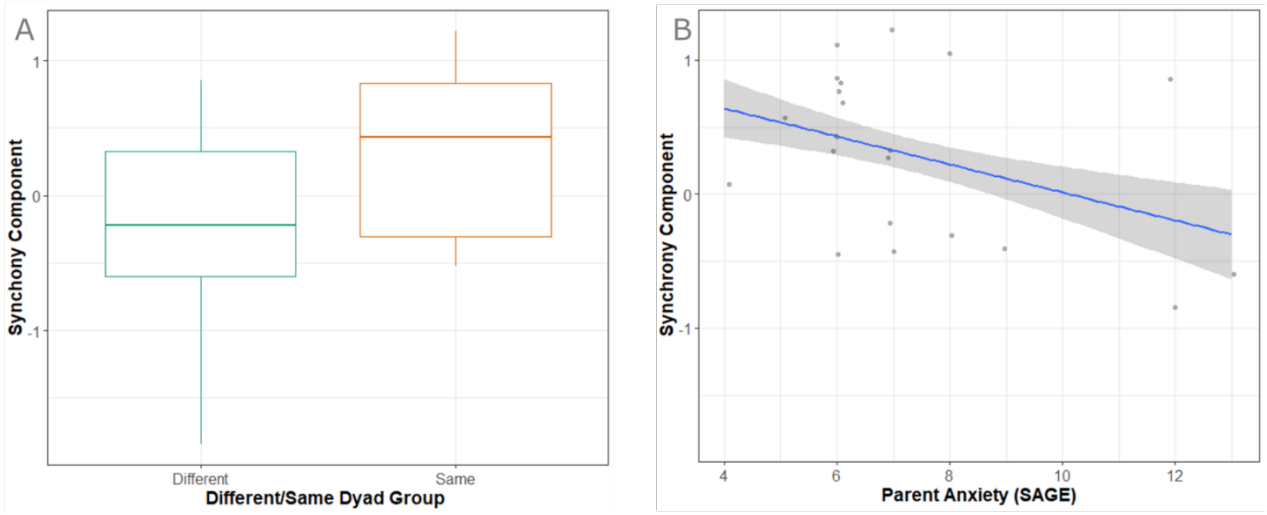

Figure 8. A. Same sex dyads had higher synchrony than different sex dyads. B. Higher parent anxiety was related to less dyad synchrony.

Next, I wanted to understand if synchrony was related to any parenting metrics. I correlated the APQ child and parent version sub scores with synchrony and found no significant correlations. I also examined whether parenting styles or parental bonding could predict synchrony but found those to not be significant (p>.05). These analyses can be found in Appendix B.

Are there group differences between youth with trauma exposure (TE) versus typically developing (TD) youth?

Lastly, I wanted to understand if trauma exposure led to differences in synchrony as exploratory analyses. First, I found that synchrony was not significantly different between typically developing and trauma exposed dyads while accounting for child age and sex (p>.05). Then, I interacted group with synchrony to predict parent and child slope during extinction, parent and child SCR during recall, expectancy, and other demographics. I found a marginally significant

group by synchrony interaction predicting parent SCR slope during extinction for the CS+ (b=.28, t(20)=1.76, p=.09, Figure 9).

Figure 9. Interaction of Trauma Exposure and Synchrony to Predict Slope of CS+ During Parent Direct Extinction

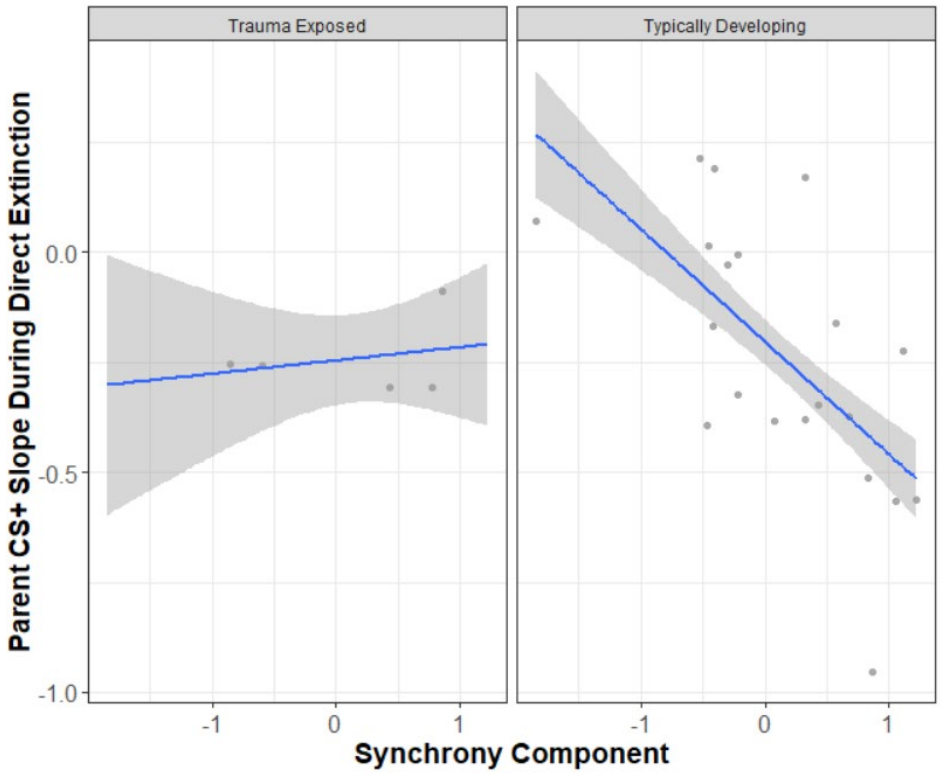

Figure 9. Group by synchrony interaction predicting slope of CS+ during parent direct extinction.

For the TD dyads, the greater synchrony, the more negative the extinction slope, while this trend was not apparent for trauma exposed dyads. I finally tested if group interacted with child slope during extinction, recall SCR, expectancy, APQ sub scores, parental bonding, and parental depression and anxiety to predict synchrony. None of these were significant (p>.05).

Discussion

In this preliminary analysis, I explored a potential biological mechanism that may be related to vicarious fear and safety learning. I hypothesized that synchrony, or the coupling of two biological systems, in this case, parent and youth psychophysiological outputs, is an important marker and mechanism of transmission of cues between dyads and this may contribute to or inhibit the extinction of fear. While study collection has not been completed, I found promising evidence that parent mental health and fear extinction ability may influence synchrony and in turn may contribute to child learning, however, more data is necessary to make more concrete claims.

First, I found that increased dyad synchrony was related to a more negative parent slope during direct extinction (Figure 7). One of the ways I measure if extinction was successfully completed is through a decrease in SCR over time from the first to the last presentation as it shows less reactivity to the CS+. Here, I see that most of the parents had a negative slope, suggestive of successful extinction learning. With this information, it appears that the parent extinguished the CS+ more rapidly in dyads that had higher synchrony. This may signify that synchrony may be indicative of how well parents distinguish fear and safety cues and thus whether youth "pay attention" to their learning. In the exploratory analyses, I saw a marginally significant interactive group effect (Figure 9). The results show a negative association between synchrony and slope for TD dyads similar to the main effect, but there was no association for the trauma exposed (TE) dyads. While there are only five data points, it may indicate parents' ability to extinguish is not related to synchrony, which may stand in contrast to TD dyads. In the future, when data collection for this project is complete, I predict that the clinical PTSD group will have a positive slope, indicating that synchrony with their parent will be higher when the parent slope is more positive. This would infer that they have better synchrony with their parent when they cannot extinguish

fear which could possibly explain why many symptoms of PTSD, like overgeneralization of fear, persists.

Next, I wanted to understand if any demographics or parenting metrics were related to synchrony. This may give insight into what can affect synchrony and potential targets for intervention. I found a marginally significant shared/different sex interaction (Figure 8A). Here I see that same-sex dyads (i.e. female/female as there were no male/male dyads) had higher synchrony than different-sex dyads. I did not have any third gender or non-binary participants. It is possible that youth preferentially, or are better able to, synchronize and learn from parents that share the same sex, and this has been supported in some literature [153,154]. This may indicate that should children need therapy like TF-CBT that utilizes parent-child learning; it may be the most prudent to use the same-sex parent if safe and possible. Relatedly, there has been evidence that parent and child sex influence learned fear and anxiety behavior in children, and that female-female dyads have better fear learning than other paired dyads [155]. I also found a marginally significant negative relationship between parent anxiety and synchrony (Figure 8B), as increased parent anxiety is related to decreased synchrony. This may be due to children understanding that their parents have inappropriate fear responses due to their anxiety, and therefore do not synchronize or learn from them as effectively. Parent anxiety is easily modeled to youth and has been shown to lead to youth to have greater anxiety, which can contribute to fear learning [156,157]. In the exploratory analyses interacting parent anxiety and group, I found no significant differences between the TD and TE groups, indicating that trauma exposure itself does not interfere with dyad synchrony when parent anxiety is present. However, when the clinical PTSD group is collected, I predict that the PTSD group will either have no relationship or a positive relationship between synchrony and parental anxiety as it is possible that this contributes to their symptoms. In the pilot

study of this task, I saw that youth with PTSD had lower synchrony with their parents, however, their parents showed little to no anxiety symptoms (Appendix C) [86]. When the full sample is collected, there should be a broader range of parent anxiety and synchrony scores that will clarify if this is an accurate prediction.

While these are promising analyses, I had some results that did not support our hypotheses. Here, I did not find that synchrony was related to any of the child outputs including slope, average SCR during recall, or expectancy, which is contradictory to previous studies using synchrony during vicarious fear learning [83,86]. This may be due to a few reasons. The child SCR was collected in the MRI scanner, which can cause artifacts due to the multiband scan sequence. I used a non-peer reviewed analysis pipeline that accounts for the specific multiband sequence, which most analysis pipelines do not as they assume a single-band sequence. Images of analysis can be found in Appendix B [147]. While, from visual inspection, the data appears to have been cleaned of MRI artifacts, it is possible that some variance is lost due to the analysis method and/or the MRI scanner itself and are unable to pick up responses of the youth. Further, it is possible that youth have a more difficult time having measurable responses to fear extinction learning. A previous study by Marusak et al. (2021) found that typically developing youth did not show a significant difference in SCRs for any CS type while in the MRI scanner. This study did however show significant brain imaging differences between CS type in the dorsal anterior cingulate cortex and anterior insula during recall. It is possible that in future analyses, brain function during extinction and recall may better represent the transmission of learned behavior than SCRs for the youth.

I further did not find any significant results with the APQ, parenting styles, or parental bonding. There was very little variance in these metrics, as most of the families had similar types of parenting due to the homogenous demographics and these are mostly TD families without a

history of trauma. I also did not see any group differences in these as well. It may be the case that there will only be enough variance of these metrics once all subjects are collected.

There are a few limitations to these analyses that should be considered. First, I currently have a relatively low sample size, with an even smaller trauma exposed group. This study is ongoing and data collection is due to be completed in 2024, and therefore this study is interim in nature. It will have 40 dyads in each group (TD, TE, PTSD) and these analyses will be repeated on a larger sample size when data collection has concluded. Another limitation is that the youth SCR goes through a different preprocessing pipeline than the parent SCR. While I processed the youth data to match the parent, there is likely more variance lost to filtering in the youth data compared to the parent. Lastly, our participants came mostly from wealthy, white families in Madison, WI. This is not an appropriate sample to make conclusions about parent-child relationships in general and should be understood through this context.

In summary, these initial analyses provide novel insights into potential biological mechanisms underlying vicarious extinction learning in youth. Greater decreases in parent SCR during extinction were related to overall greater synchrony with youth, but this may only hold true for typically developing youth and not those that are trauma exposed. Additionally, parent anxiety may be a potential target for therapeutics if youth are unable to learn safety cues from their parents, as it seems to be an adaptive response to parental mental health and targeting it first may help youth learning safety cues more efficiently. While this work is still preliminary, increased sample size and demographic variance in study completion may help to unravel how inappropriate modeling of fear to youth or altered vicarious learning may contribute to the emergence and/or persistence of fear-related disorders in youth. If substantiated, such findings also carry notable

implications for dyadic therapies, highlighting potential biomarkers that could be used to identify points of altered threat and safety transmission in the family system.

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CHAPTER 3

Summary of Research and Conclusions

In this dissertation, I have presented novel analyses to better understand the role of caregiver mental health and its effects on child neurodevelopment using multiple methods. While previous behavioral work has understood the influence of caregiver mental health on child behavior, little has been done looking at how it can affect neurodevelopmental outputs like functional connectivity and skin conductance responses (SCR). This portfolio started with a comprehensive review of neurodevelopmental and parenting theories. It then reviewed the scarce literature on how parenting and parent mental health affects the child brain. From this review, there are numerous gaps within the child neurodevelopmental literature. First, it is necessary to understand which parent symptoms and behaviors are the most detrimental or protective of child neurodevelopment. Second, how do parent symptoms or behaviors interfere with normal adaptive functioning of the child, for example, vicarious fear extinction?

I investigated how positive parenting behaviors mitigate the effect of parent psychopathology symptoms on the child's functional connectivity. I used a data-driven approach to create brain-symptom networks for the child that resulted in internalizing, externalizing, and neurodevelopmental networks. I then went on to explore what, if any, parent symptoms most greatly affected these brain-symptom networks. Overall, I found that parent personal strength was related to increases in visual-visual connectivity and to decreases in default-salience connectivity, withdrawn symptoms were related to increases in default mode-control network connectivity, and rule breaking symptoms were related to decreases in visual-visual connectivity. These networks have been notably implicated in other studies of psychopathology[37]. Then, I identified if parenting

behaviors moderated the relationship between parenting symptoms and youth brain connectivity. I found that positive parenting behaviors, parental monitoring and acceptance, mitigated the effect of negative parent symptoms on the child brain, and enhanced the effect of positive parent symptoms. Together, this illuminates how parents can affect the child brain, and potential real-world behavioral targets for the most effective ways to mitigate these effects.

Next, I wanted to explore how parent psychopathology and parent-child relationships can enhance or interrupt practical adaptive applications. Youth learn critical emotional and fear associations from their caregivers to adequately make decisions about safety. However, this may be disrupted if youth, or parents, experience psychopathology or trauma. In these analyses, I wanted to understand if biological synchrony, or the coupling of psychophysiology of the parent-child dyad, is a potential mechanism for this learning and further if aspects of the parent or parent-child relationship are related to synchrony. Overall, I found that greater decreases in parent SCR slope during extinction, a measure of better extinction learning, was related to greater parent-child synchrony. Further, I found that greater parent anxiety was related to less synchrony. Collectively, it appears that parents' mental health and parents' ability to successfully learn fear extinction may be related to biological coupling of dyads. This may be the first key to understanding how youth are able to learn effectively from their parents. For example, if this continues as a potential mechanism, researchers could utilize this as an intervention with real-time feedback to help the dyad become more in synch. Then, clinical trials could be done to understand if enhancing synchrony via intervention promotes decreases in symptom expression for the dyad post-intervention. While preliminary, this may lead to advancements in future therapies that give applicable and biological targets for parent-child dyadic interventions.

Together, this work has begun to unravel how the parent or caregiver in a child's life may affect neurodevelopment. Parental psychopathology symptoms including anxiety, withdrawal, and rule breaking seem to affect different facets of neurodevelopment, including SCR and functional brain connectivity. These interactions further have the possibility to affect child behavioral outcomes and be influenced by parent behaviors. From my work and previous theoretical and experimental material, I believe that the biobehavioral framework depicted in Figure 10 will be useful for my work going forward. For example, in future analyses of the fear extinction study, I would use this causal model to run analyses. Starting with parental anxiety, an increase in parental anxiety would increase default mode to salience connectivity in the child, as seen in Silvers et al. (2020) and due to its importance in psychopathology [37,132]. Without protective features like parental acceptance or high parent-child relationship quality, the child would potentially have increased anxiety and a decreased ability to vicariously learn fear extinction[61,68,135]. In turn, higher child anxiety and inability to extinguish fear, would positively reinforce the parent anxiety[158]. However, if positive factors like parent acceptance or relationship quality provide protective features, then the child's brain will have less connectivity between these regions. This will therefore lead to decreased anxiety and an increased ability to vicariously learn fear extinction. Again, this will then lead to decreased parent anxiety, increased parent-child relationship quality, and increased positive parental behaviors like parent acceptance in this feedback loop. Overall, I believe that neuroimaging results will show that parent mental health problems, like anxiety and depression will show differences in default mode to control and default to salience network connectivity that includes regions like the amygdala, anterior cingulate cortex, and ventromedial prefrontal cortex, especially for youth with PTSD and externalizing symptoms, when youth undergo vicarious fear extinction learning. These regions have been highly implicated in both

extinction learning and in my first aim, as they are related to externalizing symptoms [91,159]. Additionally, I predict that youth that have PTSD and more internalizing symptoms will have differences in visual-visual and visual-control connectivity during vicarious extinction learning. This is due to my previous work which found that PTSD was related to visual-control connectivity in addition to evidence from my first aim results which implicate within visual connectivity as being related to these symptoms [160].

Figure 10. Future Analysis Model

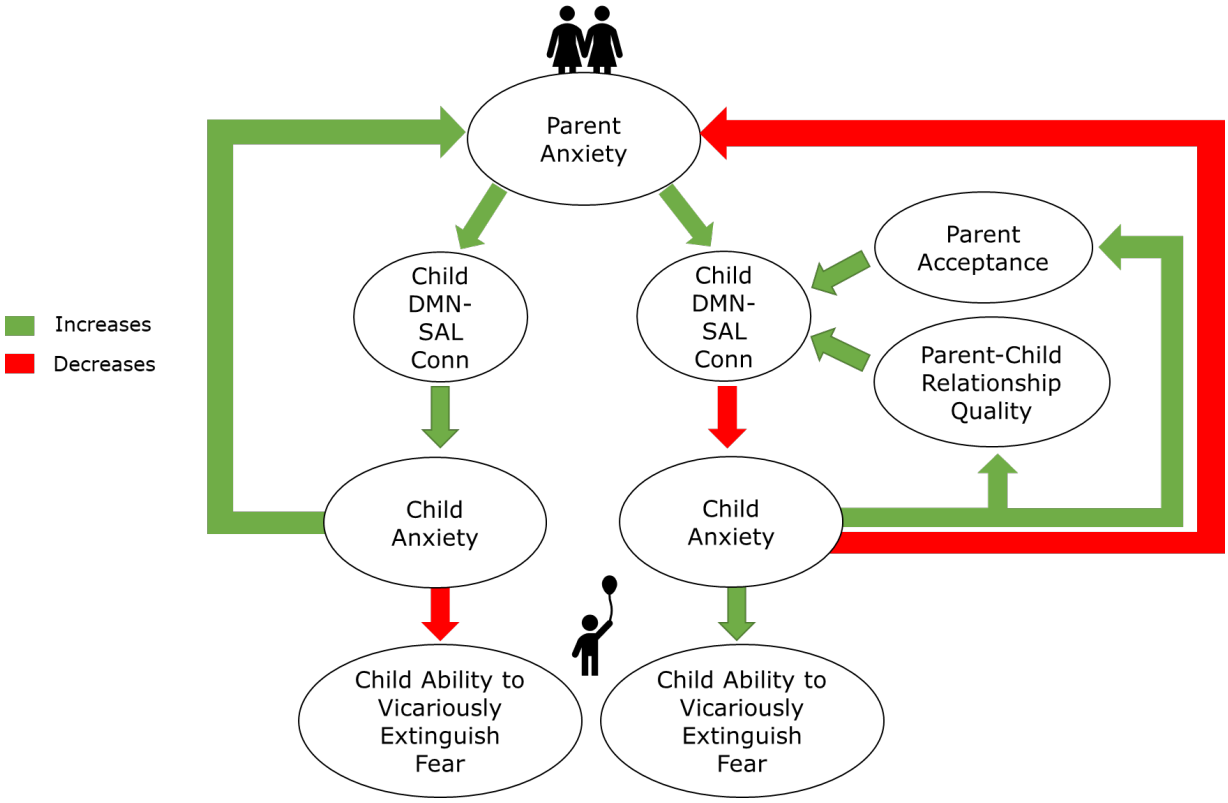

Figure 10. Depiction of causal model to be applied in future analyses.

Future Directions

This dissertation uses parenting theories and measures to understand how behavior can affect biological outcomes for children. One particular theory, the Transactional Model of Parent-Adolescent Relationship, will be important to incorporate into parent-child neuroscience work. In both of my aims, I implore a one-sided, directional approach to the parent-child relationship. However, this is not necessarily the case as depicted in my model above (Figure 10). For my first aim, it would have been more accurate to discern a way to simultaneously understand parent symptoms, child symptoms, and child brain connectivity at the same time. While this is a possibility with sCCA, it would have been difficult to effectively interpret this model given the exploratory nature of the project. It is possible that multi-level networks, like integrated network modeling or recurrent neural networks may be a better option for this as these can better use inference of causality and can take in more than two data sets [161,162]. For my second aim, the child is watching the parent undergo fear extinction in a separate room instead of being in the room with the parent. It would be interesting in the future to have both the child and parent together in the same room with psychophysiology equipment or to use functional near-infrared spectroscopy (fNIRS) which can look at the neural mechanisms of collaborators in real-time and is more similar to fMRI [163]. This way, it is likely I would get a more robust psychophysiological signal and a better understanding of the dynamics of how dyads influence each other reciprocally during vicarious fear extinction. One drawback of fNIRS, however, is that it is most useful for prefrontal cortex imaging, and is not as accurate for subcortical use, which would be a major limitation due to the importance of the amygdala and other subcortical structures in fear extinction [164]. The method in which I did the original study allowed us to use peripheral measures of learning, like SCR and heart rate, as well as high spatial resolution inherent with MRI.

Future work in the child neurodevelopment community is also looking to understand normative child development, and with this goal, it is important to include parent measures. ABCD is one of the first cohorts to have extensive parent measures in addition to child neuroimaging data. Having parent cognition, psychopathology symptoms, parent relationships, etc. may help to better understand what causes deviations from normative neurodevelopment over time as it provides information on one of the most vital contexts for child development – the parent-child relationship and the family/home environment.

Lastly, it is important to understand when it is important to include parents in preventing mental illness and in the process of therapeutics for children. A helpful first step is having parents be more involved in schools which means communicating with educators, volunteering, and attending school meetings[165]. In this study of middle schoolers, more involvement was related to better mental health outcomes, less victimization, and fewer suicidal thoughts [165]. This study also found a time component where the earlier that parents were involved, the better outcomes for their child. While parents can pursue healthy parenting behaviors, have a good relationship with their child, and be involved in their child's life, it is still possible for mental health disorders to develop due to genetics or other factors like trauma exposure. Then, it is important for parents to be involved in dyadic-centered treatments like trauma-focused cognitive behavioral therapy (TF-CBT). TF-CBT utilizes parental modeling of healthy behavior, like fear extinction, to treat youth trauma exposure and symptoms [166]. Coincidentally, parent symptoms also generally become more manageable with this type of therapy which can in turn also help therapeutic outcomes and youth mental health [167]. However, it should be noted that when parents exhibit psychopathology, this therapy may not be as effective and may potentially hinder growth [168]. It is therefore important to understand which parent symptoms interfere the most with youth healing. In the future, it will be

important to monitor parent symptoms as well as child symptoms during randomized control trials of TF-CBT. TF-CBT would also benefit from a neuroscience component of psychophysiology or neuroimaging as these could help understand the biological mechanisms of TF-CBT and what makes it effective.

Together, this dissertation provides evidence and future research directions for child psychopathology, parent psychopathology, and the child brain. It emphasizes the need to include parent-level data in our modeling of youth psychopathology and in potential treatments that result from this work. Youth and families have an immense capacity for resilience. Helping them overcome life adversities will be my priority in my future work.

CHAPTER 4

Potential Socioeconomic Effects of the CoViD-19 Pandemic on Neural Development, Mental Health, and K-12 Educational Achievement

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Abstract

The Novel Coronavirus (COVID-19) pandemic can affect more than a child's biological health. Lack of in-person schooling and increased stress can affect neurodevelopment, mental health, and later life outcomes, especially for students who are from low socioeconomic status (SES) households. Insights from neuroscience on child development reveal potential neural mechanisms and educational outcomes likely disrupted by the pandemic—and how this will disproportionally affect low-SES children. Four policies can combat these educational and emotional effects: increased access to online resources, increased access to online resources, changing of teacher curriculum for a post-pandemic world, investments in social-emotional health, and increased access to summer/out-of-school learning. Integrating the traditionally separate fields of neuroscience and educational research will be critical for developing and assessing the most impactful policies to improve the well-being and educational achievement of our most disadvantaged children.

Introduction

COVID-19 has infiltrated every state in the United States with almost 82 million cases and over 1 million deaths as of May 2022 [169]. During March of 2020, almost every U.S. state closed schools to protect students and teachers from contracting or spreading COVID-19. In the past 2 years, children have undergone online, hybrid, and in-person schooling depending on their state or school district. The inconsistency in access to internet, school resources, social interaction, and other factors have left many children with the high likelihood of mental health problems and degradation in academic outcomes. In December of 2021, the U.S. Surgeon General issued an advisory on youth mental health exposed by the COVID-19 pandemic. "Mental health challenges in children, adolescents, and young adults are real and widespread. Even before the pandemic, an alarming number of young people struggled with feelings of helplessness, depression, and thoughts of suicide — and rates have increased over the past decade." said Surgeon General Vivek Murthy. It is our duty to fully investigate and help these children that have been affected by the pandemic.

The American Academy of Pediatrics advised schools to reopen to mitigate adverse social and educational effects (*COVID-19 Guidance for Safe Schools*, 2020). At this point, most school have remained open and only close in response to massive outbreaks in classroom. While generally agreed upon that this is the most ideal plan for most children, a great number of children will continue to struggle emotionally and academically because of the pandemic for years to come due to the inconsistency of schooling. It should be expected that the lack of stability and increased chronic stress due to the pandemic will disproportionately affect students whose households were defined as low- socioeconomic status (SES) prior to the pandemic, as well as those who now find themselves in those households.

Insights from neuroscience research can help inform predictions of the pandemic's likely impact on neurodevelopmental and educational outcomes. Factors like poverty and pre-existing stress may predict differences in academic achievement and further pandemic-related stress. Children of essential workers, for example, must now cope with potential illness or navigate such stressors as parental job loss, death of a family member, or food insecurity. These types of acute and chronic stress can lead to changes in neurodevelopment. I predict that, while all children are at risk of falling behind, students from low-SES backgrounds will fall even further behind educationally, with accompanying emotional and behavioral problems due to ripple effects of the COVID pandemic. To understand the full effect on students, it is important to understand the effect of stress and poverty on emotional, neurological, and academic health. While schools prepare for and acknowledge achievement gaps, few, if any, have examined them with a neurodevelopmental approach.

I will briefly review the impact of stress due to being in a low-SES household on important brain areas, and how this may translate to emotional health and educational outcomes. Then, I will describe current federal policy that sims to help children in school and their mental health. Lastly, I will explore how policy makers can utilize funds provided for the best outcomes in four distinct ways. Integrating the traditionally separate fields of neuroscience and educational research will be critical for developing and accessing policies that have the greatest impact on improving the well-being and educational achievement of our most disadvantaged children.

Neural Mechanisms of Stress and Low-SES

SES, or the combination measure of education, income, and occupation, has been critical in assessing differences in many types of behavioral, physical, mental, and cognitive outcomes [171]. Low-SES is associated with higher levels of stress, including more daily stressors, and can

interfere with a normal, healthy stress responses [172]. Such incidents may include feeling unsafe in one's neighborhood, inadequate access to food or water, inadequate family support, housing insecurity, and domestic violence, among others [173]. These repeated chronic stressors have impacts on normal biological functioning, like the hypothalamic-pituitary-adrenal (HPA) axis, and disruption of the HPA axis can affect the immune system and cognitive processes, both of which are imperative during the COVID-19 pandemic [174].

While stress is necessary for navigating life effectively, chronic stress can be harmful to the brain. Specifically, for childhood neurodevelopment, damage to these critical brain areas could negatively affect a child's long-term outcomes. Chronic increases in stress can lead to increases in psychopathology symptoms that can manifest in the classroom and other adverse health effects [175]. SES and stress have been connected in a few studies showing increased salivary and hair cortisol levels, measures of hormonal stress, in low-SES children and parents compared to high-SES peers [176,177]; however, overall findings are mixed on these associations [178,179].

Looking at brain development, stress and low-SES have been correlated with differences in brain volume, particularly in the PFC and hippocampus which are important for social health, mental health, and overall educational achievement [180–182]. A preliminary survey has shown that stress has increased for American children during the pandemic and specifically found that parent-child conflicts have increased by 56% [183]. Overall several studies suggest that there is increased stress for children during the pandemic and that stress is worse for children and adolescent who already have financial hardships [184–186]. These studies indicate the importance of understanding the effect of stress and mental health on other aspects of children's lives, like education. Next, I highlight the role of the PFC and hippocampus in learning and memory and discuss how the effects of chronic stress on these brain circuits may compromise educational development in children.

The prefrontal cortex (PFC) and the Hippocampus are crucial brain regions for school achievement [187,188]. The PFC which is at the front of the brain towards the forehead serves as the hub for many crucial cognitive processes, and improper development may lead to lower achievement and poorer life outcomes. The processes that rely on the PFC include cognitive control, working memory, inhibitory control, problem solving, and goal directing [189,190]. The hippocampus, a small region deep within the brain, is important for formation and retrieval of memory, sensory integration and also has many implications for educational achievement [191,192]. The PFC and hippocampus are important, but sensitive areas that may be especially susceptible to stress caused by poverty due to susceptibility to change from the HPA axis [193]. Even brief stress can disrupt basic cognitive function performance in both the PFC and hippocampus [194,195].

Reduction in volume of PFC and hippocampus have been shown to be related to poverty and stress and these differences are related to worse academic outcomes in literacy and math [196–198]. Without healthy development of the PFC and hippocampus, it is difficult for children to work flexibly and show self-regulating behaviors that are related to school achievement and readiness [188,199].

However, not all stress is created equal as it is suggest that perceived control over psychological stress can help mitigate the adverse effects on brain development [200]. Children who have higher perceived stress show lower hippocampal volume compared to those who have less perceived stress [201]. During this current pandemic, however, many students have lost their sense of control and are likely facing increased psychological stress as a result [184–186]. The ability to succeed in school relies in part on the ability of the PFC and hippocampus to work effectively; crucially, chronic stress can change the developmental trajectory of these brain areas. Chronic stress can come from many sources that can compound each other; for example, instability of food

and housing, lack of educational stimulation, increased violence, and lack of healthy social engagement. These stressors are being accentuated during the COVID-19 pandemic and could potentially affect PFC and hippocampal development of children currently in the school system; therefore, it is necessary to consider this development in predicting educational outcomes.

Stress, The Brain, and Emotion

As previously discussed, the PFC and hippocampus are important for educational achievement. However, the brain is multifaceted, and each region has multiple functions as well as many regions concurrently working together to achieve behavioral outputs. Both the PFC and hippocampus, as well as their functional and structural interactions, are involved in emotion, memory, and attention. Accordingly, affective mood has been linked to children's school performance and therefore needs to be centered in the conversation of academic achievement [202]. Stress can cause emotion dysregulation over time which can lead to more aggressive behavior and potentially worse later life outcomes [203,204].

Within the PFC, the ventromedial PFC (vmPFC) is important for top-down emotional regulation across development and also has roles in cognitive and emotional regulation of cue-oriented and emotional memories [205,206]. The PFC and hippocampus together have been shown to be imperative for correct functioning of episodic memory, and specifically contextual and emotional memories [205,207]. It was proposed that emotions themselves influence how the hippocampus forms and this formation affects our memory systems further highlighting the importance that educators take emotion into account with teaching [208]. Therefore, detrimental effects of low-SES and increased stress on these brain regions do not just affect educational performance by itself, but also decrease emotion regulation and emotional memory accuracy,

leading to additional harmful effects on educational achievement. It is important to also focus on emotion regulation on a policy level to help counteract deficits caused by stress.

Current Policies and the Effect of COVID-19 on Families

To aid states in responding to COVID-19 and combat the economic effects of the pandemic, the United States Congress passed the CARES (Coronavirus Aid, Relief, and Economic Security) Act, which allocated approximately $13 billion to K-12 schools [209]. This Act gives flexible spending to help stabilize schools and help foster reopening, including money for sanitation, meals, purchasing of educational technology, and mental health services. In December of 2020, a $1.4 trillion relief funding package was passed to fund government activities and provide additional relief to education as well as numerous other provisions [210]. For K-12 schools, $54.3 billion were allocated to address similar problems described in the original CARES Act. Further, it grants waivers for state assessments for the 2019-2020 school year and gives the potential for 2020-2021 school year as well. It is estimated between $700 million and $1.7 billion is spent on standardized testing annually and is highly variable between states [211,212]. On top of being costly, standardized tests have been found to increase stress among both students and teachers, particularly in those from more disadvantaged schools [213]. Further, standardized testing leads to changes in cortisol responses and those who react most strongly scored much lower on exams than those who do not [214]. Together indicating that those from low SES may be affected more by testing and will do even worse on testing once schools are back in session. While standardized testing *is* important to offer reliable and standardized ways of measuring achievement which can in turn help policymakers and educators to know where students are struggling and require help, for many students, it has not actually produced improvement in student achievement in the United States [215]. Standardized testing was generally removed from being connected to

amount of money a school district receives with the Every Student Succeed Act [216]. Therefore, the more current policy should be continued in order to preserve health and well-being of low-SES and marginalized students.

In March of 2021, the American Rescue Plan was signed into law which allocated $122 billion to K-12 funding. This funding was given mostly through Title 1 to funding school with high levels of poverty. Each district was required to use at least 20% to address learning loss and to create a safe plan for reopening in-school learning. While schools were given money and theory should be reporting back to the US government on what they were spending , most of this funding has been underreported [217]. This leads to potential inequalities in use of funding and a districts' funding may not reflect urgent needs of the children impacted the most by the pandemic. The Biden Administration has attempted to increase the information required of school districts, but much of the first two pandemic relief funding will not have accurate accounts of where the money went. Many schools, however, are pushing back indicting that this would cause excess administrative burden on them [217]. The government and the public, therefore, have little oversight to see that their children are using the funding adequately.

For the end of the 2019-2020 school year, states adopted different methods of continuing education. Some, like the state of Kentucky, mandated that every school be switched over to already- created state-created distant learning instruction. Other states, such as Montana, did not recommend or require any distant or online learning, leading school districts to adopt divergent policies within states (Education Week, 2020). This variability in policy inherently creates educational disparities between states and even between school districts within states. Some schools attempted to restart the 2020-2021 school year in person; however, many have had to move to online-only learning after drastic increases in cases [219]. As the end of the 2022 school year,

almost every school district has gone back in person, and few have any mask mandates [220]. This is likely to continue in the future. While equitable to have every student experience the same schooling (i.e. in-person/online), it is unrealistic in our current school system. A general rule set to help schools decide on closures and in-person/online schooling would have likely helped many students and educators at the beginning of the pandemic; however, each school was allowed to make their own decisions based on infection rate and number of students with COVID-19.

Policy Recommendations

Even with the economic power behind opening schools safely, it is clear that low-SES students will continue to lag behind their peers unless action is taken immediately to combat the mental health and academics effects of the pandemic [221]. Below, I highlight four high-yield areas of investment to combat these disparities for low-SES students: increased access to online resources, changing how standardized testing works within the United States, changing of teacher curriculum for a post-pandemic world, investments in social-emotional health, and increased access to summer/out-of-school learning.

The Pew Research Center estimates around 50% of poor households have a home computer and broadband internet while 95% of high-earning households have access to these technologies [222]. If most schools implement distance/online learning, those students who lack access will struggle with their work as well as not have access to mental health resources [223]. Providing adequate internet to rural and poor urban areas has been difficult, but it soon may become a necessary utility for everyone in the United States. Local and state governments should allocate continuous funding to expand avenues for internet access – like community hotspots or citywide Wi-Fi– and subsidize internet costs. However, without congressional budget and connections, it would be difficult for states or communities themselves to build sound broadband internet

infrastructure. Without this basic infrastructure, it is unclear if online learning will be effective for keeping students on track for success. Further, if additional schooling or homework is needed to try to regain learning lost from the pandemic, having equitable access to this is imperative. Creating accessible broadband internet would also give a return on investment in as little as a year [224]. It also creates and stabilizes jobs, increases real estate value which combined will likely decreases stress of the families who need it and increase funding for local schools through real estate taxes. It should be noted, however, that some young students (1st grade and under) or some children with disabilities may not be able to do online learning no matter how accessible it is. For these children, school districts should provide special consideration for in-school learning programs. Internet access and affordability will help mitigate stress due to the pandemic and further help children learn.

Even with schools reopening and going to back towards a norm, it is important to allocate funding towards telehealth and mental health resources. Mississippi allocated money towards including schools in the Mississippi Division of Medicaid as to give telehealth coverage to any student in their districts [225]. Telehealth can both support mental and physical health for families that otherwise would not have access to healthcare, specifically those that are in low-SES households [226]. Telehealth has been found to help mental health in numerous emotion disorders and would be able to be applied to any school district [227]. While the CARES Act allows for more discretionary funding towards mental health resources, each state or school district should use part of their funding to start and maintain telehealth services. These investments may combat potential mental health difficulties and in turn help mitigate deficits in brain development due to the pandemic [185].

Social and emotional learning (SEL) is curriculum that helps children manage their emotions, create and achieve goals, and practice empathy and positive relationships [228]. One validated framework put forth by the Collaborative for Academic, Social, and Emotional Learning (CASEL) uses a five-pronged SEL model to increase social, emotional, and personal skills (see Ross & Tolan, 2018). This program focuses on childhood and early adolescence, which have generally been found to be the most impactful developmental points for SEL interventions. In a study of 5th-7th graders, CASEL's SEL intervention decreased risky behaviors, delinquency, and improved academic performance. Adding SEL programming is likely to have a pronounced effect on mitigating the impacts of COVID-19 stressors and lost educational opportunities for low-SES youth. States should consider adding SEL curriculum moving forward with discretionary funding from Congress. It should be noted that there are many SEL curriculums available, and each district should consider which one is most appropriate for their demographics and cultural values. Another possible direction states or districts could take is trauma-informed schooling, which has been shown to increase resilience and decrease problematic behaviors [229]. Emotion-based learning may become especially necessary for children who have PTSD or show increased stress symptoms due to the pandemic. While there is little research on how these interventions effect the brain, it should be noted that many interventions lead to better symptom outcomes [230]. Ideally, this would be added to teacher curriculum and then additional trainings would be available for teachers to take once out of school. This should be added to budgets and allow teachers to be paid during these trainings as to keep emotionally strong educators and will hopefully lessen the burden on teachers to do this on their own.

The last two years it has become clear that teachers were not adequately prepared or supported during the pandemic, which caused mental health problems and stress for teachers,

students, and parents. One of the first issues was most teachers were not prepared to teach virtually or use hybrid models and schools did not support them in this transition [231,232]. Administrations are further asking teachers to care for the students emotionally and mentally during a global traumatizing event. With over 1 million deaths in the United States as of May 2022, and more than 200,000 kids have lost a parent of caregiver during covid [233,234]. For many teachers, it was up to them to care for their students [235]. A longitudinal study found that generally teachers mental health and wellbeing significantly declined during the past two years [236]. To foster emotional wellbeing with their students, teachers need to have adequate mental health support, to have training in trauma informed practices, and to be able to effectively use technology in their teaching. Without these supports, policymakers and administrators are requiring too much from their staff and this will greatly affect their students in the long run.

It is likely that most students, but especially those who have higher stress and poverty due to the pandemic, will need increased support and year-round schooling to combat these effects. It will likely take years to put students back on their original academic trajectory. There should be adequate funding for summer school for any student that needs it, based on the district funding distribution laid out in the CARES Act (funding is given per pupil, but also % low-income of the district), and should continue for years to come to make up for lost months or years of adequate schooling due to the pandemic[209]. While enriched learning opportunities will be important for low-SES students, as shown in some interventions [237], it will be vital to similarly address other disparities accentuating the SES learning gap, including access to adequate nutrition, housing, and stable incomes for parents in order to fully combat the effects of poverty and stress on child behavioral and neural development [238].

Future Directions

Neuroscience has the potential to help shape education policy and make schooling more accessible and effective for disadvantaged students. While there are few research studies that directly combine neuroscience and educational interventions and outcomes, it is a growing field that will be useful for future policy decisions. It is important to incorporate biology and behavior when making policy recommendations that address disparities. This article serves as a starting point for policy makers, educators, and scientists to understand the larger picture of child development and create science- and research-based policy designed to reduce the vast inequities in social, emotional, and educational outcomes facing our most disadvantaged children.

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APPENDIX A: SUPPLEMENTAL MATERIALS FOR CHAPTER 1

Supplemental Methods

Questions removed from the CBCL are: q2, q15, q18, q59, q67, q72, q79, q96, q99, q101, q105, q106, q110.

The parent symptoms consisted of 12 t-scores from the ASR, including: anxious/depressed, withdrawn, somatic complaints, thought problems, attention problems, aggressive behavior, rule-breaking behavior, personal strength, and intrusive behavior symptoms as well as general internalizing, externalizing, and total problem symptom scores. For clarity the personal strength symptom questions include: “I make good use of my opportunities”, “I work up to my ability”, “I am pretty honest”, “I meet my responsibilities to my family”, “I try to be fair to others”, and “I am a happy person”.

All functional and structural MRI data (N= 11,875) was acquired on 3T Siemens scanners over 22 different sites across the country. Youth watched a movie while 3D T1-weighted images were collected during a magnetization-prepared rapid acquisition gradient echo (MPRAGE) with the following parameters: repetition time (TR)=2500 ms; echo time (TE)=2.88 ms; image matrix=256x256; voxel resolution=1x1x1 mm3 isotropic; field of view (FOV)=256 x 256 mm; flip angle=8 degrees. Prospective motion correction (PROMO) was implemented during acquisition. Cortical reconstruction and volumetric segmentation of images were conducted using FreeSurfer Analysis suite.

Resting-state MRI data were collected in four 5-minute scans using the following parameters: TR = 800 ms, multiband EPI with slice acceleration factor 6, 2.4 mm isotropic. Head motion and between-scan motion was accounted for in preprocessing. TR’s with excessive movement above

0.3 mm were removed and a 0.009-0.08 Hz bandpass filter was applied. After quality control measures, a total of 7,210 scans were included in subsequent analyses.

I used the community-processed neuroimaging data from ABCD-BIDS Community Collection 84-86. This includes standard structural (brain extraction, normalization, parcellation, segmentation) and functional (registration, motion correction, bandpass filtering, global signal regression) preprocessing to produce CIFTI time series files. I then used the time series files with the Schaefer 400-parcel Atlas 90 and subcortical volume labels form the Melbourne subcortex Atlas (54 parcels 91). Finally, I censored any volumes above .2 mm threshold 92.

Because I have many more observations (454x454 regions of interest) than the number of participants, I first performed a dimension reduction within the connectivity matrix. Xia et al., used a median absolute deviation (MAD) strategy to assess variance in the dataset. It takes the top 10% of connectivity variables across participants with the most variance [98]. Alternatively, the use of a principal component analysis (PCA) may have resulted in similar findings, a PCA creates latent variables which make interpretability difficult, if not impossible. Therefore, I chose also implement the MAD strategy for neuroimaging data reduction in this analysis [98]. Item-level clinical data was used without further data reduction. In order to account for potential confounds, to regressed age and sex from both the clinical and neuroimaging data. Then, I used an elastic net regularization method on both the symptom and connectivity data with the sCCA to obtain an interpretable model.

Supplemental Results

sCCA Results

Supplemental Table 1: Externalizing Network Symptom Table.

Clinical Symptom	Load
Disobedient at school	0.561554
Can't concentrate, can't pay attention for long	0.367572
Poor school work	0.314586
Can't sit still, restless, or hyperactive	0.246916
Talks too much	0.237429
Hangs around with others who get in trouble	0.230233
Gets teased a lot	0.201467
Doesn't seem to feel guilty after misbehaving	0.197924
Lying or cheating	0.182935
Destroys his/her own things	0.164411
Breaks rules at home, school or elsewhere	0.158407
Clings to adults or too dependent	0.142896
Unusually loud	0.11436
There is very little he/she enjoys	0.110426
Not liked by other kids	0.100066
Repeats certain acts over and over; compulsions	0.091144
Confused or seems to be in a fog	0.049796
Steals at home	0.046818

Supplemental Table 2: Neurodevelopmental Network Symptom Table.

Clinical Symptom	Load
Overweight	0.491002
Sleeps less than most kids	0.363144
Speech problem	0.358546
Poorly coordinated or clumsy	0.349091
Problems with eyes (not if corrected by glasses)	0.201353
Swearing or obscene language	0.078904

Supplemental Table 3: Internalizing Network Symptom Table.

Clinical Symptom	Load
Overweight	0.410395
Speech problem	-0.39302
Daydreams or gets lost in his/her thoughts	-0.37155
Would rather be alone than with others	-0.31643
Doesn't eat well	-0.28746
Withdrawn, doesn't get involved with others	-0.28467
Stubborn, sullen, or irritable	-0.238
Unhappy, sad, or depressed	-0.18867
Worries	0.184193
Can't get his/her mind off certain thoughts; obsessions	-0.17239
Wets the bed	-0.09608

Bites fingernails	-0.08465
Showing off or clowning	-0.07905
Rashes or other skin problems	-0.06221
Bragging, boasting	-0.0576
Feels he/she has to be perfect	0.046617
Teases a lot	-0.01152
Gets hurt a lot, accident prone	-0.00084

Mediation Analysis Results

For the first externalizing brain-symptom network mediation model, higher parent personal strength were related to higher parental monitoring (b=.017, t(7144) = 5.397, p=6.99e-8), as well as higher personal strength led to decreased connectivity in the default to salience/ventral attention networks (b=-3.33e-4, t(7151) = -3.802, p=.00015). Parental monitoring was also related to decreased connectivity while controlling for parent personal strength (b=-1.07, t(7143) = 5.397, p=.001). Lastly, the indirect effect was significant (b =-1.84e-5, p=<2e-16).

For the second externalizing brain-symptom network mediation model, higher withdrawn symptoms were related to decreased parental monitoring (b=-.043, t(7144) = -7.307, p=3.04e-13) and higher withdrawn symptoms is related to higher connectivity in the control to default mode networks (b=.00041, t(7151) = 3.159, p=.0016). Parental monitoring still significantly predicted child connectivity while controlling for withdrawn symptom (b=-.00082, t(7143) = -3.131, p=.00175). Finally, the indirect effect was significant (b=3.49e-05, p=.002).

For the first internalizing brain-symptom network mediation model, higher parent personal strength were related to higher parental monitoring (b=.017, t(7144) = 5.397, p=6.99e-8) and more within visual connectivity (b=0.0005778, t(7151) = 3.422, p= .000624). Parental monitoring was related to significantly higher internalizing within visual connectivity when controlling for personal strength (b=0.0018817, t(7143) = 3.015, p=. 00258) and the indirect effect was significant (b= 3.25e-05, p=.004).

The second internalizing brain-symptom network mediation model showed that more parental rule breaking problems were related to lower parental monitoring (b=-0.033804, t(7144) = 5.558, p=2.83e-08) and lower within visual connectivity (b= -0.0011310, t(7151) = -3.527, p=. 000423). Parental monitoring was related to significantly higher internalizing within visual connectivity when controlling for rule breaking symptoms (b=.0018725, t(7143) = 3.000, p=. 002707) and the indirect effect was significant (b=-6.33e-05, p=.004).

The third internalizing brain-symptom network mediation model showed that increased parental personal strength was related to increased parental acceptance (b=0.009648, t(7140) = 5.017, p=5.38e-07) and higher within visual connectivity (b=0.0005778, t(7151) = 3.422, p= .000624). Increased parental acceptance was also related to increased within visual connectivity when controlling for personal strength (b=0.0031515, t(7139) = 3.032, p=0.00244). The indirect effect was significant (b= 3.04e-05, p=.004).

The fourth internalizing brain-symptom network mediation model showed increased parental rule breaking symptoms was related to lower parental acceptance (b=-0.013742, t(7140) = -3.76, p=.000171) and lower within visual connectivity (b= -0.0011310, t(7151) = -3.527, p=. 000423). Parental acceptance was significantly positively related to within visual connectivity while

controlling for parent rule breaking symptoms (b=. 003195, t(7139) = 3.076, p=.002102) and the indirect effect was significant (b= -4.39e-05, p=.004).

Supplemental Table 4: Reverse Mediation Analysis Results

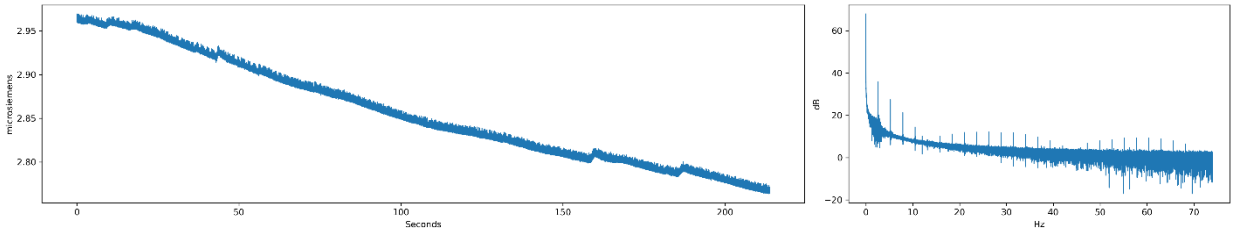
Symptom network	ROI-ROI	Parent Behavior	Mediator(Parent Symptoms)	Effect of IV on Mediator (a)	Unique effect of mediator (b)	Indirect effect (ab)	BC 95% CI	
							Lower	Upper
Externalizing	DMN-SAL/VAN	Parental Monitoring	Personal Strength	.23** (.044)	-3.19e-04** (8.79e-05)	-.7.5e-05	-1.27e-04	-2.85e-05
	DMN-CTL	Parental Monitoring	Withdrawn Symptoms	-.17**(.023)	.0004* (.0004)	-6.44e-05	-1.30e-03	-2.03e-05
Internalizing	VN-VN	Parental Monitoring	Personal Strength	.23** (.044)	.0005* (.0001)	1.28e-04	4.56e-05	2.31e-04
		Parental Acceptance		.36** (.073)	.0005* (.0001)	1.99e-04	7.14e-05	3.66e-04
		Parental Monitoring	Rule Breaking	-.13** (.023)	-.001** (.0003)	1.37e-04	4.73e-05	2.41e-04
		Parental Acceptance		-.14** (.039)	-.001** (.0003)	1.55e-04	4.79e-04	3.00e-04

APPENDIX B: SUPPLEMENTAL MATERIALS FOR CHAPTER 2

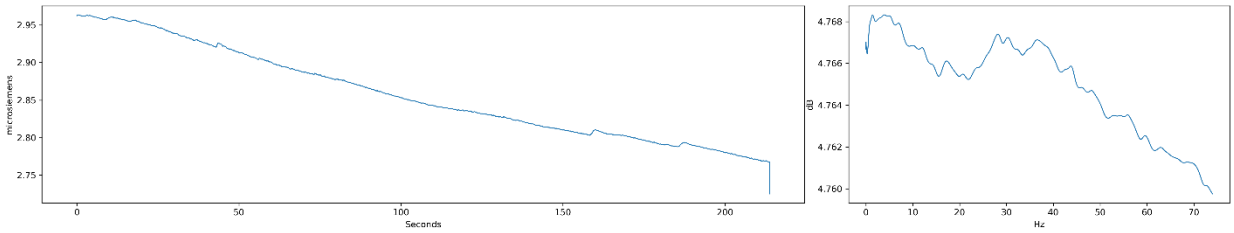
Supplemental Methods

Supplemental Figure 1:

A.



B.



Supplemental Figure 1. A. Visual of a youth subject's raw SCR during vicarious extinction. B. Visual of SCR trace after cleaning.

Supplemental Results

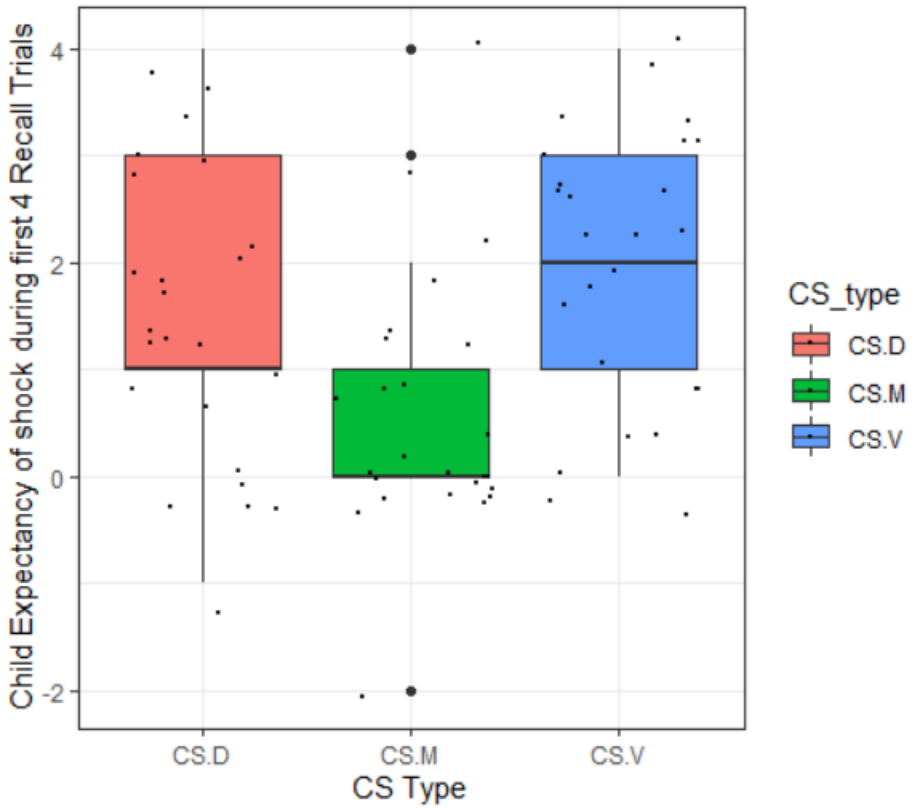
Supplemental Table 5: Correlation Table

Synchrony	Parenting Variable	cor	P value	FDR p value
PCA_Vice	APC_invol_m	0.067	0.758	0.859

PCA_Vice	APC_invol_d	0.14	0.518	0.859
PCA_Vice	ALC_postp	0.21	0.326	0.698
PCA_Vice	ALC_incon	0.29	0.163	0.630
PCA_Vice	ALC_monit	-0.12	0.578	0.859
PCA_Vice	ALC_harsh	0.27	0.21	0.630
PCA_Vice	APP_invol_m	0.037	0.859	0.859
PCA_Vice	ALP_postp	0.08	0.705	0.859
PCA_Vice	ALP_incon	0.27	0.19	0.630
PCA_Vice	ALP_monit	0.36	0.073	0.547
PCA_Vice	ALP_harsh	0.039	0.853	0.859
PCA_Vice	Autv	0.078	0.709	0.859
PCA_Vice	Autn	-0.047	0.823	0.859
PCA_Vice	Perm	0.24	0.254	0.635
PCA_Vice	PBI	-0.38	0.0633	0.5475

Supplemental Table 5. Correlation table for synchrony with APQ child version, APQ parent version, parenting styles, and parental bonding instrument. Everything was FDR corrected for multiple comparisons. Only APQ parent version of monitoring and the parental bonding instrument were marginally significant without FDR correction ($p<.1$).

Supplemental Figure 2: CS type Significantly Predicts Child Shock Expectancy During Recall



Supplemental Figure 2. Overall, youth expected the CS- during recall to shock the least, then CS+D and expected the CS+V to shock the most between first and last presentation. Indicating that they did not learn to extinguish the CS+V as well as the others.

APPENDIX C: HEYN ET AL., 2022

Parent-Child Autonomic Synchrony During Vicarious Extinction Learning

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Abstract

Objective. Though threat-extinction models continue to inform scientific study of traumatic stress, knowledge of learning and extinction as mechanisms linking exposure to psychopathology remains critically limited among youth. This series of studies seeks to advance the study of threat-extinction in youth by 1) use of electrodermal stimulation (ES) which has high translational potential to other work, 2) study of vicarious extinction learning in the parent-child dyad, 3) examination of individual and social threat learning in pediatric PTSD (pPTSD).

Methods. Typically developing (TD) and PTSD-diagnosed youth in 37 mother-child dyads completed one of three extinction learning paradigms incorporating ES as the UCS across two-days (Study 1), and three-days with (Study 2) or without (Study 3) vicarious extinction via video of their caregiver's direct extinction. Threat acquisition and extinction were monitored using skin-conductance response, and participants report on expectations of UCS experiences.

Results. Threat acquisition and extinction were best facilitated within a three-day paradigm, wherein youth additionally demonstrated vicarious extinction via observing the parent, though with critical differences in PTSD-youth. Our results also highlight the ES-conditioning to be highly feasible and well-tolerated by trauma-exposed youth.

Conclusions. This pilot study is the first to show pPTSD-specific impairments in vicarious learning processes in a threat conditioning and extinction paradigm. Moreover, our work establishes validation, tolerability, and feasibility of successful direct and vicarious extinction learning using electrodermal stimulation in youth. Altogether, the current methodology allows for more direct translation of animal models to human studies of parent-child dynamics and youth psychopathology.

Introduction

Threat extinction learning has been used in animal models and humans to study mechanisms of the development and flexibility of memory since the 1920's[239,240]. The study of vicarious or observational learning, or the ability to learn through others' experiences, has further been well documented across species[241]. This ability to acquire a threat association without direct experience of aversive stimuli is an adaptive mechanism that contributes to survival, and research on social learning suggests that youth (ages 6-10 years-old) may primarily learn threat and safety associations through parental observation[242]. Disruption of this learning process may contribute to child psychopathology[243]. For example, parent anxiety has been found to predict increased threat learning and hyperactive neural responses to threat in children[40]. While genetic factors likely contribute to this association, parental modeling of threat and safety discrimination is also thought to play a role. Thus, understanding the contribution of parental and adult modeling in safety learning, and how differences contribute to anxiety and threat disorders in youth is of great importance. If differences in vicarious learning are apparent in vulnerable populations, like those exposed to maltreatment, parsing out which processes are specifically affected (e.g. youth perception or interpretation of cues, increased threat learning, decreased threat extinction) could provide insight for future treatment development.

Threat learning paradigms have been salient targets when trying to characterize affective disorders like anxiety, depression, and PTSD[23]. Several specific processes involved in threat learning have been proposed as salient to PTSD and other threat disorders, including enhanced acquisition, stimulus (over-)generalization and impaired extinction learning and extinction memory[244–246]. While these processes are well-documented in adult humans[23], little work has been

done so far investigating mechanisms of threat and extinction learning in adolescent populations, let alone in youth that have been exposed to trauma and/or with affective disorders. To our knowledge, Marusak and colleagues (2021) and McLaughlin and colleagues (2016) are the only studies that have implemented an extinction learning paradigm in maltreated youth populations[247,248]. Both studies utilized short paradigms (either one- or two-days) and an aversive noise burst as the unconditioned stimulus (UCS). In maltreated youth, these studies reported blunted threat responses during acquisition[248] and an overgeneralization of threat behaviors to all stimuli regardless of previous UCS pairing during extinction recall[247]. Much research is needed in this domain to further explore extinction memory recall that is vicariously acquired and the study of clinical populations of youth with affective disorders such as PTSD[248].

One mechanism through which vicarious extinction may occur is through parent-child physiological synchrony. Synchrony is the temporally-matched coordination of responses between two people[137]. For parent-child dyads, synchrony is a critical method of learnt emotion regulation in children and a way to foster healthy attachments[88]. Physiological synchrony uses peripheral nervous system methods like skin conductance response (SCR) or heart rate variability (HRV) to evaluate the degree to which dyads are coupled[137]. While trauma may lead to differences in physiological, or autonomic, synchrony in youth and parents alike, how these variations affect real world behaviors like threat learning is still unknown[138,139]. Understanding the biological mechanism behind vicarious learning is crucial for understanding transmission of threat and safety cues between dyads, especially in those with threat -related disorders like PTSD.

The current study was adapted from a vicarious threat extinction paradigm we recently implemented in typically developing (TD) children and their caregivers[83]. It is the first, to our knowledge, to test the feasibility and tolerability of using ES in a typically developing and PTSD

population of youth, and whether the use of a longer, expanded paradigm that may allow for understanding of key mechanisms in the observational learning process. Due to the *a priori* interest in the tolerability and feasibility of ES in a developmental population, mother-child dyads across a large adolescent age range were recruited. We further explored alterations in threat learning and direct/vicarious extinction learning in pediatric PTSD to inform future hypothesis testing in larger samples of youth. Namely, we examined whether there are differences in extinction learning in youth with and without PTSD, as measured by SCR and self-reported UCS expectancy, and how parental threat extinction translates to youth extinction via observation and physiological synchrony.

To achieve our objectives, we conducted a series of three studies. Study 1 tested the tolerability and feasibility of a two-day direct conditioning paradigm (without a vicarious phase) in TD youth. Study 2 tested a three-day modification of the two-day direct conditioning paradigm with TD youth to allow for enhanced memory consolidation, as clinicians have previously postulated that the process of threat learning consolidation may be heavily influenced by the passage of time [249], where the amount of time between acquisition and extinction may be important for the consolidation of CS-US associations. Following successful evidence of the 3-day paradigm in TD youth, Study 3 introduced a vicarious extinction component, including TD youth and youth with PTSD to test the aversive stimulus tolerability in a clinical population. Across all three studies, 37 mother-child dyads completed a full paradigm series. This sample size was small due to the discontinuation of recruitment after 18 dyads completed Study 3 due to acquisition of funding for an expanded neuroimaging-based study of the three-day vicarious extinction paradigm (Study 3) in trauma exposed youth and youth with PTSD (R01MH117141), which is currently ongoing. Despite the early end to recruitment, we continue to report preliminary analyses of the

development and validation of the current behavioral paradigm in typically developing youth and youth with PTSD.

The current study tested the following *a priori* hypotheses: (1) All mother-child dyads, regardless of PTSD status in youth, will tolerate a threat paradigm using electrodermal stimulation equally or better than paradigms involving other aversive stimuli (e.g. air blast to the larynx, loud tones or white noise, or human screams), as evidenced by lower study attrition than reported in other studies with similar samples; (2) Using ES with parents and youth, we will be able to invoke anticipated physiological and behavioral indices of successful threat acquisition (i.e. increased arousal and expectancy of ES) as well as both direct and vicarious threat extinction (i.e. decreased arousal and expectancy of ES); and (3) We will detect PTSD-specific differences in arousal during vicarious extinction learning that may be mechanistically linked to aberrant physiological synchrony between parents and youth.

Methods

I. PARTICIPANT INCLUSION

This pilot study recruited a total of 39 youth ages 7-17 years and their mothers across a series of three threat extinction studies, culminating in a successful three-day paradigm incorporating direct and vicarious extinction training. Study 1 enrolled 9 TD parent-child dyads, Study 2 enrolled 10 TD parent-child dyads, and Study 3 enrolled 20 parent-child dyads (PTSD, n=15; TD, n=5). Typically developing youth across all three studies were recruited from the community, while youth with trauma-exposure and current PTSD in the final version of the paradigm were recruited from local outpatient mental health facilities. Two youth in the PTSD group did not qualify for current PTSD on all symptom criteria but have been included due to the pilot nature of this study. Exclusion criteria for all youth participants included past or present substance abuse, brain injury with ongoing symptoms or significant developmental delay, severe/unstable medical condition(s) such as newly diagnosed Type I diabetes or rheumatoid arthritis, acute suicidality, or ongoing exposure to abuse. Exclusion criteria for TD youth included past or current use of psychiatric medication, and past or current mental health diagnosis. Youth in the PTSD group could be currently taking psychotropic medications provided they were not sympatholytic agents. All youth were accompanied by a parent, which was the mother in all three of these pilot studies. All study procedures were approved by the University of Wisconsin Health Sciences IRB. Parental consent and child assent were obtained from every parent-child dyad prior to participation.

II. CLINICAL ASSESSMENT

Mother-child dyads underwent an initial clinical assessment screening of past and current mental diagnoses using the Mini-International Neuropsychiatric Interview Screen (MINI)[250]. The

child version of this structured clinical diagnostic interview, the MINI-KID has evinced good to excellent concurrent validity on average with other established measures of child psychopathology[251]. The MINI was used to categorize youth as TD or with PTSD. In addition, all PTSD participants completed a series of questionnaires assessing current depression, anxiety, and PTSD symptom severity, including the Mood and Feelings Questionnaire (MFQ)[142], Screen for Child Anxiety-Related Emotional Disorders (SCARED)[141], and UCLA PTSD Reaction Index for DSM IV (PTSD-RI)[143], respectively. The PTSD-RI for DSM-V (PTSD-RI-V) was given to five PTSD subjects due to the timing of the release. For valid direct comparison of the two measures, only congruent questions were used from each version, where subscale and total scores were calculated using only the congruent questions.

III. THREAT LEARNING PARADIGM

In general, a threat learning paradigm includes the following phases: (1) Habituation, where participants view all CS stimuli without a US pairing, (2) Acquisition, where the CS+ is paired with electrodermal stimulation (US) while the CS- is not, (3) Extinction, where the CS+ and CS- are presented without stimulation in a new (extinction) context, (4) Recall, where the CS+ and CS- are again presented in the extinction context without stimulation to assess extinction learning retention.

In the current study, parents and youth both underwent a multi-phase conditioning paradigm adapted from Milad and colleagues' (2007) protocol used with healthy and clinical samples of adults[145]. The experimental phases were similar across parents and children, although all phases were completed by parent and child separately. Here, visual stimuli consisted of neutral pictures of lamps in two different contexts (Supplemental Figure 3). The CS- is a lamp with a

yellow light on, while the CS+ stimuli are the lamp with either a blue or red light. Across all trials and phases, each presentation of a CS (6 seconds) was preceded by a brief presentation of a fixation cross (randomly jittered between 9 and 15 seconds) followed by the scene with the lamp turned off (3 seconds). During acquisition, both CS+ types were followed by a brief electrodermal stimulation (0.5 seconds) at an intensity previously chosen by the participant and at a 50% reinforcement rate. The order of which CS+ color was presented first during acquisition was counterbalanced across all participants and studies. Acquisition and recall phases included 8 presentations of each CS type (randomized order), while direct extinction consisted of 6 trials of the CS+ and 4 trials of the CS. The current study first attempts an exact replication of the previously cited two-day paradigm[145] (Study 1, "Replication Paradigm"), and is then adapted to fit our population and research questions (Study 2, "Adapted Paradigm"; Study 3, "Vicarious Paradigm"), as outlined below.

Study 1: Replication Paradigm. A total of 9 parent-child dyads, consisting of all TD youth, completed the Replication Paradigm over the course of two days, without completing vicarious extinction. The first day, parent and child separately completed a brief habituation phase, followed by acquisition and direct extinction, followed by recall on the second day. In this design, there were both directly extinguished (CS+D) and unextinguished (CS+U) conditioned stimuli.

Study 2: Adapted Paradigm. In response to preliminary results from the Replication Paradigm, we then recruited a total of 10 TD parent-child dyads to complete a version of the paradigm over the course of three days rather than two to allow for increased time for learning consolidation. In this

Adapted Paradigm, the first day consisted of habituation and acquisition, followed by direct extinction on the second day, and recall on the third day, all approximately 24 hours apart.

Study 3: Vicarious Paradigm. Finally, we recruited a sample of 18 parent-child dyads (PTSD, n=13; TD, n=5) to complete the final Study. This version was identical to the Adapted Version for parents, however youth also completed vicarious extinction on the second day, which consisted of youth watching a video of their parent undergoing direct extinction of the child's other CS+ (red; CS+V) without receiving ES. The order of the direct and vicarious extinction phases was counterbalanced across subjects to reduce order of learning as a confounding variable.

IV. ELECTRODERMAL STIMULATION

The tactile electrodermal stimulation was delivered and synched with the experiment in ePrime software (Psychology Software Tools, Pittsburgh, PA). Prior to the experiment, all participants were able to select an electrodermal stimulation intensity between 0.02 and 4.0 mA through a comprehensive intensity calibration procedure. Here, participants had electrodes attached to the index and middle finger of their right hand. They were told to select an intensity that was "annoying, but not painful"[252], as measured using a 10-point Likert rating scale (ranging from "I feel nothing" to "painful", with the optimal goal of rating the intensity as an 8/10). In a step-wise process, beginning with no stimulation given, participants would rate the intensity of each new ES level until reaching the optimal intensity. The chosen level of stimulation on the first experimental day remained consistent throughout the duration of the study.

V. MEASUREMENT VARIABLES

For this study, we include two primary variables of interest that encompass both conscious behavioral responses and threat response physiology: (1) explicit expectation of ES for each CS type at the beginning and end of each phase, and (2) skin conductance response immediately preceding each stimulus presentation. Details on collection of each outcome measure are outlined below.

Expectancy. An expectancy questionnaire was used to assess explicit memory and perceptions of the learning task and was adapted from previous threat extinction paradigms[253]. Portions of the questionnaire were verbally administered after each experimental phase. In relation to each phase, participants were first asked whether they received the ES, which color light(s) they recalled seeing, and which (if any) of those lights were followed by the ES as attentional control check. Each attentional control question for each phase was coded as correct or incorrect, and participant performance for each study is reported as the percent correct across all phases for parents and youth. Finally, participants were then asked the following questions about each color light they reported seeing in that particular phase: "On a scale from 1 (not at all) to 5 (very much), how much did you expect a shock for the 1st trial of [blue, yellow, red]?" and "On a scale from 1 (not at all) to 5 (very much), how much did you expect a shock for the last trial of [blue, yellow, red]?".

Skin Conductance. Skin conductance levels (SCL) were collected from the index and middle fingers of the left hand for each participant continuously across all trials during every phase of the paradigm (MP150 recording system, Biopac Systems Inc., Goleta, CA). The skin conductance responses (SCRs) used in subsequent analyses were consistent with previous methods in threat extinction paradigms [83] by first extracting the peak SCL during the 6-second CS presentation for

each trial. This value was then normalized by subtracting out the average SCL during the 2-seconds prior to CS presentation while viewing the office scene and a final square-root transformation. For the purposes of this study, only the first four trials of each stimulus for each phase were included due to diminishing response and to be consistent with previous comparable paradigms[83]. SCR synchrony analyses used the full SCL time series during direct extinction (parents) and vicarious extinction (youth) after a low-pass filter of 1Hz and 8Hz down sampling. Data quality assurance included dropping any participants found to be SCR non-responders, or subjects with greater than 50% of trials with no detected significant above-threshold responses within the stimulus response window (as defined during continuous decomposition analysis) in a particular phase. This resulted in dropping one youth participant and one parent participant from Study 1. No participants from Study 2 or 3 were identified as a non-responder.

VI. STATISTICAL ANALYSES

Primary Analyses. All statistical analyses were completed in [254] and RStudio[148]. In order to evaluate explicit learning during each Study, expectancy and SCR were separately analyzed using linear mixed effect (LME) modeling. Models were run separately for each Study and participant type (parents and youth). Each model tested the interaction of phase (acquisition, extinction, and recall), stimulus type (CS-, CS+D, CS+V/CS+U), and order/trial number (for expectancy or SCR, respectively) on both ES expectancy and trial-wise baseline-corrected peak SCRs, controlling for age and subject as a random effect. Due to low power, SCR models were also run separately across each phase. Across expectancy and SCR models, only youth models also included sex as a covariate, as all parents were mothers in this study. Significant interactions were further

decomposed using subsequent LME's and t-tests, where appropriate. Due to the preliminary nature of this feasibility study and differences in methodology across paradigms, no multiple-comparison correction methods were employed.

Autonomic Synchrony Analyses. Group-related differences in parent-child autonomic synchrony, as quantified by recurring properties and patterns of two distinct time series, was analyzed using cross-recurrence quantification analysis (CRQA) via the R package *crqa*[149] implementing previously validated parameters[11]. Here, parent direct extinction and youth vicarious extinction SCR time series were used as primary inputs. CRQA analyses output three highly correlated metrics (Determinism, Entropy, and Laminarity; $r^2 > 0.90$). Due to the high correlation between individual synchrony metrics, a Principal Component Analysis was run with varimax rotation to create a single composite score of synchrony using the *psych* package in R to increase interpretability. Linear modeling was used to estimate group differences (TD vs PTSD) in synchrony during parent and youth extinction training, covarying for child age and sex. Lastly, we examined whether synchrony could explain extinction recall, where parent-child synchrony during extinction training was predictive of youth arousal during extinction recall using average SCR for each CS-type during the first four trials of recall. Due to the skew of the recall data, all recall SCR data was log-transformed and then Z-scored prior to modeling.

Symptom Analyses. To further elucidate the relationship between threat learning and PTSD within Study 3, exploratory analyses using linear mixed effect modeling tested the interaction of symptom severity and stimulus (CS type) in SCR during each phase. Models were run across depression (MFQ total), anxiety (SCARED total), and PTSD (PTSD-RI total, PTSD-RI Subscale

B, C, and D) symptoms, controlling for youth age and sex. Due to the preliminary nature of this feasibility study and differences in methodology across paradigms, no multiple-comparison correction methods were employed.

Results

I. PARTICIPANT CHARACTERISTICS

Parent and youth demographics and clinical characteristics for each study are summarized in Supplemental Table 8. Across all paradigms, a total of 33 parents (TD=20, PTSD=13) and 26 youth (TD=23, PTSD=13) completed a Study. Youth participants had an average age of 12.17 (± 2.73), and TD and PTSD youth did not significantly differ in age ($t_{(20)}$=-1.37, p=0.19). Across all paradigm versions, children selected a stimulation level comparable to that of the adult participants (youth: M = 2.02 mA, SD = .92; parents: M= 2.05 mA, SD = .85; $t_{(68)}$=-0.153, p=0.88). Youth's stimulation level selection was not significantly correlated with age (r(34)=0.19, p=0.26). Furthermore, youth in the PTSD group did not differ in selected stimulation levels compared to TD youth ($t_{(32)}$=0.45, p=0.66). Between all three studies, we report a 5% dropout rate, where 37 of the 39 mother-child dyads completed a full paradigm. Both participant dropouts occurred during Study 3, which were due to self-reported boredom with the study (n=1) and suspicion of ongoing abuse (n=1). Both participants were in the PTSD group. Notably, no participants dropped out due to intolerance of the electrodermal US.

II. STUDY 1: REPLICATION PARADIGM

Participant performance during attentional control questions were high overall, with 90% correct responses across all phases for parents and 89% correct responses across all phases for youth, confirming participants were engaged with each task. Results of expectancy and SCR analyses for the Study 1 are summarized in Supplemental Figure 4. Here, we detected a significant Stimulus by Phase by Order (first or last) interaction in ES expectancy in youth participants ($F_{(5,164)}$=8.24, p<0.001) and a Phase by Order interaction in parents ($F_{(3,101)}$=6.06, p<0.001). As

expected, participants endorsed higher ES expectancy for both CS+ types at the end of acquisition and beginning of direct extinction training, as well as no difference in expectancy to the CS- and CS+D at the end of extinction training, plausibly suggesting successful learning and threat extinction. Unexpectedly, when looking at extinction recall on the second day, youth continued to express higher ES expectancy for both the CS+D and CS+U, as compared to the CS-. Further, expectancy at the end of acquisition and beginning of recall did not significantly differ ($t(15)=1.09$, $p=0.29$), suggesting that extinction learning may have failed to consolidate even though it may have been effective within-session.

SCR analyses similarly support the hypothesis of a lack of physiological learning and retention in a two-day paradigm. Surprisingly, neither parents nor youth exhibited expected differences in stimulus type during acquisition (Youth, $F_{(2,83)}=0.68$, $p=0.51$; Parent, $F_{(2,61)}=1.89$, $p=0.16$) or during parent direct extinction ($F_{(1,37)}=0.79$, $p=0.38$). While parents and youth show the expected pattern of a lack of differences in arousal during extinction recall between CS-types (Youth, $F_{(2,80)}=1.15$, $p=0.32$; Parent, $F_{(2,58)}=0.36$, $p=0.70$), when considered within context of the ES expectancy differences during recall, this is likely due to an overall lack of threat acquisition and consolidation.

III. STUDY 2: ADAPTED PARADIGM

A total of 10 parent-child dyads, consisting of all non-trauma exposed TD participants, completed this adapted paradigm over a three-day period. Participant performance during attentional control questions were high overall, with 96% correct responses across all phases for parents and 88% correct responses across all phases for youth, again confirming participants were engaged with each task. Expectancy and SCR results are summarized in Supplemental Figure 5.

When evaluating explicit ES expectancy, we detected a similar Stimulus by Phase by Order (first or last) interaction in ES expectancy in both parents ($F_{(5,189)}$=2.98, p=0.01) and youth ($F_{(5,187)}$=2.25, p=0.05), in which patterns mirror results from the Replication Paradigm (as seen in Supplemental Figure 2). In contrast, SCR responses now show expected differentiation in learning and extinction in parents and youth. On the first day, we detected a significant main effect of stimulus during acquisition in parents ($F_{(2,94)}$=3.49, p=0.03) and a trending effect in youth ($F_{(2,105)}$=1.88, p=0.15). We now detect expected increases in arousal to the CS+D (Parent, $t_{(56)}$=-2.73, p=0.007), and trending effects in youth (CS+U, $t_{(70)}$=-1.87, p=0.06; CS+D, $t_{(77)}$=-1.70, p=0.09), as compared to CS-, suggesting successful acquisition. Interestingly, when youth models are run across all trials, rather than the first four, we see expected significant effects ($F_{(2,207)}$=4.88, p<0.001), signaling that youth may need more trials than parents to consolidate learning.

On the second day, there was no main effect of stimulus detected during direct extinction youth ($F_{(1,182)}$=2.38, p=0.13), suggesting both that acquisition of threat association and extinction training were successful. Finally, during extinction recall on the third day, there was no main effect of stimulus in either youth ($F_{(2,105)}$=1.29, p=0.28) or parents ($F_{(2,282)}$=0.97, p=0.38). This lack of differentiation between the CS- and CS+ stimuli lends additional support for the success of extinction training with the additional day. Further, during extinction recall, youth did show increased arousal to the CS+U as compared to the CS- ($t_{(18)}$=-2.02, p=0.05), showing differentiation between the extinguished and unextinguished conditioned stimuli.

IV. STUDY 3: VICARIOUS PARADIGM

Results from the full cohort analyses for the vicarious paradigm are summarized in Supplemental Figure 6, while PTSD-specific findings are included in Supplemental Figure 7. First,

participant performance during attentional control questions were high overall, with 96% correct responses across all phases for parents and 87% correct responses across all phases for youth, again confirming participants were engaged with each task. Correct responses did not significantly differ between TD (87%) and PTSD (86%) youth.

Across TD and PTSD youth, we first ran the standard validation models across both ES expectancy and SCR in parents and youth. Replicating the two previous Studies, we see a Stimulus by Phase by Order (first or last) interaction with ES expectancy in both parents ($F_{(6,333)}$=5.85, p<0.001) and youth ($F_{(7,403)}$=2.73, p=0.008), again mirroring the previous two Studies. In addition, SCR show expected main effect of stimulus type, where parent and youth participants show increased SCRs to the CS+D and CS+U/V during acquisition (Parent, $F_{(2,193)}$=4.51, p=0.01; Youth, $F_{(2,189)}$=4.66, p=0.01), parents show significantly increased SCR to the CS+D during direct extinction training, with youth showing a trending effect in the same direction (Parent, $F_{(1,122)}$=8.42, p=0.004; Youth, $F_{(1,115)}$=2.72, p=0.10), and no significant differences between the CS- and CS+D during extinction recall (Parent, $F_{(1,190)}$=0.89, p=0.41; Youth, $F_{(2,193)}$=1.36, p=0.26).

Interestingly, in analyses investigating the impact of PTSD, we first detected a significant main effect of group in youth SCR responses ($F_{(1,15)}$=4.84, p=0.044), where youth with PTSD show an overall increased physiological response during the learning paradigm, regardless of phase, stimulus type, or trial number. When analyzing within each phase, we see a compelling pattern of PTSD-related variance in arousal specifically underlying the vicarious learning process. We detected a significant group by stimulus interaction during the parent direct extinction ($F_{(1,112)}$=4.65, p=0.03), where parents of PTSD youth exhibited higher levels of arousal during the presentation of CS+D as compared to the CS- ($t_{(100)}$=-3.49, p < 0.001) and CS+D in parents of TD

youth (CS+D, $t_{(63)}$=-2.16, p = 0.03, Figure 5A). Within vicarious extinction learning, we detected a significant main effect of group ($F_{(1,12)}$=4.59, p=0.05, Figure 5B), where youth with PTSD show significantly increased physiological arousal while watching their parent complete extinction training as compared to TD youth. While only a main effect was detected, exploratory analyses were conducted to further explore this phase of interest, which suggest that this increase may be driven by increased arousal to the CS+V specifically, as compared to the CS- in both PTSD ($t_{(20)}$=-2.46, p = 0.02) and TD youth ($t_{(20)}$=-3.25, p = 0.009). While we did not detect any group differences in SCR response between TD and PTSD youth during extinction recall on day three ($F_{(1,14)}$=0.79, p=0.38), we do see a significant interaction between PTSD symptom severity and stimulus type ($F_{(1,139)}$=3.18, p=0.04). During extinction recall, PTSD reexperiencing symptoms (PSTD-RI Subscale B) are predictive of increased arousal during CS+V presentation (Figure 5C).

Finally, we investigated physiological synchrony during extinction training as a possible mechanism of PTSD-related deficits in vicarious extinction, and results can be found in Figure 5D. Here, we detected a significant main effect of group in SCR parent-child synchrony (b=1.25, t(13)=2.34, p =0.037, $\eta 2$=0.31). A similar effect was not identified whe using direct extinction from both parent and child (b=-0.18, t(13)=0.35, p=0.62), lending additional evidence to this effect being specific to the vicarious learning process. Next, we detected a main effect of synchrony on youth recall arousal ($F_{(11,12)}$=4.62, p=0.032), where parent-child synchrony was inversely related to average SCR during extinction recall regardless of stimulus type.

Discussion

The current study tested vicarious parent-child threat extinction learning in adolescents using a novel multi-day paradigm using electrodermal stimulation (ES) in typically developing (TD) youth and youth with PTSD using explicit and physiological correlates of threat. Youth and parents underwent threat conditioning using ES at 50% reinforcement, followed by direct extinction or vicarious threat extinction via observing a video of their parent. Extinction recall was tested 24-hours after extinction learning. A series of three studies were conducted to first identify the most effective multi-day paradigm in typically developing youth via the identification of expected physiological responses using skin conductance response, and a pilot of the resulting paradigm in a cohort of PTSD youth. Importantly, we found that a three-day paradigm (as opposed to the two-day paradigm) was feasible and the most effective in parent-child dyads, as it resulted in the expected physiological correlates of direct and vicarious threat learning and no study attrition. Further, this is the first study to show feasibility of such a paradigm in youth with PTSD and identify PTSD-specific deficits during vicarious extinction learning that may be related to PTSD symptom expression and parent-child physiological synchrony. Altogether, this preliminary study provides strong evidence that a three-day paradigm using ES is a feasible and useful tool in future research on the development of threat learning in youths and the expression of pediatric PTSD, that the underlying process of vicarious threat-safety discrimination learning may be mechanistically related to pediatric PTSD through parent-child synchrony, and offers potentially novel mechanisms, biomarkers, and therapeutic targets.

Study 1 (Replication Study) first aimed to replicate a two-day threat conditioning and extinction paradigm within a pediatric population (between the ages of 7-17), variations of which have been implemented in clinically healthy adults[145] and youth[83]. Interestingly, the two-day

replication study did not show predicted expectancy or physiological responses in youth. While youth and parents reported proper differentiation in expectancy of stimulus-US pairing during acquisition and extinction, all participants continued to expect higher rates of stimulation to the CS+ during extinction recall. Further, we found no evidence of CS-specific differentiation during any phase, and youth even exhibited comparable levels of arousal during acquisition and extinction recall. We hypothesize that a lack of stabilized stimulus differentiation into long-term memory, as evidenced by the absence CS-specific arousal, may be due to a disrupted consolidation of threat learning memories. Animal models of memory and suggest that consolidation happens over a period of hours to days following acquisition training[255]. Further, sleep is hypothesized to be a critical regulator of key neuronal processes underlying memory storage and consolidation[256,257] and recently has been found to be a critical mechanism of visually-cued threat memory consolidation after acquisition training[258]. As Study 1 provided only minutes between acquisition and extinction training, it may be that participants need more time after threat acquisition to stabilize the stimulus differentiation into long-term memory.

In order to facilitate threat memory consolidation, the paradigm was expanded to a three-day protocol in Study 2, adding an additional day between acquisition and extinction training. The expansion was overall successful in demonstrating the expected psychophysiological and behavioral correlates of threat learning and extinction, where parents and youth both showed expected CS+ differentiation in both threat acquisition and direct extinction learning. However, parents interestingly did not show expected indices of absent or incomplete extinction learning to the CS+U during extinction recall, where we would expect continued increases in arousal to the CS+U due to a lack of extinction training, overall suggesting that they may have generalized the extinction learning across all CS+ types. This over-generalization effect is consistent with prior

research suggesting that when two similar stimuli about undergo UCS pairing, it is possible to generalize the actively extinguished stimulus to the non-extinguished stimulus[259].

Full-cohort results of Study 3 (Vicarious Paradigm) again confirm successful threat acquisition and extinction, and further explore efficacy and mechanisms of vicarious threat learning in PTSD and their parents. Interestingly, under full-cohort analyses, youth showed increased arousal to the vicariously extinguished CS+ during both vicarious extinction training and recall, suggesting a possible decreased ability to vicariously extinguish threat-related cues from their parents as compared to direct extinction. There may be two mechanisms underlying the detection of this effect: (1) the sample demographics of Study 3, which was heavily skewed towards youth with PTSD, and (2) parents of PTSD youth exhibited unexpected hyperarousal while viewing the CS+ during direct extinction training.

In response, exploratory analyses aimed to characterize pPTSD-specific effects in Study 3. We first, unsurprisingly, identified globally increased arousal across the entire paradigm in youth with PTSD, regardless of phase or stimulus type. PTSD has consistently been characterized by global hyperarousal symptoms and impaired inhibitions of threat responses[260–263]. Our findings of significantly increased SCR across an entire threat learning paradigm supports this characterization. Next, we found that parents of PTSD youth exhibit preferentially increased arousal while viewing the CS+D during direxT extinction - a pattern not observed in TD parents. While parents in the current study did not undergo as rigorous of clinical assessments as youth, 38% of PTSD parents also met criteria for current diagnoses of an internalizing disorder using the MINI, as compared to only 9% of TD parents. In conjunction with increased prevalence of psychiatric disorders in youth who have parents with psychiatric conditions[264,265], and known threat extinction impairments of adults with anxiety[266] and depression symptoms[267], it may be that

parents are also exhibiting diagnosis-related impairments in extinction learning, further inhibiting the success of their child's vicarious extinction. While this study is inherently unable to determine whether youth with PTSD could successfully learn from a demonstrator with normative direct extinction psychophysiology, it does lend additional support for the importance of considering parent well-being and parent-child relationships in the long-term therapeutic outcomes such as trauma-focused cognitive behavioral therapy[268].

Next, the recording of parent direct extinction training was shown to the PTSD youth, who exhibited increased arousal to all stimuli during vicarious extinction training. Although this was a main effect, exploratory analyses suggest that this effect may be specifically driven by arousal to the CS+V. A youth's ability to learn safety and threating cues from their parents is especially important for development to learn about the world around them[40,131]. This requires both youth and parents to be able to transmit and receive behavior and emotions effectively. If parents are not able to transmit healthy safety and threat cues, it may lead to behavioral problems or affective disorders like anxiety[8]. One possible mechanism that can help characterize the success of vicarious threat and safety learning is physiological synchrony[11]. Synchrony is the bidirectional coupling of two separate systems, in this case the parent and youth, so that their biological responses are correlated in time[138] and this time-dependent parent-child synchrony may reflect effective learning. For youth with PTSD in the current study, it may be that this transmission could have been disrupted due to decreased synchrony with their parent compared to TD children. Alternatively, synchrony could be intact between PTSD youth and their parent, and instead may be reflecting successful learning of the heightened parental threat response during their own extinction learning.

Exploratory analyses of parent-child synchrony in physiological arousal during direct and vicarious extinction, respectively, directly tested these hypotheses. Here, we identified overall lower parent-child synchrony in youth with PTSD as compared to TDs, and synchrony estimates were further inversely correlated with arousal during extinction recall. Coupled with the already identified group differences in SCR during direct and vicarious extinction, social threat learning may represent an influential process in trauma-related disorders for youth, though further study is warranted

Finally, subsequent analyses exploring the relationship between threat extinction learning PTSD symptom severity reveal reexperiencing symptoms to be positively predictive of physiological arousal to the same CS+V during extinction recall that exhibited differential impairments during direct and vicarious exiction training. No other symptom domains were predictive of any learning or extinction correlates, supporting the specificity of vicarious learning deficits to pPTSD. PTSD has already been theorized as disorder characterized by impairments in threat extinction deficits and overall social functioning[247,269]. Together with our findings, this may indicate that youth with pPTSD are not able to engage in social threat tasks in an adaptive manner, either due to impaired learning or heightened threat modeling in their parent, and lends additional evidence that there is a deficit in learning threat and safety cues for youth with PTSD that may specifically contribute to the expression of pediatric PTSD.

One particularly novel methodology of the current study was the use of electrodermal stimulation as a UCS in a clinical youth population. This is partly due to the fact that, while threat extinction paradigm designs have been similar across human and animal models, the specific type of UCS used to elicit learned threat behavior has been less consistent. Electrodermal stimulation has been the most commonly utilized aversive stimulus to elicit learned threat behavior in animal

models and adults [270], while other UCSs (e.g. air blast to the larynx, loud tones or white noise, or human screams) are more commonly utilized in pediatric studies[271]. While these alternatives may be preferred by researchers who view electrodermal stimulation as "unethical to use with youth because it may invoke distress and discomfort"[272] these different UCSs are not necessarily more tolerable. In recent studies in pediatric populations, a "screaming lady" stimulus resulted in 43% dropout[273], a large noise burst study reported 16.7% dropout[274], and an air blast resulted in a 14.3% participant drop-out rate[275]. Critically, the current study reports only a 5% dropout rate across all three studies, with neither of the two dropouts attributed to tolerability of the UCS. Therefore, implementing ES as the UCS in youth populations may not only increase generalizability and translational potential to the crucial animal model and adult human literature, but could also prove to be a more tolerable paradigm with decreased dropout as compared to previous similar paradigms.

The underlying neurobiological mechanisms of the vicarious extinction deficits exhibited by youth with PTSD are yet to be understood. Previous rodent work proposes the existence of a threat extinction network that involves the amygdala, hippocampus, dorsal anterior cingulate cortex, and ventromedial prefrontal cortex as important nodes in this process[79]. Studies with PTSD have further found that these areas have structural and functional deficits related to the disorder[159,244,276]. Due to this overlap in biomarkers and the preliminary results in our study, including differences in the time-dependent nature of threat learning consolidation in youth as discussed above, future experiments should include neuroimaging to explore the possible biological mechanisms that relate to youth, PTSD, and direct versus vicarious threat learning.

While the current preliminary study provides evidence of effectiveness and feasibility of implementation in pediatric and PTSD populations, there were important limitations to address.

First, all three of these studies have limited sample sizes. The statistics presented in this paper should be taken in context to the sample sizes, particularly the small sample of TD youth in Study 3. Further, we were unable to collect any genetic information in this pilot. It would be beneficial for future work in this parent-child paradigm to have DNA and RNA to assess the unique role of heritable versus behaviorally modeled/learned threat. On the other hand, the absence of direct extinction learning differences in PTSD vs. TD youth, nor any relationship of direction extinction to PTSD severity, supports the notion of vicarious threat beyond heritable factors. In Study 3, we collected measures on child psychopathology, but did not collect any information on parent psychopathology symptom severity. This would be useful in future studies to see whether parent psychopathology may be related to or a mediator of youth direct and vicarious extinction success. Future studies could utilize this information in conjunction with genetic information to understand the full picture of parent-child biological and behavioral interactions. Finally, another limitation is our lack of a trauma-exposed comparison group. While we saw preliminary evidence that PTSD symptoms are related to vicarious extinction learning, we do not have a way to distinguish if this is due to trauma exposure itself or with PTSD diagnosis. Integrating a trauma-exposed comparison group would help clarify any differences in exposure versus more extreme symptoms.

In summary, these preliminary studies support the notion of direct and vicarious threat extinction learning as a viable paradigm to investigate parent-child interactions, and how these interactions may be disrupted in youth with psychopathology. In our studies, we saw that a three-day paradigm using electrodermal stimulation is not only feasible with significantly lower dropout rates than seen in comparable studies using an alternative UCS in typically developing and youth with PTSD, but was also able to produce reliable behavioral and physiological responses. We also found that vicarious extinction learning may produce similar SCRs to direct extinction, but also

that youth with PTSD may have deficits in this particular form of threat extinction learning, as evidenced by increased arousal during extinction training and the positive relationship between PTSD reexperiencing symptoms and vicariously extinguished stimuli. Further studies with expanded sample sizes would be warranted to more definitively explore the roles of threat learning, direct extinction learning, and parent to child vicarious extinction learning as potential mechanistic contributors to threat disorders in youth.

Tables

Supplemental Table 8 Demographics and Clinical Characteristics

	Full Cohort	Study 1	Study 2	Study 3	
		TD	TD	TD	PTSD
DEMOGRAPHICS					
n	37	9	10	5	13
Child Age	12.71 (±3.11)	14.60 (±1.18)	10.81 (±1.72)	11.18 (±3.89)	13.73 (±3.59)
Child Sex	26 F	5 F	6 F	4 F	11 F
Child Pubertal Stage	3.10 (±1.34)	4.13 (±0.58)	2.28 (±1.12)	2.13 (±1.60)	3.35 (±1.30)
Child ES Intensity (mA)	2.06 (±0.90)	1.79 (±0.94)	2.16 (±1.11)	2.28 (±1.08)	1.97 (±0.74)
Parent Age	43.52 (±6.90)	47.25 (±5.49)	43.83 (±6.72)	44.73 (±4.96)	40.84 (±7.89)
Parent ES Intensity (mA)	2.01 (±0.77)	1.70 (±0.50)	2.16 (±1.08)	1.88 (±0.34)	2.22 (±0.90)
CLINICAL CHARACTERISTICS					
Child PTSD Symptoms	-	-	-	-	50.08 (±16.35)
Child Depression Symptoms	-	-	-	-	18.08 (±8.89)
Child Anxiety Symptoms	-	-	-	-	31.67 (±11.68)
Child Medication History (n)	-	-	-	-	9
Parent Psychiatric Diagnoses (n)	-	-	-		Current Internalizing (4) Past Internalizing (2) No past/current diagnosis (3) Unknown (4)

Parentheticals denote standard deviation. Child PTSD symptoms represent total UCLA PTSD Reaction Index (PTSD-RI) scores, child depression symptoms represent total scores of the Mood and Feelings Questionnaire (MFQ), and child anxiety symptoms represent total Screen for Child Anxiety-Related Emotional Disorders (SCARED) scores.

Abbreviations: TD, typically developing; PTSD, posttraumatic stress disorder; ES, electrodermal stimulation.

Supplemental Figure Legends

Supplemental Figure 3 Observational Threat Extinction Paradigm in Parent-Child Dyads. Schematic of the phases within both parent (top) and child (bottom) threat extinction paradigms. The US, electrodermal stimulation, is represented by a yellow lightning bolt.

Abbreviations: CS, conditioned stimulus; CS-, unpaired CS; CS+D, directly extinugished CS; CS+V, vicariously extinugished CS; CS+U, unextinguised CS.

Supplemental Figure 4 Patterns of Expectancy and SCR during the 2-Day Replication Paradigm. For each CS type, the average youth expectancy of the US for the first and last presentation (a) and skin conductance response (SCR) during the first four trials of each stimulus (b) are graphically presented. Parent expectancy (c) and SCR (d) are graphed in in similar fashion. Expectancy and SCR values are averages, residualized for age and for biological sex in youth participants. Error bars in all graphs represent standard error. Brackets and asterisks represent statistical significance ($p < 0.05$).

Abbreviations: US, unconditioned stimulus; CS, conditioned stimulus; CS-, unpaired CS; CS+D, directly extinugished CS; CS+U, unextinguised CS; skin conductance response (SCR).

Supplemental Figure 5 Patterns of Expectancy and SCR during the 3-Day Adapted Paradigm. In response to the Replication Paradigm results, the 3-day Adapted Paradigm was created. Here, extinction learning phases were completed on a separate day between acquistion and recall days. For each CS type, the average youth expectancy of the US for the first and last

presentation (a) and skin conductance response (SCR) during the first four trials of each stimulus (b) are graphically presented. Parent expectancy (c) and SCR (d) are graphed in in similar fashion. Expectancy and SCR values are averages, residualized for age and for biological sex in youth participants. Error bars in all graphs represent standard error. Brackets and asterisks represent statistical significance ($p < 0.05$).

Abbreviations: US, unconditioned stimulus; CS, conditioned stimulus; CS-, unpaired CS; CS+D, directly extinugished CS; CS+U, unextinguised CS; skin conductance response (SCR).

Supplemental Figure 6 Patterns of Expectancy and SCR during the 3-Day Vicarious Paradigm. The 3-day Vicarious Paradigm mimics the Adapted Paradigm while also including a novel vicarious extinction phase on Day 2 for youth. For each CS type, the average youth expectancy of the US for the first and last presentation (a) and skin conductance response (SCR) during the first four trials of each stimulus (b) are graphically presented. Parent expectancy (c) and SCR (d) are graphed in in similar fashion. Expectancy and SCR values are averages, residualized for age and for biological sex in youth participants. Error bars in all graphs represent standard error. Brackets and asterisks represent statistical significance ($p < 0.05$).

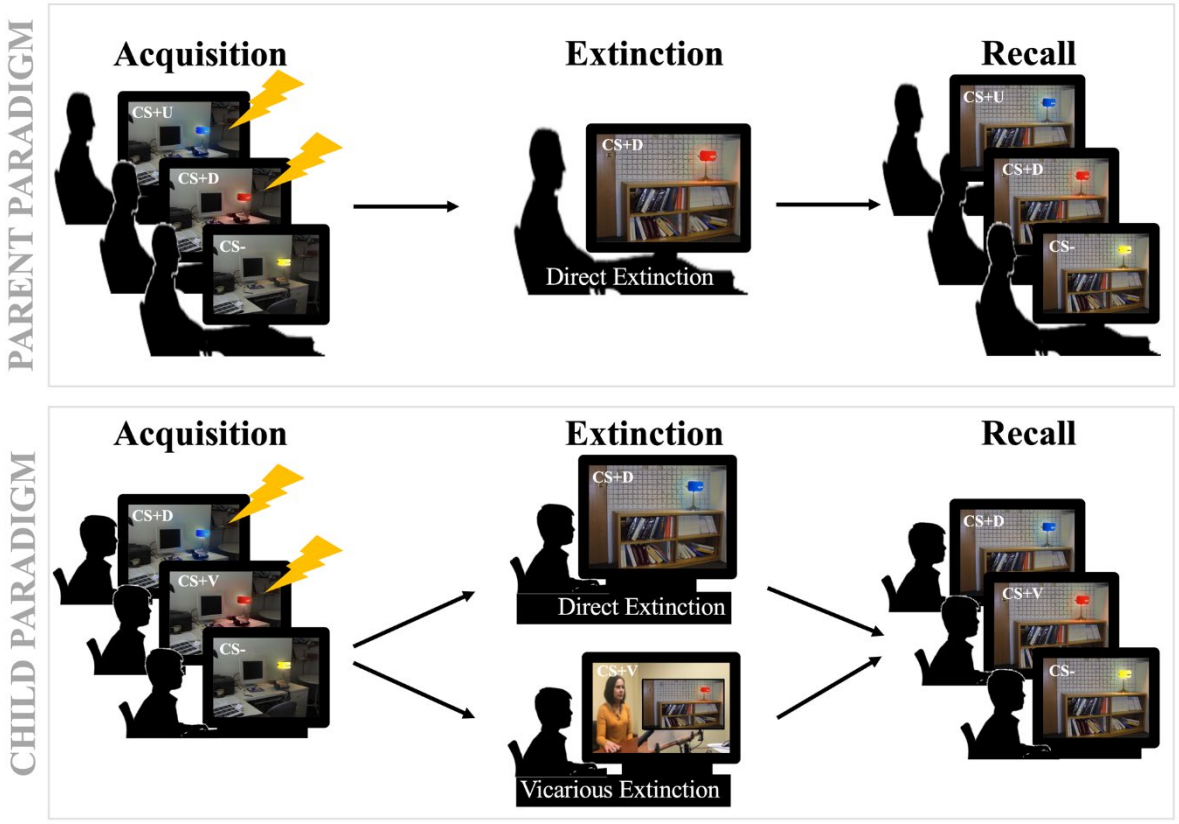
Abbreviations: US, unconditioned stimulus; CS, conditioned stimulus; CS-, unpaired CS; CS+D, directly extinugished CS; CS+V, vicariously extinguised CS; CS+U, unextinguised CS; skin conductance response (SCR).

Supplemental Figure 7 Differential patterns of vicarious extinction learning in pediatric PTSD. Average SCR responses to each CS-type during parent direct extinction (A) and child vicarious extinction (B) are visualized by group (TD, PTSD). (C) Scatterplot representing the

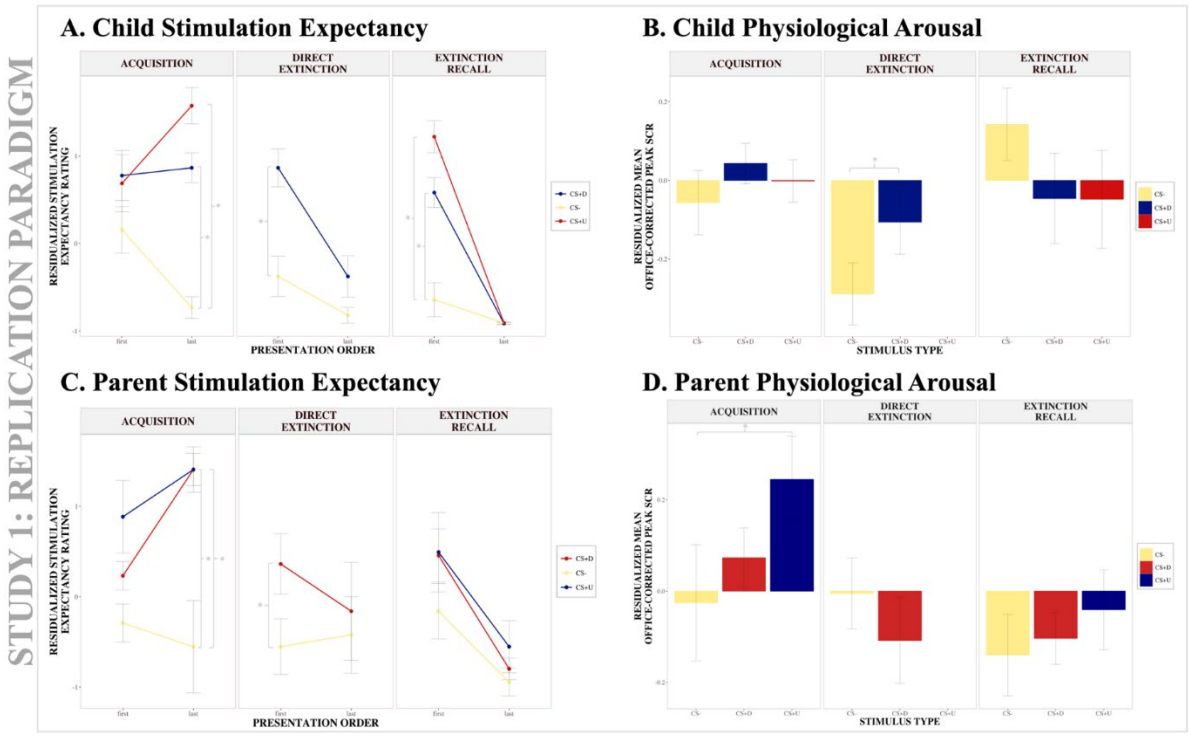
relationship between child SCR response per stimulus type and PTSD reexperiencing symptom severity (PTSD-RI Subscale B) during extinction recall on day 3. (D) Average parent-child SCR synchrony during direct/vicarious extinction training, respectively, by group status (TD, PTSD), and the relationship between parent-child SCR synchrony and average youth SCR response during extinction recall. SCR and synchrony values have been residualized for age and for biological sex in youth participants. Error bars in all graphs represent standard error. Brackets and asterisks represent statistical significance ($p < 0.05$).

Abbreviations: PTSD, posttraumatic stress disorder; US, unconditioned stimulus; CS, conditioned stimulus; CS-, unpaired CS; CS+D, directly extinugished CS; CS+V, vicariously extinguised CS; CS+U, unextinguised CS; skin conductance response (SCR).

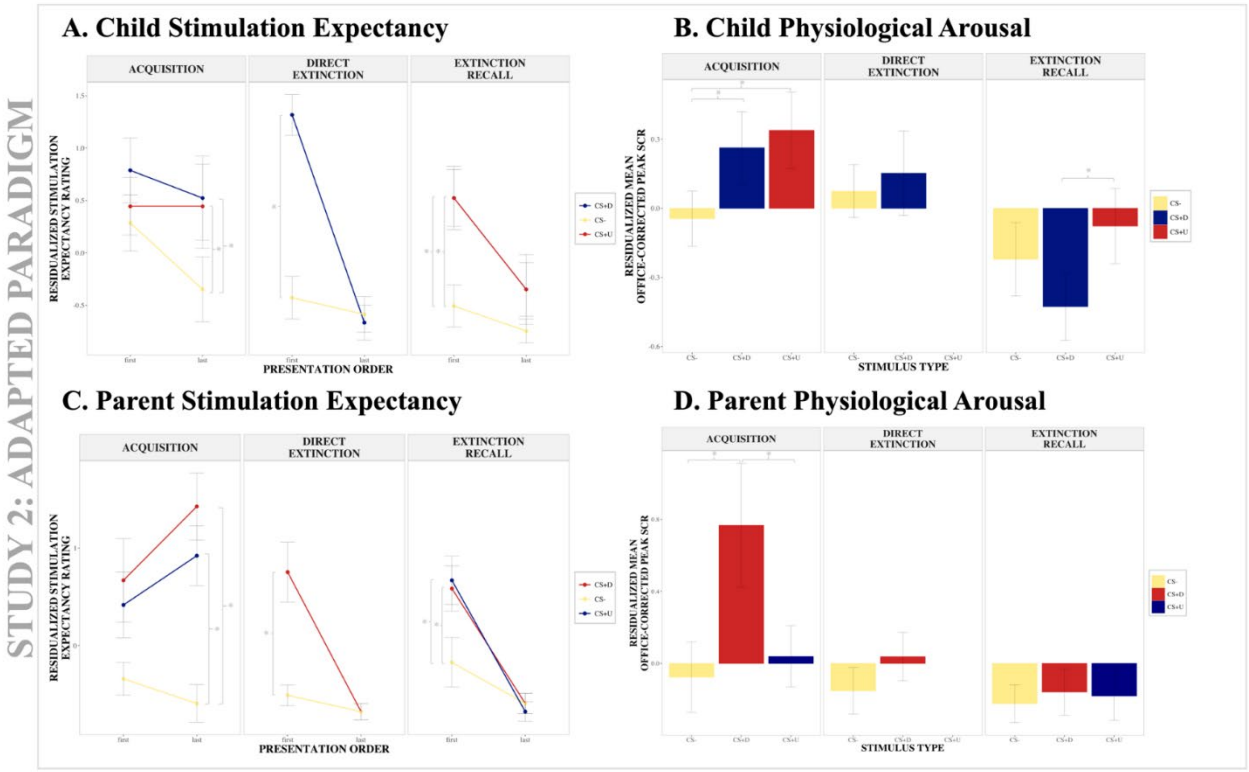
Supplemental Figure 3



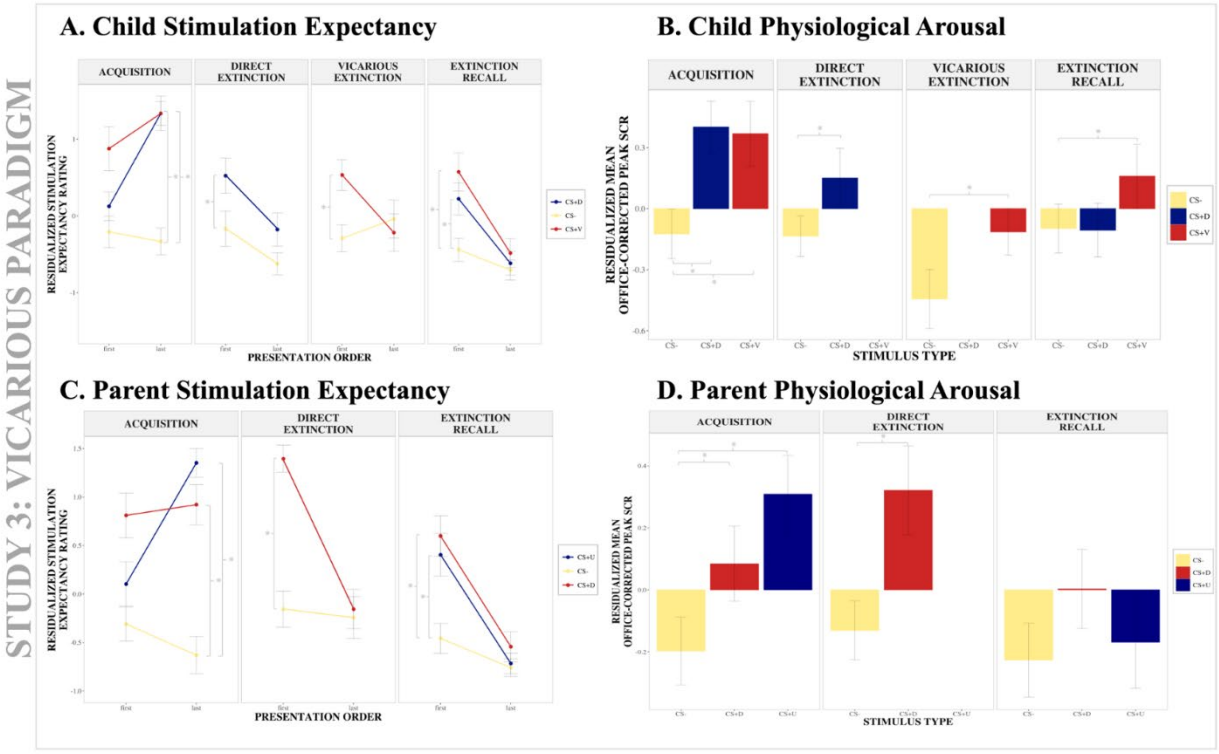
Supplemental Figure 4



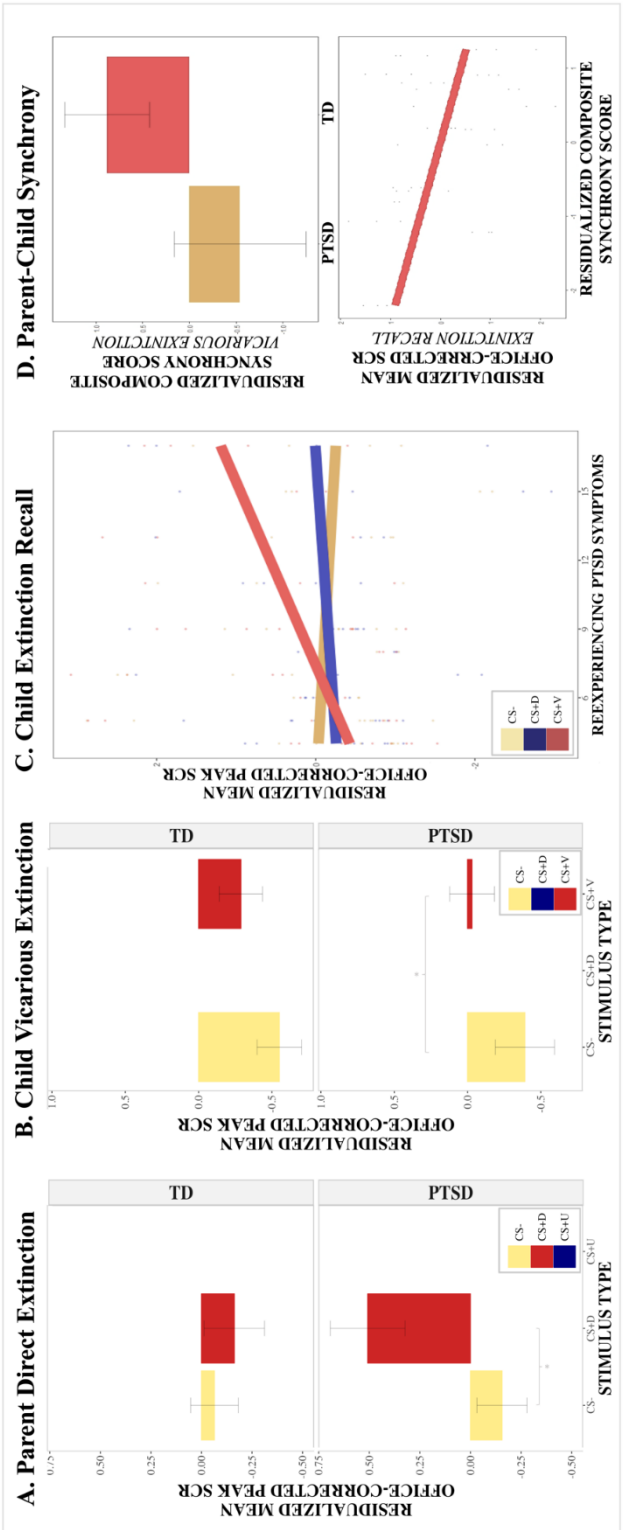
Supplemental Figure 5



Supplemental Figure 6



Supplemental Figure 7



STUDY 3: VICARIOUS PARADIGM

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