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Leveraging Intersubject Representational Similarity Analysis to Explore Individual Differences in Early Life Adversity and Cortico-Amygdala Connectivity in a Preadolescent Sample

Amira Hmidan, *Western University*

Supervisor: Morton, J. Bruce, *The University of Western Ontario*

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Abstract

Preadolescence is a critical developmental phase characterized by changes in the functional connectivity (FC) between the cortex and amygdala, which are essential for emotional processing and regulation. Early life adversity (ELA), such as exposure to childhood maltreatment, familial dysfunction, and poverty, is associated with negative physical and mental health outcomes (Felitti et al., 1998). Emerging research indicates that disturbances in cortico-amygdala FC could act as a mechanism linking ELA to various mental health issues; however, most focus on adult populations and overlook individual differences. Here, intersubject representational similarity analysis (IS-RSA) was leveraged to explore how individual variations in ELA relate to differences in bilateral cortico-amygdala FC within a large preadolescent cohort (N = 745). A significant positive association between ELA and cortico-amygdala FC was found after controlling for sex, and this association generalized across resting-state acquisitions. These findings demonstrate the potential neural embedding of ELA on neural circuits involved in emotional regulation.

Keywords

Early life adversity, amygdala connectivity, functional connectivity, resting-state fMRI, intersubject representational similarity analysis, individual differences.

Summary for Lay Audience

During preadolescence, significant changes occur in how specific brain regions—specifically those involved in emotional regulation and fear—connect and communicate. Early life adversities (ELA) such as neglect, abuse, and poverty are known to have a lasting impact on mental health and well-being (Felitti et al., 1998). Research tells us that ELA can lead to early changes in brain connectivity, which may contribute to these mental health challenges. However, previous studies have primarily focused on adults, with little exploration of how unique histories of ELA relate to brain connectivity. In this study, we asked the question of whether preadolescents (mean age = 9.5) with similar ELA histories would also be similar in their brain connectivity patterns. By using a large sample of preadolescents (N = 745) from the Adolescent Brain and Cognitive Development Study, we found that preadolescents with similar ELA histories also had similar brain connectivity patterns between the cortex and amygdala, regions essential for emotional processing and regulation. This relationship suggests that ELA may impact brain areas associated with emotional regulation among preadolescents. Understanding these connections can provide insights into how early adversities shape mental health outcomes and may help in identify interventions for children who experience ELA.

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Select List of Abbreviations

ABCD®	Adolescent Brain and Cognitive Development Study
ACC	Anterior cingulate cortex
ACEs	Adverse life experiences
BLA	Basolateral amygdala
BOLD	Blood oxygen level dependent signal
CMA	Centromedial amygdala
CSF	Cerebral spinal fluid
DAN	Dorsal attention network
DD	Delay discounting
dlPFC	Dorsolateral prefrontal cortex
DMAP	Dimensional Model of Adversity and Psychopathology
DMN	Default mode network
DSM-5-TR	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision
DWI	Diffusion weighted imaging
ELA	Early life adversity
FC	Functional connectivity
fMRI	Functional magnetic resonance imaging
FPN	Frontoparietal network
FWHM	Full width at half maximum
GLM	General linear model
HPA	Hypothalamic-pituitary-adrenal axis
ICC	Intraclass correlation coefficient
ISC	Intersubject correlation
IS-RSA	Intersubject representational similarity analysis
LB	Limited bedding
MNI	Montreal Neurological Institute
mPFC	Medial prefrontal cortex
MRI	Magnetic resonance imaging
NDA	National Institute of Mental Health Data Archive

PFC	Prefrontal cortex
PI	Previously institutionalized
PTSD	Posttraumatic stress disorder
RDM	Representational dissimilarity matrix
ROI	Region of interest
RSA	Representational similarity analysis
rs-fMRI	Resting-state fMRI
RSM	Representational similarity matrix
SC	Structural connectivity
SPM-12	Statistical parametric mapping
TE	Echo time
TR	Repetition time
VAN	Ventral attention network

Chapter 1

1 Introduction

Early life adversity (ELA), defined as exposure to adverse events before the age of 18-years, is a ubiquitous experience, with over half of preadolescents reporting at least one exposure in their lifetime (McLaughlin et al., 2012). Although most preadolescents do not develop trauma-related psychopathology (Copeland et al., 2007), frequent experiences of abuse, neglect, and household dysfunction can significantly increase the risk for chronic disease, depression, anxiety, addiction, and suicide (Brennan et al., 2024; Chapman et al., 2004; Dube et al., 2001, 2009; Felitti et al., 1998; McLaughlin et al., 2012).

The amygdala, a brain area broadly implicated in emotional processing, and its functional connectivity (FC) with the cerebral cortex, is thought serve as a mechanistic conduit in the pathway from ELA to negative physical and mental health outcomes (Berboth & Morawetz, 2021; Hosseini-Kamkar et al., 2023; Kraaijenvanger et al., 2023). Recent functional magnetic resonance imaging (fMRI) studies support this developmental perspective, showing that ELA can differentially impact neurobiological systems necessary for emotion control and stress regulation (Belsky & Pluess, 2009; Fadel et al., 2021; Hosseini-Kamkar et al., 2021; Tottenham & Sheridan, 2009). These alterations, specifically in cortico-amygdala FC, can increase vulnerability to emotional dysregulation and heightened stress sensitivity, leading to difficulties in executive functions such as working memory, cognitive flexibility, decision making, planning, and organization (Berboth & Morawetz, 2021; Di et al., 2017; Gunther et al., 2023; Tottenham & Galván, 2016).

Despite the recognition of these broad impacts, empirical gaps remain. The present impetus in developmental neuroscience is to prioritize individual variability over group-based inferences, and to integrate behavioral science with systems neuroscience (E. S. Finn et al., 2020; Hasson et al., 2008; Kriegeskorte et al., 2008; J. Sheng et al., 2023). However, extant neuroimaging studies lack the statistical and computational power to identify multivariate relationships between environmental risk factors and FC (Noble et al., 2019). Moreover, the substantial heterogeneity in

outcomes associated with ELA make it challenging to identify risk and resiliency factors across individuals and contexts (Pollak & Smith, 2021).

This chapter addresses the current challenges and perspectives on ELA and its empirical connection to cortico-amygdala FC. A topological lens is used as a philosophical framework for conceptualizing ELA, illustrating how multidimensional factors—such as environmental risk, features of the event, and social contexts—instantiates the experience of ELA (Pollak & Smith, 2021). Model free approaches, such as intersubject representational similarity analysis (IS-RSA), are proposed as methods to bridge topological perspectives with developmental neuroscience (E. S. Finn et al., 2020). Finally, the current study is presented, which leverages IS-RSA to explore individual differences in ELA and bilateral cortico-amygdala FC in a large preadolescent sample.

1.1 Models of early life adversity

The conceptualization of ELA continues to evolve, making it challenging to arrive at a unified definition. At the broadest level, ELA refers to negative, or aversive environmental experiences that deviate from anticipated developmental milieus (McLaughlin & Sheridan, 2016). These events, be they acute or chronic, occur during the formative years of development and can include, but are not limited to: childhood abuse, such as physical, emotional, and sexual abuse; caregiver neglect; exposure to domestic violence; poverty; family instability (e.g., conflict, divorce, and changing households); parental substance abuse and psychopathology; and loss of a loved one through death or separation (McLaughlin & Gabard-Durnam, 2022). Importantly, ELA encompass more than just severe instances of abuse; it includes a wide range of daily interactions and experiences that unfold over time. These experiences are continuously shaped by the interplay between genetic factors, individual differences, and environmental conditions throughout a person's development (Hertzman, 2013; Hyde et al., 2011).

1.1.1 Cumulative Risk

The *cumulative risk* model of adversity posits that the accumulation of multiple adverse events or stressors in childhood will lead to more severe and negative health outcomes than single events alone (McLaughlin & Sheridan, 2016; Sheridan et al., 2017). These models treat adverse events as additive, with each adversity compounding an individual's overall risk for future illness

and disability. This approach is useful in epidemiological studies for assessing the prevalence and collective impact of ELAs on the general population and demonstrates strong predictive utility for anticipating future health outcomes (Chapman et al., 2004; Danese & McEwen, 2012; Dube et al., 2001, 2009).

In a seminal study by Felitti and colleagues (1998), it was found that adults with greater exposure to adverse childhood experiences (ACEs) had more physical and mental health problems than adults with fewer ACEs. Individuals with over four ACEs had up to 12 times the risk for developing alcohol use disorder, major depressive disorder, and dying by suicide (Felitti et al., 1998). One of the most prominently cited findings was the graded association between ACEs and various physical health conditions, including cardiovascular disease, liver disease, musculoskeletal problems, and cancer. This work led to a concerted effort to understand the cumulative effects, prevalence and outcomes associated ELA.

Cumulative models propose that alterations to the stress system serve as a mechanism in the pathway from ELA to adverse health outcomes (Danese & McEwen, 2012). Chronic dysregulation of the stress response system, *allostatic load or overload* (McEwen, 2000), is theorized to trigger a cascade of neurobiological effects that eventually compromise physiological, cognitive, and socio-emotional functioning (Evans et al., 2013; McEwen, 2000; McLaughlin & Sheridan, 2016). For instance, chronic exposure to ELA can elicit dendrite shortening in the PFC, affecting executive functions such as attention and working memory, while also accelerating synaptogenesis in the amygdala, which can interfere with the extinction of fear-memories (Danese & McEwen, 2012; McEwen & Gianaros, 2011). Chronic exposure to psychosocial stressors also contributes to accelerated cellular aging through various mechanisms including disruptions to the immune, nervous, and endocrine systems (Colich, Rosen, et al., 2020), which, in turn, can increase one's vulnerability to diseases like dementia, depression, diabetes, osteoarthritis, and hypertension (Chapman et al., 2004; Danese & McEwen, 2012; Nurius et al., 2019).

Despite their predictive utility, cumulative risk models lack specificity. They provide a broad overview of potential risks, but fail to identify the specific factors that contribute to mental health outcomes (McLaughlin et al., 2021). This is in part due to the lack of differentiation between types of adversity or the degrees of severity associated with the experience (McLaughlin &

Sheridan, 2016; Smith & Pollak, 2021). For example, a child with a history of sexual violence and physical abuse would receive the same cumulative risk score as a child who experienced neglect and poverty, despite the marked differences in the quality and severity of their experiences (Berman et al., 2022; McLaughlin & Sheridan, 2016). Moreover, empirical evidence from extensive animal research demonstrates that exogenous influences can elicit variable in vivo stress responses, spanning from hyper to hypoactivation, which is not captured in cumulative models (Morin et al., 2020; Sánchez et al., 2001; Sheridan et al., 2017; Teicher et al., 2006; R. Yuan et al., 2021)

1.1.2 Dimensional Model: Threat verses Deprivation

The *Dimensional Model of Adversity and Psychopathology* (DMAP) is a framework concerned with the mechanisms through which ELAs exert their influence on cognitive, emotional, and behavioural development (McLaughlin et al., 2014; McLaughlin & Sheridan, 2016). DMAP differentiates two dimensions of ELA – *threat* and *deprivation*. Experiences of threat are classified similarly to criterion A of Posttraumatic Stress Disorder (PTSD) in the Diagnostic and Statistical Manual for Mental Health Disorders –5th Edition Text Revision (DSM-5-TR), which includes exposure to real or threatened death, serious injury, or sexual abuse (American Psychiatric Association, 2022). It is theorized that exposures to threat during formative periods of development will alter brain circuits involved in fear processing and learning in ways that enhance the detection of threatening environmental cues (McLaughlin et al., 2014).

In contrast, deprivation involves the absence of expected environmental inputs necessary for healthy development, commonly through emotional neglect, poverty, and institutionalization (McLaughlin & Sheridan, 2016). Deprivation can also include the absence of basic needs that are considered necessary for healthy development such as nutrition, stable caregiving, emotional support, cognitive stimulation, and a safe environment (McLaughlin et al., 2014; McLaughlin & Gabard-Durnam, 2022). Deprivation is theorized to precipitate synaptic pruning and diminished neural connectivity in brain regions responsible for language acquisition and higher-order cognitive processes, leading to poor achievement and socio-emotional function (McLaughlin et al., 2014; A. B. Miller et al., 2018).

DMAP stipulates that threat and deprivation are not orthogonal but instead represent a gamut of experiences along the continua of threat and deprivation. Although the boundary between threat and deprivation is nuanced, their delineation has been useful in understanding risk associated with ELA. For instance, threat is closely linked to hyperactivity in the amygdala, leading to heightened vigilance and emotional dysregulation (Hosseini-Kamkar et al., 2023). Conversely, deprivation is theorized to contribute to deficits in executive functions and memory (Behen et al., 2009; Vargas et al., 2020). Both types of adversity, however, share overlapping mechanisms (Heim et al., 2008; Hosseini-Kamkar et al., 2021; McEwen, 2000). Both can lead to chronic dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, a neuroendocrine system involved in stress regulation, which can result in prolonged elevation of cortisol levels, altered immune and metabolism function, and chronic inflammation (Dube et al., 2009; Hosseini-Kamkar et al., 2021; J. A. Sheng et al., 2021; J. P. Yuan et al., 2022).

1.1.3 Harshness unpredictability model

The *harshness-unpredictability* model provides an evolutionary rationale for the differential influences of ELA on life history strategies and development (Ellis et al., 2009, 2022). It posits that decision making occurs in response to exogenous inputs along the continuum of harshness. Harshness encompasses a diverse spectrum of factors indicating the potential for acquiring illness and disability and the perceived likelihood of early mortality. Unpredictability refers to the fluctuation in environmental harshness an organism endures over time and space (Ellis et al., 2009). Challenges that are perceived as threatening and unpredictable contribute to higher levels of environmental harshness.

Harsh environments are believed to exert selective pressures on individuals, driving evolutionary adaptations that promote intra-individual resilience and enhance reproductive fitness through natural selection (Belsky, 2019). The *psychosocial acceleration hypothesis* is an example of an adaptive strategy to ELA (Ellis et al., 2022). Individuals exposed to harsh and unpredictable environments tend to mature quicker, have earlier pubertal onset, engage in early sexual activity, and have more children at younger ages than their privileged counterparts (Colich, Platt, et al., 2020; Colich, Rosen, et al., 2020). Indeed, sexual abuse, frequent changing of households, father-absence, low socio-economic status, natural disasters, war exposure, and even the COVID-19

pandemic have all been linked to precocious puberty in young girls and, to a lesser extent, boys (Belsky, 2019; Colich, Platt, et al., 2020; Magnus et al., 2018; Prosperi & Chiarelli, 2023; Webster et al., 2014).

These ontogenetic adaptations to ELA have associated benefits and costs (Belsky, 2019; Ellis et al., 2009). In the short term, accelerated maturation is thought to allow children and adolescents to better cope with daily stress and emotional hardships, thereby mitigating the risk for developing internalizing problems (Herringa et al., 2016). In contrast, exposure to childhood deprivation and maltreatment have been shown to accelerate telomere attrition, which is a widely recognized biomarker of cellular aging (Ridout et al., 2018; Shalev et al., 2013) and a causal mechanism linking ELA to physical and mental health problems (Blackburn et al., 2015). Moreover, there is evidence to support that earlier age at menarche mediates the relationship between childhood threat exposure and the post-pubertal development of fear, distress, and externalizing behaviours in girls (Colich, Platt, et al., 2020).

1.1.4 Hybrid categorical-dimensional model

A significant source of variability in the study of ELA stems from the dearth of conceptual frameworks that explicitly differentiate between trauma and adversity (Hosseini-Kamkar et al., 2021; Krupnik, 2019). The conflation of trauma and adversity resides at the confluence of two divergent perspectives: one advocating for narrowly defined, categorical definitions of trauma and the other supporting broadly inclusive, dimensional perspectives (Krupnik, 2020). The lack of consensus not only obfuscates the operationalization of ELA but also hinders the comparability and generalizability of findings across studies.

The *hybrid-categorical-dimensional model* addresses this issue by defining trauma as a stress response that is qualitatively distinct from both normative and pathogenic (adversity-related) responses (Krupnik, 2019, 2020). Pathogenic responses are characterized by temporary transitions to an allostatic state in reaction to stressful events. In contrast, traumatic responses incorporate pathogenic shifts and abnormal disruptions to the self-regulatory mechanisms necessary for restoring homeostatic equilibrium. The hybrid-categorical-dimensional model makes a clear, qualitative distinction between adversity and trauma. At the same time, adversity and trauma can be understood as existing along a continuum with varying degrees of severity and impact. For

example, an inverted U-shaped function has been proposed to underly the relationship between cortisol reactivity and ELA severity, with adversity being associated with cortisol *hyper*-reactivity and trauma being associated with cortisol *hypo*-reactivity (Hosseini-Kamkar et al., 2021).

1.1.5 Topological approach

The *topological approach* posits that individual experiences and developmental trajectories can be represented as a complex network of interconnected events, relationships, and milestones, which undergo significant translation over time and space (Pollak & Smith, 2021; Smith & Pollak, 2021). Topology is a mathematical construct that reflects how an object can undergo significant dimensional transformations while retaining its initial properties. To illustrate, a Möbius strip is an object that is created by joining the ends of a rectangular strip with a half twist in the middle. The twist effectively transforms the two-dimensional surface into an object with one continuous edge. While the Möbius strip contains higher-dimensional properties, it does not lose its lower dimensional embeddings.

Human development can be described in similar terms. In a topological approach, The biological relevance of ELA emerges from the *Gestalt* or integrated structure of such experiences rather than their discrete properties (Pollak & Smith, 2021; Smith & Pollak, 2021). This position is supported by evidence of substantial overlap across ELA subtypes, including physical and emotional maltreatment (including abuse and neglect), and sexual abuse (Matsumoto et al., 2023). These dimensions may reflect the same underlying construct (Smith & Pollak, 2021).

ELA is nested within a broader ecological context that is fluid and resistant to simple classifications. Put another way, the "essence" of ELA is distributed across several interconnected dimensions, shaped by the features of the adverse event (chronicity, intensity, and developmental timing), environmental conditions (predictability and contingency), social contexts (safety and social support), and individual risk factors (temperament and genetics) (Pollak & Smith, 2021; Smith & Pollak, 2021).

1.2 Summary: theoretical models of ELA

Extant models of ELA offer valuable frameworks for understanding the complex interplay between environmental factors and developmental outcomes. Among the models discussed, cumulative risk and DMAP have been extensively applied in research settings. Cumulative risk models demonstrate how multiple sources of ELA can increase the risk for developing adverse physical and mental health outcomes; however, its ability to disentangle complex mechanistic pathways remains limited. In contrast, DMAP distinguishes between the dimensions of threat and deprivation (McLaughlin et al., 2014), which dovetails with evolutionary perspectives of accelerated development and adaptative responses to harsh environments (Belsky, 2019; Ellis et al., 2009, 2022). These perspectives are valuable for understanding how distinct experiences and environments contribute to different risk and resilience factors for brain development and overall health. However, they may overlook the phenomenological aspects of ELA that contribute to individual differences in psychosocial and neurobiological outcomes. Finally, the topological approach offers a holistic, panoramic view of ELA and its diverse impacts (Pollak & Smith, 2021; Smith & Pollak, 2021), but has yet to be empirically investigated.

While conceptual differences exist across various theories of ELA, most acknowledge the amygdala as a brain region affected by ELA (Behen et al., 2009; Gee, Gabard-Durnam, et al., 2013; Guadagno et al., 2018; Liang et al., 2014). This consensus is supported by evidence from both human and animal studies (Gee, Gabard-Durnam, et al., 2013; Morin et al., 2020; Sánchez et al., 2001), which demonstrate that weakened cortico-amygdala connectivity imparts risk for major depressive disorder, anxiety, suicidality, self-injury, PTSD, and personality pathology (Cheng et al., 2020; Jedd et al., 2015; X. Li et al., 2023; Vai et al., 2017; VanTieghem & Tottenham, 2018; Wang et al., 2020). However, the strength and direction of the association is mixed (Colich, Platt, et al., 2020; Gaffrey et al., 2021), which may relate to individual differences neurobiological systems impacted by ELA.

By treating ELA as a culmination of multivariate factors, a topological approach can help resolve inconsistencies present in the literature (Pollak & Smith, 2021; Smith & Pollak, 2021). It should be noted, however, that there are currently no empirical or neuroimaging studies that explicitly define ELA using a topological approach. Therefore, the evidence presented later in this

chapter should not be interpreted as supporting this framework or its superiority over other models of ELA. Instead, this chapter explores how the topological approach can be leveraged to investigate individual differences in ELA and amygdala function.

1.3 Amygdala function and development

The amygdala, a small, almond-shaped cluster of nuclei within the medial temporal lobe, is an essential component of the limbic system (Hariri & Whalen, 2011; Murray & Fellows, 2022). The amygdala plays a critical role in the processing of emotions such as fear, anger, and pleasure, and is implicated in fear detection and responding (Hariri et al., 2002, 2003). The amygdala is densely innervated by glucocorticoid receptors, which facilitates its responsiveness to a gamut of environmental stressors (Hariri et al., 2002; VanTieghem & Tottenham, 2018). There are two anatomical subdivisions of amygdala nuclei: the centromedial (CMA) and the basolateral amygdala (BLA; Miller et al., 2020). The BLA contains cortical neurons which allows it to receive sensory inputs from the neocortex (Hariri et al., 2003; Mosher et al., 2010). It encodes sensory inputs based on their arousal and salience properties and is biased toward fearful and threatening stimuli (Gale et al., 2004). The CMA receives input from the BLA, neocortex, and parts of the midbrain, forebrain, and brainstem (Mosher et al., 2010) which facilitates enhanced attention, arousal, and orienting behaviours necessary for fear processing and detection.

Infancy and early childhood are critical periods for amygdalar development due to significant structural changes and increased sensitivity to environmental stressors (Gabard-Durnam et al., 2018; Gee, Gabard-Durnam, et al., 2013; Tottenham & Gabard-Durnam, 2017). *Structural connectivity* (SC) refers to the physical connections between different brain regions, primarily formed by white matter tracts between cortical and subcortical regions (Honey et al., 2009; Sporns, 2013). Anatomical tracer studies in rodents reveal that the amygdala sends projections to the cortex in what is theorized to be a "bottom-up" developmental process (Bouwmeester et al., 2002; Tottenham & Gabard-Durnam, 2017). Diffusion weighted imaging (DWI) studies also demonstrate age-related changes in amygdala SC, with children exhibiting greater overall subcortical FC, which becomes sparser and more localized in adulthood (Saygin et al., 2015). This early maturation of subcortical/limbic circuitry, is thought to precede the development top-down SC (i.e., cortex to amygdala) later in adolescence (Berboth & Morawetz,

2021; Etkin et al., 2006; Gee, Gabard-Durnam, et al., 2013; Hariri et al., 2003) and may explain age-related differences in fear responsivity and emotional regulation (Silvers, Insel, et al., 2016).

In contrast, *Functional connectivity* (FC) refers to the temporal correlation of the time courses of two distinct brain regions (Biswal et al., 1997). While SC reflects the physical architecture of the brain, FC is dynamic and can substantially vary at small timescales (Honey et al., 2009; Hutchison & Morton, 2015). FC is estimated from fMRI, a neuroimaging technique that rapidly acquires T2*-weighted images to detect regional changes in blood oxygenation levels in the brain, known as the blood oxygenation level-dependent (BOLD) signal (Khanna et al., 2015). Brain areas that exhibit similar BOLD signal activations are thought to be involved in related neurophysiological and cognitive processes; however, causality cannot be inferred from this relationship (Sporns, 2013). Additionally, although there is a strong relationship between SC and FC (van den Heuvel et al., 2009), one cannot be inferred from the other (Honey et al., 2009).

Amygdala FC emerges in infants as young as 3-months-old, with spatial patterns that are similar to adolescents and adults (Gabard-Durnam et al., 2014, 2018). When considering amygdala activation separately from FC, Children under 10-years-old exhibit greater emotional reactivity and bilateral amygdala activation to both neutral and aversive faces than adolescents and adults (Silvers, Insel, et al., 2016). Additionally, preschoolers and school-aged children exhibit positive patterns of cortico-amygdala FC relative to older age groups (Gee, Gabard-Durnam, et al., 2013; Gee, Humphreys, et al., 2013) which has been shown to negatively correlate with affective regulation (See Gaffrey et al., for a contrasting view). Positive cortico-amygdala FC is speculated to reflect the immaturity of endogenous top-down mechanisms necessary to attenuate amygdala activation in children (Park et al., 2018; Silvers, Insel, et al., 2016). The lack of early self-control mechanisms may partially account for why children exhibit strong and autonomic reactions to perceived threats (Murray & Fellows, 2022; Tottenham & Gabard-Durnam, 2017).

Amygdala activation decreases as individuals transition from adolescence to adulthood (Hare et al., 2008; Monk et al., 2003; Tottenham & Sheridan, 2009). This decline is associated with a shift from positive (immature) to negative (mature) cortico-amygdala FC and reduced emotional reactivity to emotional stimuli (Gee, Humphreys, et al., 2013; Silvers, Insel, et al., 2016). One interpretation, albeit speculative, is that enhancements in emotion regulation reflect

greater top-down control over subcortical processes (Gabard-Durnam et al., 2014; Gee et al., 2022; Gee, Humphreys, et al., 2013). For example, the PFC orchestrates several higher order cognitive functions, like planning, decision-making, and inhibitory control (Niendam et al., 2012), and confers cognitive flexibility through specialized mechanisms, while the anterior cingulate cortex (ACC) facilitates processes of conflict resolution, error monitoring, social cognition, and volition (Apps et al., 2016; Etkin et al., 2006; Stevens et al., 2011; Velanova et al., 2008). Greater cortical recruitment is thought to attenuate amygdala activation, contributing to the negative association cortico-amygdala FC.

Adult-like FC patterns may serve as an ontogenetic adaptation to normative stressors, providing protection against internalizing and externalizing problems (Gabard-Durnam et al., 2014; Gee, Gabard-Durnam, et al., 2013; Gunther et al., 2023; Hyde et al., 2011; Silvers, Insel, et al., 2016). However, this transition is preceded by a period of pronounced amygdala activation in response to environmental stimuli (Tottenham & Gabard-Durnam, 2017). For instance, during preadolescence (ages 9-12), there is a unique combination of heightened amygdala activation *and* a shift toward negative cortico-amygdala FC (Casey et al., 2008; Gee, Gabard-Durnam, et al., 2013; Gee, Humphreys, et al., 2013; Hare et al., 2008; Monk et al., 2003; Tottenham & Sheridan, 2009). These associations are theorized to emerge from the rapid hierarchical reorganization of the cortex, which requires an extended period of maturation and refinement (VanTieghem & Tottenham, 2018). This renders preadolescents vulnerable to internalizing and externalizing problems like anxiety, impulsivity, and risky behaviours (Casey et al., 2008; Mlouki et al., 2021; Monk et al., 2003; Tottenham & Galván, 2016).

1.4 ELA and cortico-amygdala FC

Cross-sectional and longitudinal neuroimaging studies reveal that early disruptions to amygdala function can compromise resting-state and task-evoked cortico-amygdala FC, and lead to heightened amygdala activation (Gehred et al., 2021; Holz et al., 2023; Kraaijenvanger et al., 2023). These disruptions have long-lasting implications for internalizing and externalizing problems, emotion dysregulation, and heightened vulnerability to stress (Dash et al., 2023; Dich et al., 2015; Fadel et al., 2021; Holz et al., 2023; McLaughlin et al., 2014). The following section

explores the relationship between ELA and cortico-amygdala FC across resting-state and task-based contexts and its association with mental and physical health outcomes.

1.4.1 Associations between ELA and task-based studies of FC

Alterations in amygdala activation and FC have been observed in individuals exposed to ELA in response to task-based fMRI paradigms. Threat-exposed individuals (children and adults combined) exhibit greater right amygdala activation (83 studies; 801 coordinates) and lower PFC (medial frontal gyrus) activation (47 studies; 278 coordinates) relative to controls, irrespective of task domain (Hosseini-Kamkar et al., 2023). Emotional processing tasks elicit greater amygdala and lower PFC activation (superior frontal gyrus) in those exposed to threat. Individuals who met DSM-5 Criterion A of PTSD exhibited greater bilateral amygdala and lower medial frontal gyrus, ACC, and striatal activation relative to those with moderate adversities. However, no clusters of activation were found when the analysis was stratified by age (i.e., child or adolescent), and there was insufficient evidence to link deprivation-based ELA to task-evoked amygdala activation (Hosseini-Kamkar et al., 2023).

A general effect of task-domain on amygdala activation has not been consistently observed among individuals exposed to ELA. However, ELA has been shown to alter left CMA activation during emotional processing tasks and left precuneus activation during memory tasks. (Kraaijenvanger et al., 2020). Moreover, postnatal ELA is associated with significant clusters of activation within the left CMA and left putamen, while prenatal exposures do not reflect these trends. Further evidence supports the differential impact of ELA on fronto–CMA and BLA FC in the transition to puberty, with greater ELA severity corresponding to heightened CMA activation and weakened CMA-vmPFC FC in response to emotional faces relative to those with lower severity scores (J. G. Miller et al., 2020).

Distinct cognitive processes such as face recognition, fear processing, and emotional regulation selectively modulate extrinsic (task-evoked) cortico-amygdala FC. ELA has been linked to functional alterations between the amygdala and hippocampus (Kraaijenvanger et al., 2023), and weakened amygdala FC with the parietal area (Vai et al., 2017), mPFC, ACC, fusiform gyrus, insula, thalamus, and basal ganglia (Berboth & Morawetz, 2021) during emotional processing tasks. Moreover, previously institutionalized (PI) children demonstrate negative

cortico-amygdala FC in response to fearful faces in comparison to control children who exhibit positive coupling in these areas (Gee, Gabard-Durnam, et al., 2013). Likewise, the negative patterns observed in PI children were statistically indistinguishable from PI and control adolescents (Gee, Gabard-Durnam, et al., 2013).

1.4.2 Associations between ELA and resting-state FC in animals

Resting-state fMRI (rs-fMRI) measures the spontaneous coupling of low-frequency BOLD signals in the absence of exogenous influence (Arbuckle et al., 2019; Shan et al., 2014; Yeo et al., 2011). In contrast to task-evoked states, resting-state patterns of FC are thought to reflect the cumulative effects of past experiences, environmental influences, and neurobiological processes on current brain organization and function (Laird et al., 2011; Sadaghiani & Kleinschmidt, 2013). The intuition is that aberrant resting-state cortico-amygdala FC may be an enduring artifact of ELA (Cheng et al., 2020; Wang et al., 2020; Wu et al., 2022).

Experimental manipulation of ELA in animal models demonstrates that the developmental timing, severity, and types of ELA can embed unique biological signatures on cortico-amygdala FC (Liang et al., 2014; Morin et al., 2020; Parker et al., 2019; Sánchez et al., 2001). For instance, rats exposed to feline odor exhibit weaker negative resting-state amygdala-mPFC FC than control rats, who exhibit stronger negative FC in this circuit. Moreover, exposed rats engage in significantly more anxious behaviours 7 days after the exposure than control rats (Liang et al., 2014). This finding suggests that transient forms of ELA can confer immediate and long-term alterations to intrinsic amygdala FC and internalizing behaviours in adult rats.

In the transition to adolescence, rodent pups raised in resource abundant environments exhibit greater BLA-PFC FC compared to pups reared in deprived environments (i.e., limited bedding; LB), who exhibit blunted amygdala-mPFC and lateral amygdala-ACC FC (Yan et al., 2017). By adulthood, LB rats spent significantly less time socializing and demonstrated premature cessation of swimming in a compulsory swim test compared to controls (Yan et al., 2017). Moreover, LB pups and adult rats demonstrate differential alterations in the anterior BLA networks relative to age-matched controls (Guadagno et al., 2018). Specifically, LB pups demonstrate weaker right BLA-mPFC FC that persisted into adulthood, which corresponded heightened anxiety behaviours and weaker fear extinction.

A premature emergence of mature cortico-amygdala FC is also evident among maltreated primates, along with weaker connectivity in adolescence compared to controls (Feng et al., 2023; Morin et al., 2020; Murray & Fellows, 2022; Sánchez et al., 2001; R. Yuan et al., 2021). In rhesus monkeys, maltreatment during infancy is associated with either uncoupling or negative cortico-amygdala FC as opposed to stronger positive coupling exhibited in controls (Morin et al., 2020). Stronger cortico-amygdala FC in infancy is also associated with less anxious behaviour, a brain pattern more often observed in typically developing monkeys relative to those who experienced maternal separation (Feng et al., 2023). However, this relationship may be moderated by the number of exposures (Parker et al., 2019). For example, monkeys with 1 to 2 ELA exposures demonstrate lower anxiety levels than monkeys with no previous ELA history; however, monkeys 3 or more exposures exhibit significantly higher anxiety levels than any other group (Parker et al., 2019). This non-linear J-shaped relationship indicates that moderate ELA exposures may confer some protection against internalizing problems, but that more frequent exposures may overwhelm the system's ability to cope and regulate, contributing to higher anxiety levels.

1.4.3 Associations between ELA and resting-state FC in humans

Due to the ethical constraints associated with experimental manipulation of ELA, causal evidence on the impact of ELA on brain development is nonexistent. However, cross-sectional and longitudinal studies show a strong association between ELA and resting-state cortico-amygdala FC, particularly during the transition from childhood to adolescence (Colich, Rosen, et al., 2020; McLaughlin et al., 2014; J. G. Miller et al., 2020; Silvers, Lumian, et al., 2016).

ELA has been linked to decreased resting-state amygdala-ACC FC across child and adult samples, with children demonstrating alterations in the left ACC specifically (Kraaijenvanger et al., 2023). These findings align with evidence showing that children with higher ELA exhibit weaker/less negative amygdala-ACC connectivity, which interacts with various genetic markers to predict reduced amygdala FC with the middle and inferior frontal gyri (Pagliaccio et al., 2015). Alterations in amygdala-ACC FC also emerge in studies using subjective (self-report) and retrospective measures of ELA, but there is insufficient evidence to compare this relationship to prospective ELA measures (Kraaijenvanger et al., 2023). There is further evidence that emotional

abuse weakens amygdala-ACC FC, which predicts elevated state anxiety during a stressful task (Fan et al., 2014), and is partially mediated systemic inflammation (Kraynak et al., 2019).

Greater amygdala-mPFC FC has been shown to be positively correlated with connectivity within the limbic and default mode network (DMN) (Cisler, 2017). Adolescent girls with higher levels of emotional abuse exhibit more negative amygdala-mPFC FC and greater network modularity than girls with lower levels of emotional abuse. Adolescent girls with a history of physical and sexual abuse demonstrate weaker (less positive) left amygdala-mPFC FC and limbic-DMN FC than controls, who exhibit more positive FC in these circuits. Alterations in network global efficiency – a measure of information transmission capacity within a functional network – has been observed in individuals with a history of ELA (Wu et al., 2022). Specifically, adults who report childhood abuse or neglect demonstrate greater efficiency of the salience network and diminished efficiency of the DMN relative to healthy controls. Moreover, increases in the global efficiency of the salience network was found to mediate the relationship between childhood neglect and trait impulsivity, while increases in the DMN mediated childhood neglect and lower trait impulsivity.

1.5 Summary: ELA and cortico-amygdala FC

Across animal and human studies, ELA has been consistently linked to alterations in amygdala function and its connectivity with the cortex (Berboth & Morawetz, 2021; Feng et al., 2023; Gabard-Durnam et al., 2014; Gee, Gabard-Durnam, et al., 2013; Kraaijenvanger et al., 2023; Morin et al., 2020). The evidence suggests that ELA is associated with: a) heightened amygdala activation (Hosseini-Kamkar et al., 2023); and b) accelerated maturation of cortico-amygdala FC (Gee, Humphreys, et al., 2013; Guadagno et al., 2018). There is also evidence that ELA may modulate larger scale brain networks for which the amygdala and areas of the cortex derive (Wu et al., 2022).

Accelerated cortico-amygdala development may be an ontogenetic adaptation to ELA (J. G. Miller et al., 2020; Silvers, Lumian, et al., 2016), proximally promoting resilience in harsh environments by prioritizing rapid development of neural circuits associated with emotional regulation (Colich, Rosen, et al., 2020; Gee, Gabard-Durnam, et al., 2013; Herringa et al., 2016;

McLaughlin & Gabard-Durnam, 2022; J. G. Miller et al., 2020). However, this hypothesis has not been consistently supported across the literature, highlighting the need for further research.

1.6 Problem Scope

Despite recent progress, much remains unclear about how individual differences in ELA relate to cortico-amygdala FC in preadolescence. Is it currently stands, most metanalyses focus on adult samples, or group children and adolescents together (Berboth & Morawetz, 2021; Hosseini-Kamkar et al., 2023; Kraaijenvanger et al., 2020, 2023). Moreover, child and adolescent studies frequently oversample extreme and non-overlapping manifestations of ELA (Gee, Gabard-Durnam, et al., 2013; Silvers, Lumian, et al., 2016), which fails to capture the plurality of experiences represented in typically developing samples.

A conceptual obstacle pertains to the definition and measurement of ELA and its purported dimensions (McLaughlin & Sheridan, 2016; Pollak & Smith, 2021; Smith & Pollak, 2021). While DMAP has been widely adopted in the study of ELA, evidence regarding the impact of deprivation on cortico-amygdala FC is limited (Colich, Rosen, et al., 2020; Hosseini-Kamkar et al., 2023; McLaughlin et al., 2014). Dimensional definitions often do not account for the intrinsic overlap and high comorbidity of ELA subtypes (Smith & Pollak, 2021), which may contribute to systematic measurement error (e.g., multicollinearity) and low reproducibility.

The direct comparison of brain and behavioural data is restricted by their respective theoretical assumptions and methodologies (Kriegeskorte et al., 2008). For example, there is debate about the most appropriate measurement models of ELA (e.g., formative verses reflective) (Baldwin et al., 2019; McLaughlin et al., 2023). In reflective measurement models, the latent construct is assumed to beget the emergence of multiple indicators (i.e., ELA → poverty, abuse, and neglect); while formative models assume that the latent construct is manifest from multiple indicators (e.g., poverty, abuse, and neglect → ELA). Despite ELA being better understood as a formative construct, reflective models are more commonly used (McLaughlin et al., 2023).

The wide-spread prevalence of underpowered studies is a practical concern in neuroimaging research. For instance, up to 96% of fMRI studies conducted between 2017 and 2018 had a median sample size of 12 participants (Szucs & Ioannidis, 2020), and studies from the

past decade have generally low test-retest reliability (intraclass correlation = 0.29) (Noble et al., 2019). Moreover, common mass univariate and voxel wise approaches require correction for multiple comparisons, which can reduce statistical power and increase the risk of Type I and Type II errors. Cross-validation procedures are recommended to address these issues, which involve analyzing partitioned sections of data to ensure the predictive model generalizes across all sets (Nichols & Holmes, 2001). However, these methods are not consistently implemented across neuroimaging studies.

To address these challenges, model-free approaches such as intersubject connectivity (ISC) and representational similarity analysis (RSA) offer promising alternatives to univariate methods and strict measurement models. Both account for the complex and interconnected relationships among variables in brain and behavioural spaces, which permits the exploration of individual differences in multivariate spaces (Hasson et al., 2008; Kriegeskorte et al., 2008; Nastase et al., 2019). From a topological perspective, multivariate approaches offer a more holistic exploration of the neurological representations of ELA, and how they may relate to disparate developmental outcomes. Additionally, by assessing multiple variables at once, these approaches offer greater statistical power over mass univariate methods (McIntosh & Mišić, 2013).

1.7 Intersubject representational similarity analysis

ISC analysis is a multivariate procedure for studying brain-behavior associations. In brief, ISC is used to assess patterns of regional activation or FC between individuals in response to a common stimulus or task (Hasson et al., 2008; Nastase et al., 2019). Intersubject representational similarity analysis (IS-RSA) is a computational adaptation to ISC that permits the subject-wise comparison of FC and behavioural phenotypes by summarizing their respective representations into a representational dissimilarity matrix (RDM). RDMs capture the multivariate dissimilarities between participants in terms of their brain responses or behavioural traits, which can be compared using a second-order isomorphism to infer brain-behaviour relationships (Chen et al., 2020; E. S. Finn et al., 2020; Kriegeskorte et al., 2008; J. Sheng et al., 2023; van Baar et al., 2019). A schematic for IS-RSA can be found in **Figure 1**.

Within the respective native spaces of the data (e.g., behavioural, neural, and cognitive measures), correlations (i.e., *Pearson's r, Spearman's rho*) are calculated between all possible participant pairs, yielding a subject-by-subject correlation matrix representing the degree of similarity between participants on a given feature of interest. This can easily be transformed into an RDM by subtracting the correlation matrix from 1 (*1 – Pearson's r*). A behavioural RDM can be estimated from a collection of survey items or composite scores (E. S. Finn et al., 2020). In contrast, neural RDMs can be rendered at the voxel or ROI level. Because behavioural and neural RDMs share the same dimensions, they can be directly compared using correlation methods (Kriegeskorte et al., 2008; Popal et al., 2019).

The advantage of IS-RSA lies in its flexibility and adaptability, allowing for a data-driven exploration of the association between FC and behaviour (van Baar et al., 2019). Unlike traditional methods that rely on predefined models or hypotheses, IS-RSA permits the examination of neural data without imposing strict assumptions about the structure of the data (E. S. Finn et al., 2020; Hasson et al., 2008; Nastase et al., 2019). Moreover, RDMs can be understood as topological configurations, similar to a Möbius strip, that contain potentially valuable information about ELA in higher representational spaces. (van Baar et al., 2019).

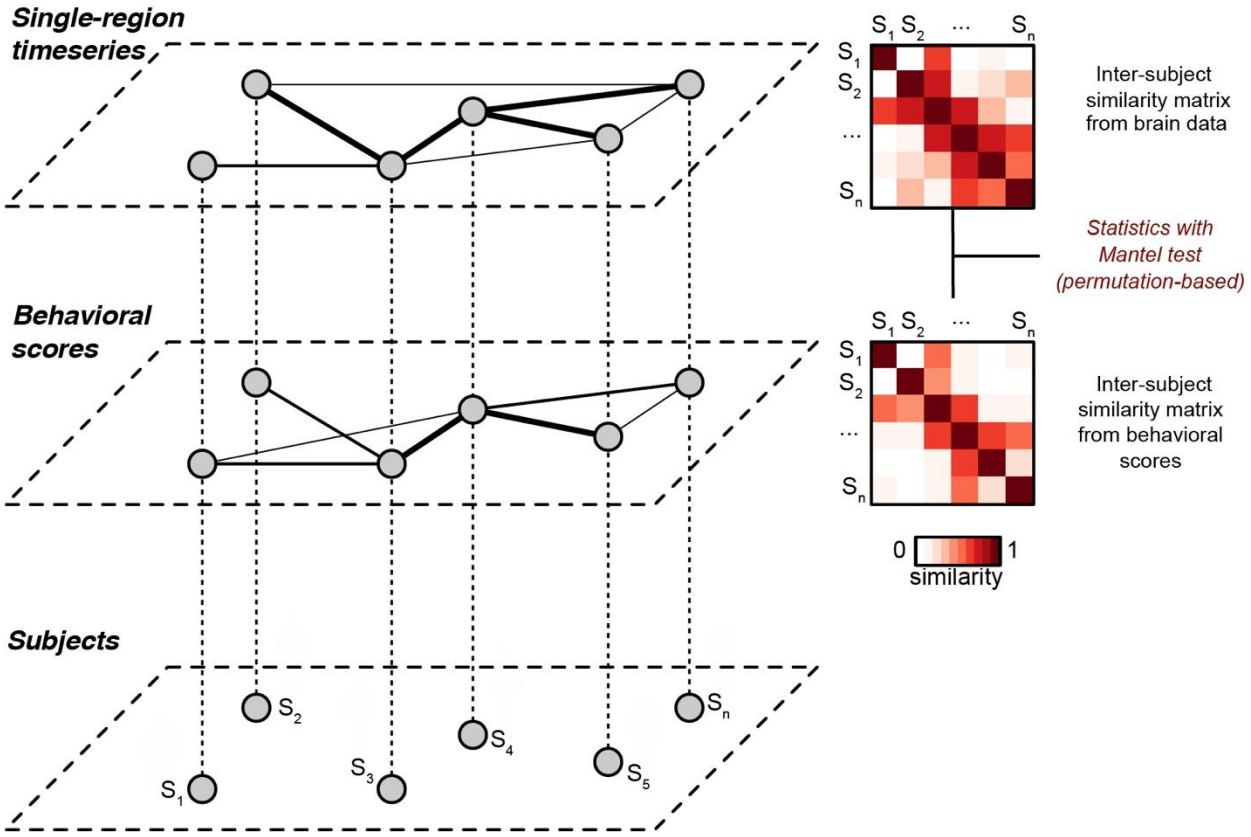
1.7.1 Empirical evidence in support of IS-RSA

IS-RSA has been used to explore individual differences in various domains, including affective responding (Qiu et al., 2024), memory (A. S. Finn et al., 2017), sexual preferences (Chen et al., 2020), decision making (Mehta et al., 2023), and antisocial personality traits (Rhoads et al., 2020). For instance, individual differences in impulsive decision have been found in resting-state brain networks such as the DMN, dorsal and ventral attention networks (DAN and VAN) (Mehta et al., 2023); and individuals with similar mentalizing abilities tend to share similarities in brain morphometry and resting-state FC. These methods have been successfully applied across child, adolescent, and adult samples, as well as in naturalistic and resting-state paradigms (Chen et al., 2020; A. S. Finn et al., 2017; Hasson et al., 2008; Mehta et al., 2023).

1.8 Rationale

The objective of this cross-sectional analysis is to evaluate whether individual differences in ELA correspond to individual differences in cortico-amygdala FC in typically developing preadolescents ages 9-10 years old. Here, IS-RSA was used to assess whether pairs of preadolescents who share similar multivariate patterns of ELA would also have similar patterns of cortico-amygdala FC. It was hypothesized that individual variation in cortico-amygdala FC would correlate with individual variation in ELA after controlling for biological sex. The second objective was to establish whether these associations would replicate across rs-fMRI acquisitions. It was hypothesized that these patterns would be consistent across acquisitions, providing support for the reliability of individual differences in cortico-amygdala FC related to ELA.

Figure 1. Methodology of Intersubject Representational Similarity Analysis



The methodology used in IS-RSA as originally depicted in the paper by Finn et al., 2020. Each participant (shown at the bottom) has corresponding behavioral metrics (middle tier) and patterns of functional connectivity (top tier). The middle and top layers represent *participant-by-participant* representational dissimilarity matrices (RDM), with thicker lines representing greater similarity among participants. RDMs can be compared using permutation-based methods like Mantel Test to infer brain-behaviour relationships. Note: The original figure was published in NeuroImage, Vol 215, Finn and colleagues (2020), *Idiosynchrony: From shared responses to individual differences during naturalistic neuroimaging (Fig 1).*

Chapter 2

2 Methods

2.1.1 Participants

Participants included 749 children (53% female) who participated in the first wave of the ABCD study. The ABCD study is a large-scale longitudinal research project involving over 11,000 typically developing children and adolescents in the United States. Each wave of data collection includes the acquisition of resting-state and task-based fMRI data as well as a large corpus of cognitive-behavioural and survey measures. Wave 1 data were obtained from the ABCD® 5.0 Data Release on the The National Institute of Mental Health Data Archive (NDA) and all protocols and procedures can be found at https://abcdstudy.org/scientists/protocols/. A total of 749 children met the minimum criterion for cross validation, which was having at least two rs-fMRI runs with framewise displacement less than 0.5mm for no more than 7.5% of frames. Four participants were subsequently removed for having missing time courses, leaving a final sample of 745 parent-child dyads.

2.2 Imaging procedure

The ABCD neuroimaging protocol is standardized for three 3T scanner machines (i.e., Siemens Prisma, General Electric 750, and Philips) across 21 research sites in the United States (see Casey et al., 2018 for a comprehensive review of the imaging protocol). Participants underwent a fixed sequence of scans, including a localizer, 3D T1-weighted images, two rs-fMRI runs, diffusion weighted images, 3D T2 weighted images, and 1-2 additional rs-fMRI runs. The rs-fMRI data were acquired with the following parameters: matrix size = 90 × 90, slices = 60, field of view = 216 × 216 mm, resolution = 2.4 × 2.4 × 2.4 mm, repetition time (TR) = 800 ms, echo time (TE) = 30 ms, and flip angle = 52° (Casey et al., 2018). Children watched a developmentally appropriate movie during the acquisition of the 3D T1, localizer, and 3D T2 and diffusion weighted images. Children were instructed to fix their gaze on a crosshair for twenty minutes for the acquisition of rs-fMRI runs.

2.3 Data preprocessing

A total of 1490 fMRI datasets underwent standard preprocessing using Statistical Parametric Mapping (SPM-12) software in MATLAB 2023a. The fMRI data underwent realignment to correct for inter-scan head motion (i.e., aligning all volumes in a time series to its initial volume). Motion parameters (translation and rotation) were estimated and recorded for further analysis. The functional data were co-registered with the high-resolution structural image to ensure precise alignment between functional and anatomical volumes. fMRI volumes were then warped into Montreal Neurological Institute (MNI) space. Spatial smoothing with a Gaussian kernel (full width at half maximum, FWHM, 8mm) was performed to enhance the signal-to-noise ratio and account for inter-subject anatomical variability.

The cerebral cortex was divided into seven functional networks based on the Yeo-7 parcellation (Yeo et al., 2011) **(see Figure 2).** Five of these networks were selected due to their established empirical associations with ELA (Berboth & Morawetz, 2021; Cisler, 2017; Di et al., 2017; Etkin et al., 2006; Hariri et al., 2003; Kraaijenvanger et al., 2023; Silvers, Lumian, et al., 2016; Wu et al., 2022), which included ROIs in the DMN (10 ROIs), DAN (6 ROIs), VAN (11 ROIs), limbic network (4 ROIs), and frontoparietal network (FPN; 16 ROIs). The ROI component names and network labels can be found in **Appendix A.** The Wake Forest University PickAtlas was used to delineate the boundaries of the right and left amygdala (Maldjian et al., 2003).

Voxel time courses within ROIs were averaged and denoised by regressing out white matter, cerebral spinal fluid (CSF), and global signal fluctuations, as well as 6 motion parameters and their first derivative. Residuals were then filtered using a Butterworth bandpass filter that retained frequencies from 0.0625 Hz to 0.8 Hz. To ensure data quality, the first five fMRI volumes were discarded due to the acquisition of dummy volumes while magnetic fields stabilized. This resulted in a dataset comprising 378 time points available for analysis.

2.4 ELA measures

ELAs were conceptualized across a broad spectra of parent and youth reported postnatal events, including childhood maltreatment and neglect, parent psychopathology, parental involvement, family conflict, and neighborhood risk (Kraaijenvanger et al., 2023; Pollak & Smith,

2021). Individual items were selected from parent and youth self-report measures based on their theoretical and empirical connections to ELA and their established usage in previous ABCD studies (Brieant et al., 2023; Kraaijenvanger et al., 2023; Orendain et al., 2023).

Detailed tables for both parent and child variables can be found in **Appendix B and C.** Parent measures included Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS-5) –Background Items Survey and Traumatic Events Module, Adult Self Report (ASR), Child Behaviour Checklist (CBCL), Demographics Survey, Family History Assessment (FHX), Neighborhood Safety/Crime Survey (NSC), Family Environment Scale – Family Conflict Scale (FES), and the Medical History Questionnaire (MHX). Youth measures included the Youth NSC, Parental Monitoring Survey (PMS), School Risk and Protective Factors Survey (SRPF), Children's Report of Parental Behaviour Inventory – Acceptance Subscale (CRPBI-ASQ), Youth FES, and the KSADS-5 – Background Items Survey (Barch et al., 2017).

Given the considerable overlap between adversity subtypes (Pollak & Smith, 2021; Smith & Pollak, 2021), individual items were not treated as separate dimensions of threat or deprivation or summed into single composite score. Instead, individual item responses for each participant were treated as inputs in the RDM to capture multivariate patterns of ELA. Variables with a high degree of missingness (i.e., ≥ 20%), low endorsement, or evidence of multicollinearity (i.e., Pearson's $r \geq 0.8$) were excluded. This resulted in a total of 261 items – 38 child-report items across 6 measures and 223 parent-report items across 9 measures.

The 'mice' (Multivariate Imputation by Chained Equations) package was used to handle missing data (S. V. Buuren & Groothuis-Oudshoorn, 2011; S. van Buuren et al., 2023). Following Rubin's (1987) recommendations, 5 imputations were performed with 10 iterations per imputation. The 'flux' function was used to identify the most relevant predictor variables from the ABCD Demographics Survey, which included child sex, child age, parent age, education, income, and racial identity. Predictive mean matching ('pmm'), logistic regression ('logreg'), and proportional odds logistic regression ('polr') were used to impute missing values for continuous, logistic, and ordinal variables, respectively. Statistical analyses were completed for each imputed dataset and pooled according to Rubin's Rules (Rubin, 1987).

2.5 Statistical analyses

The IS-RSA procedures for this study can be found in **Figure 3.** All statistical analyses were performed separately on the right and left amygdala, for each rs-fMRI run, and for each imputed dataset using custom MATLAB and R scripts. Pearson's correlation was used to estimate the similarity between amygdala time courses and 47 ROIs from the Yeo 7 parcellation. This yielded two 47-element amygdala-seeded whole-brain FC vectors for all participants. All vectors were combined into a single 47 x 745 matrix, with rows representing cortico-amygdala FC measures and columns representing participants.

To establish an upper bound for validity (Noble et al., 2021), an intra-class correlation coefficient (ICC) was used to establish the within-subject stability of resting-state FC measurements and then averaged across participants. The 'irr' package in R was used to calculate single score ICC values based on a two-way random effects consistency model (i.e., ICC[2,1]) (Gamer et al., 2019). This model is appropriate for evaluating the stability of measurements over time within the same subjects (Noble et al., 2021). The overall ICC score was estimated by averaging individual scores across participants.

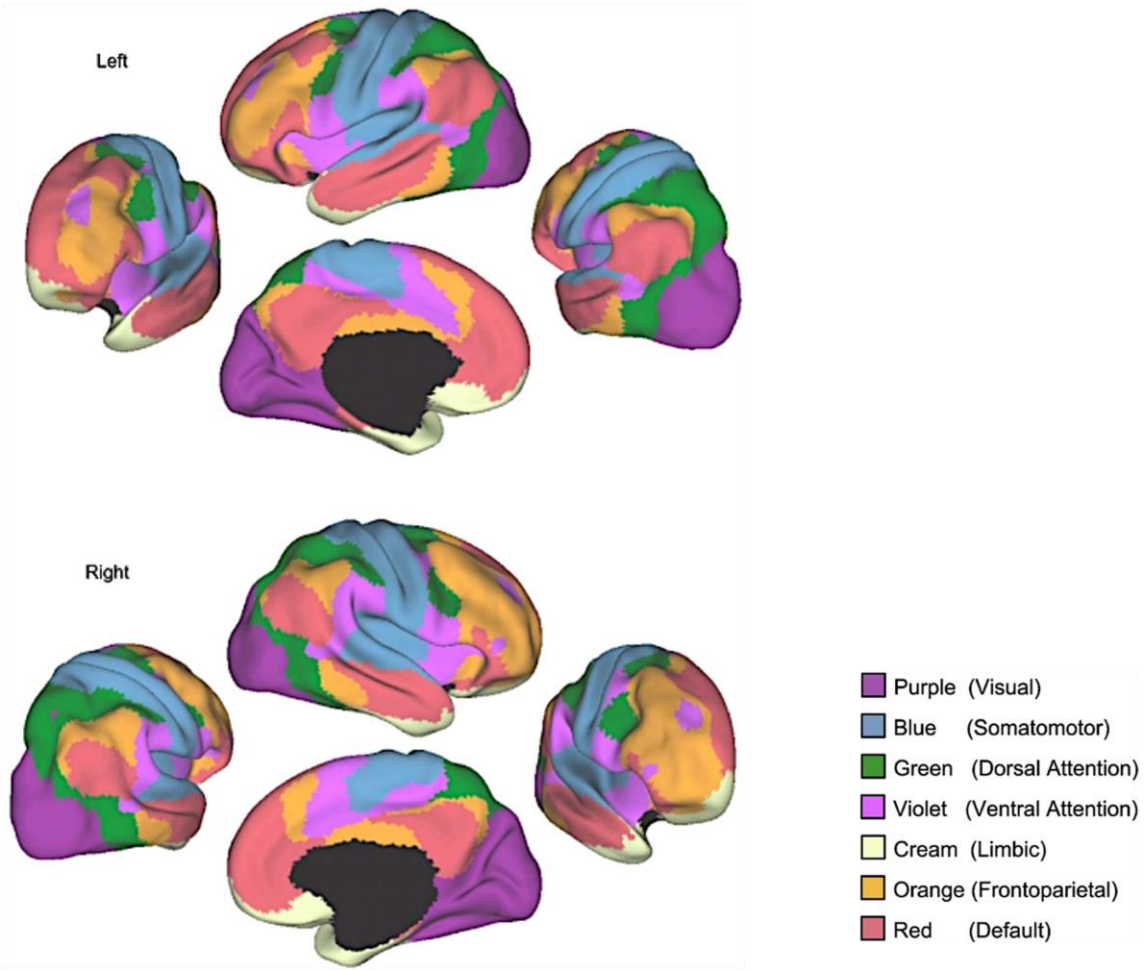
Pearson's correlation was used to calculate the inter-subject correlation (ISC) between participants' cortico-amygdala FC values, resulting in a 745 x 745 matrix where each element representing the degree of similarity between participants *i* and *j*. A simple transformation (*1 – Pearson's r*) was applied to convert the similarity matrix into an RDM where higher values represent greater dissimilarity between participants' FC profiles. A Mantel Test was used to establish the degree of cross-run generalizability in the RDMs. This was selected as a secondary method for assessing the veracity of the association between ELA and brain FC.

The same principles were applied to construct an RDM for the ELA data, with items as rows and columns as participants (i.e., 261 x 745). Previous work has demonstrated that sex modulates the effect of ELA on large-scale brain networks (Wu et al., 2022). Therefore, to control for erroneous similarities in subsequent analyses, child sex was used as a regressor for all ELA items. This was achieved by fitting a linear regression model for each ELA item, with the item score as the dependent variable and child sex as the independent variable. The residuals from these regressions, which represent the variation in ELA scores independent of sex, were then used to

construct the ELA RDM. Spearman's correlation was then used to calculate the pairwise similarities in item responses between participants, and this was converted into an RDM (*1 – Spearman's rho*). The final transformation resulted in a 745 x 745 matrix, with each element representing the dissimilarity between participants on a given ELA item. The order of subjects remained consistent across RDMs.

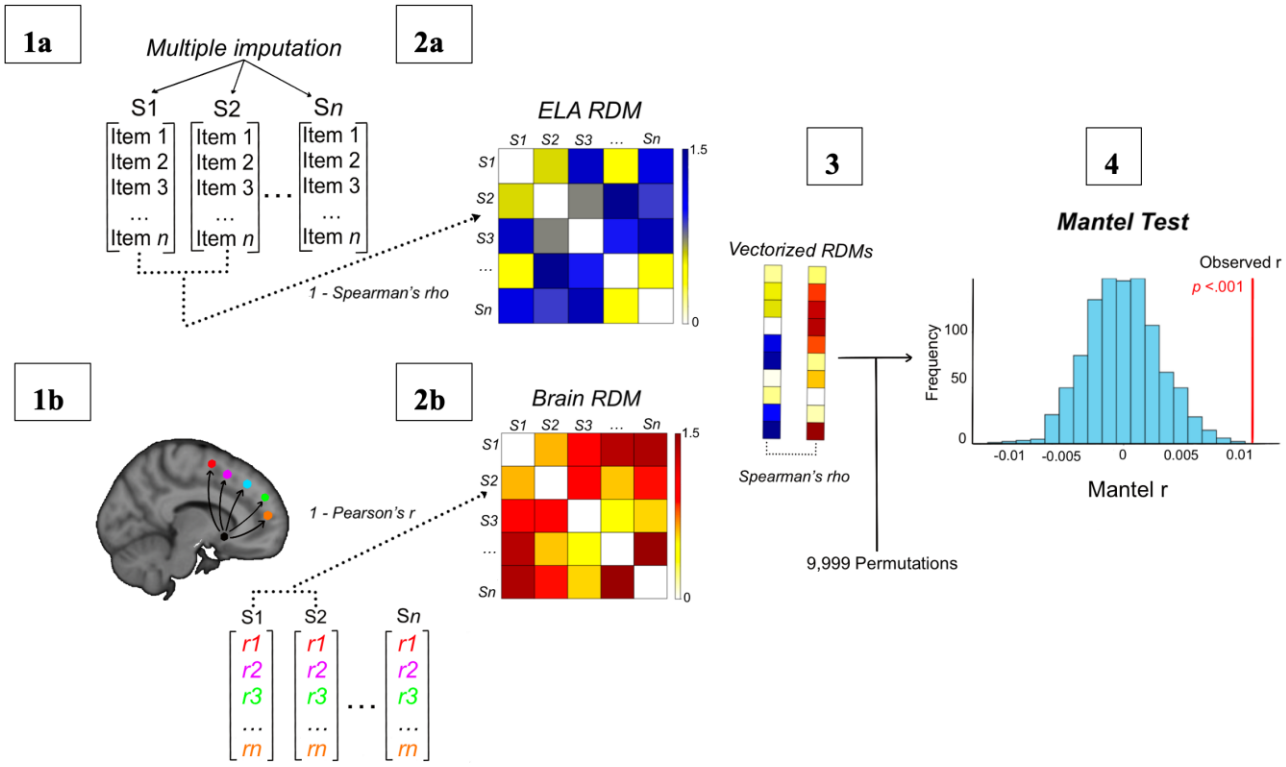
The 'ecodist' package in R was used to perform the Mantel Tests (S. C. Goslee & Urban, 2007; S. Goslee & Urban, 2023). The Mantel function vectorizes the lower triangles of each RDM and calculates a single Spearman's rank correlation coefficient. A null distribution was generated by randomly shuffling the first RDM and recalculating the correlation coefficient 9,999 times. This process yielded a distribution of *rho* values that would be expected by chance. The 'true' correlation coefficient was compared to the bootstrapped null distribution to assess its statistical significance. Significance was determined as any coefficient that fell in the extreme tails of the null distribution (i.e., $p < .05$).

Figure 2. Yeo-7 Network Parcellation of the Human Cerebral Cortex



The colours represent distinct resting-state brain networks identified in a sample of 1,000 adults. There are 51 ROIs distributed bilaterally across the 7 networks. Note: The original figure was published in The Journal of Neurophysiology, Vol 106, Issue 3, Yeo and colleagues (2011), *The organization of the human cerebral cortex estimated by intrinsic functional connectivity (Fig 11).*

Figure 3. IS-RSA Pipeline



The schematic for the IS-RSA pipeline. **1a)** Missing variables were multiply imputed and child sex was regressed from each item **2a)** Intersubject correlation was performed using Spearman's rank coefficient and transformed into a representational dissimilarity matrix (RDM; *1 – Spearman's rho*). **1b)** Time courses from the amygdala (left and right) were correlated with the 47 ROIs from the Yeo 7 parcellation for each participant (Yeo et al., 2011). **2b)** Pearson's correlation was used to create the functional connectivity RDM (*1 – Pearson's r*). **3)** The brain and ELA RDMs were vectorized and compared using Spearman's *rho*. **4)** A null distribution was created by randomly permuting one vector and recalculating the correlation again (9,999 times). In the resulting plot, the red line represents the observed *rho* value generated from step 2, and the bars depict the bootstrapped *rho* obtained from step 3.

Chapter 3

3 Results

3.1 Demographic Information

The mean age was 40.4 years (*SD* = 6.64) for parents and 9.5 years (*SD* = 0.51) for children. There was a relatively equal representation of boys (47%) and girls (53%) in the sample. Additional demographic information is presented in **Table 1.** The average (mean) ELA score was 106.77 across imputations (SE_{pooled} = 1.09, 95% CI: [104.62-108.91]; **Table 2**). The total ELA score prior to the imputation was 105.22 (*SD* = 29.04). The total percentage of missing values across ELA measures was 0.62%.

3.2 Reliability

A two-way single score ICC was used to assess the intrasubject consistency in bilateral cortico-amygdala FC between runs. The calculated *ICC*(2,1) was 0.28 in cortico-right-amygdala FC, indicating modest reliability of the FC measures across runs. An *F*-test was performed to test the null hypothesis that the true ICC was equal to zero. The results of this test were significant, $F(744) = 1.79$, $p < .001$, [95% CI: 0.22-0.35]. Similar consistency values were found for cortico-left-amygdala FC, *ICC*(2,1) = 0.28, $F(744) = 1.81$, $p < .001$, [95% CI: 0.22-0.35].

A Mantel Test using Pearson's product-moment was used to assess the intersubject similarity in cortico-amygdala RDMs estimated across runs. A modest positive association was found in cortico-left-amygdala RDMs ($r = .23$, $p < .0001$) and cortico-right-amygdala RDMs ($r = .21$, $p < .0001$) across runs **(Table 3).** These associations were established by comparing the observed correlation coefficients to the bootstrapped null distribution for the sample.

3.3 Relationship between ELA and cortico-amygdala FC

IS-RSA was used to test whether individual differences in ELA was associated with individual differences in cortico-amygdala FC, and if these results would replicate across runs after controlling for sex. Consistent with **Hypothesis 1 and 2** (**Table 4**), there was a positive association in ELA and cortico-(left) amygdala connectivity in the first (*rho* = .013) and second runs (*rho* = .011; **Figure 4a**). Likewise, a significant positive association was found between ELA and cortico-

(right) amygdala connectivity across runs (Run 1: *rho* = .011; Run 2: *rho* = .012; **Figure 4b**). All observed effects were significant at the $p < .0001$ level. The observed *rho* values in both the first and second runs were compared against their corresponding bootstrapped null distributions, confirming that the positive associations between ELA and cortico-amygdala FC were not due to random chance but reflected meaningful relationships.

Table 1. Demographic Information

Characteristic	*N* = 745[1]
Child sex	
Male	350 (47%)
Female	394 (53%)
Child age	9.5 (0.51)
Parent age	40.4 (6.64)
Parent education*	16.9 (2.39)
Household income*	74.4 (22.97)
Race	
White	537 (72%)
Black	119 (16%)
Native American	13 (1.7%)
Asian or Pacific Islander	36 (4.8%)
Other	38 (5.1%)
Ethnicity	
Hispanic	126 (17%)
Non-Hispanic	610 (82%)
Unknown	9 (1.2%)

[1]n (%); Mean (*SD*)

* Income values are represented in thousands; education values are represented in years

Note: Missing values are omitted

Table 2. Pooled Estimates and Confidence Intervals for Total ELA Scores

Imputation[1]	*M*	*SD*	Median	Min	Max	*SE*
0*	105.22	29.04	99	46	238	1.06
1	106.73	29.88	100	55	239	1.09
2	106.81	29.85	100	55	239	1.09
3	106.75	29.84	100	55	239	1.09
4	106.77	29.83	100	55	239	1.09
5	106.78	29.87	100	55	238	1.09
Pooled	**106.77**	**29.85**				**1.09**

[1]Note: Pooled estimates for each imputation were calculated using Rubin's (1987) rules. * Original dataset

Table 3. Cross-run Comparison of Cortico-Amygdala RDMs

Region	*r*-value[1]	*p*-value	95% CI	
			Lower	Upper
Left Amygdala	.23	< .0001	.22	.24
Right Amygdala	.21	< .0001	.19	.22

[1]Note: Mantel's *r* was estimated using Pearson's product moment with 9,999 permutations

Table 4. IS-RSA Results: ELA and Cortico-Amygdala FC

Region	*r*-value[1]	*p*-value	95% CI	
			Lower	Upper
Left Amygdala				
Run 1	.013	< .0001	.008	.017
Run 2	.011	< .0001	.008	.015
Right Amygdala				
Run 1	.011	< .0001	.007	.016
Run 2	.012	< .0001	.008	.015

[1]Note: Mantel's r was estimated using Spearman's rho with 9,999 permutations. The pooled estimates are depicted in the table.

Figure 4. Mantel Test Results

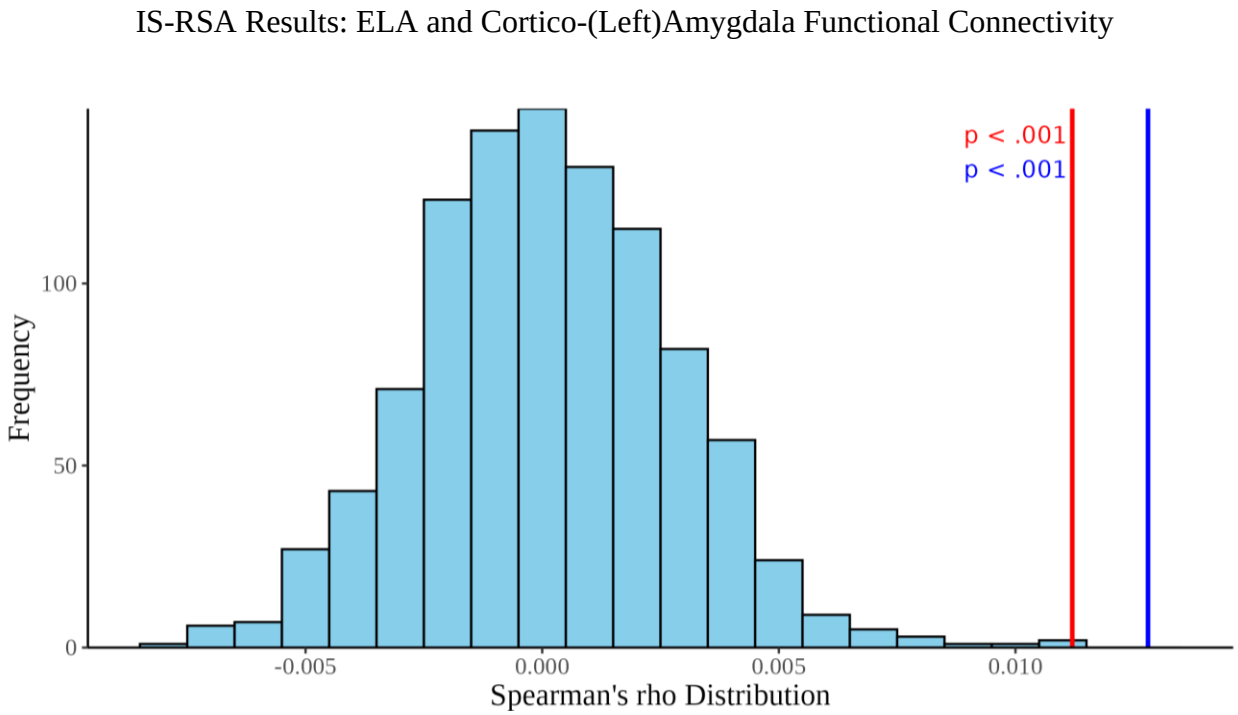


Figure 4a. The histogram represents the distribution of permuted statistics and the blue and red lines represent the observed statistic for the first and second rs-fMRI runs, respectivley. Functional connectivity values are seeded in the left amygdala. The 'vegan' package in R was used to bootstrap a smaller null distribution (n = 999) for representation purposes (Oksanen et al., 2024).

IS-RSA Results: ELA and Cortico-(Right)Amygdala Functional Connectivity

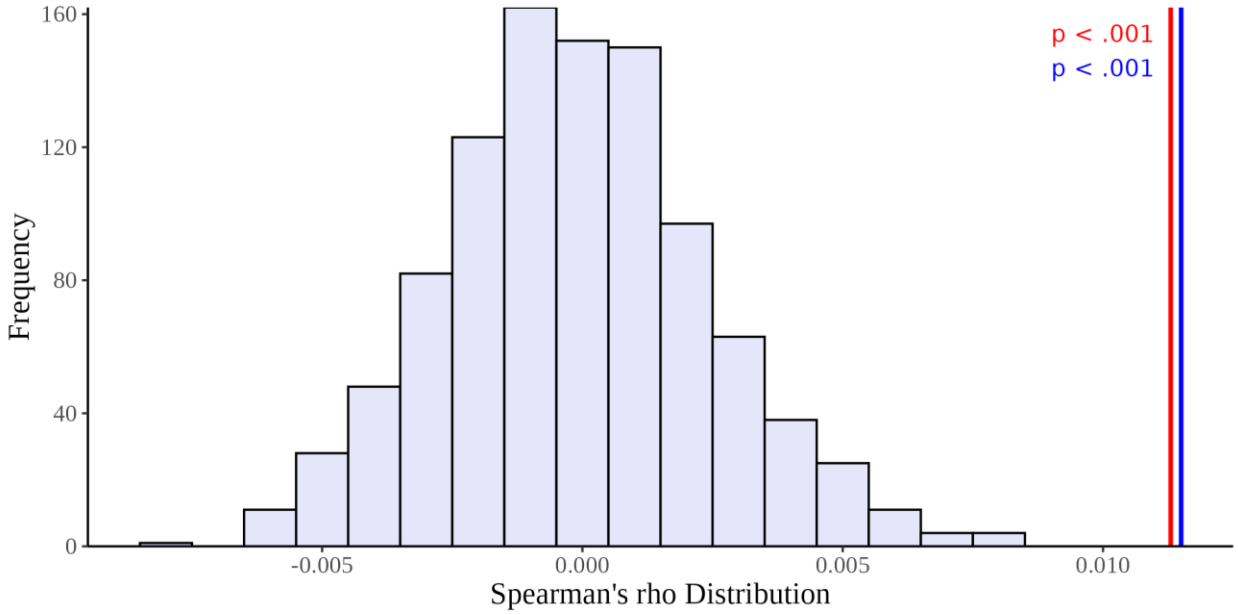


Figure 4b. The histogram represents the distribution of permuted statistics and the blue and red lines represent the observed statistic for the first and second rs-fMRI runs, respectivley. Functional connectivity values are seeded in the right amygdala. The ‘vegan’ package in R was used to bootstrap a smaller null distribution (n = 999) for representation purposes (Oksanen et al., 2024).

Chapter 4

4 Discussion

The current study used IS-RSA to assess the relationship between ELA and cortico-amygdala FC in 745 typically developing preadolescents. It was found that individual differences in ELA was positively associated with variability in whole brain cortico-amygdala FC. Moreover, the associations between ELA and cortico-amygdala FC generalized across resting-state conditions, despite the modest test-retest reliability in bilateral cortico-amygdala FC, and intersubject cortico-amygdala RDM across runs. Taken together, these findings provide preliminary evidence that ELA is associated with a common cortico-amygdala FC profile.

4.1 Individual differences in ELA relate to cortico-amygdala FC

The central research question was whether individual differences in ELA are associated with individual differences in cortico-amygdala FC. Consistent with **Hypothesis 1**, participant-wise variability in ELA exposure was associated with variation in resting-state cortico-amygdala FC. Participants who were dissimilar in their ELA experiences tended to be dissimilar in their cortico-amygdala FC patterns. Thus, the configuration of participants in ELA space mirrored the configuration of participants in brain connectivity space. Importantly, these associations were not driven by biological sex. Additionally, the narrow age range of the ABCD sample and the selection of high-quality fMRI datasets serve as additional safeguards against spurious individual differences across ELA and brain space.

This finding demonstrates the feasibility of IS-RSA in exploring multivariate associations in functional brain synchrony and psychological phenomena. IS-RSA has previously been used to explore the neural correlates of impulsivity, decision making, mentalizing ability, callous-unemotional characteristics, and affective temperaments (Z. Li et al., 2023; Mehta et al., 2023; Qiu et al., 2024; Rhoads et al., 2020; van Baar et al., 2019). This study extends the application of IS-RSA to the domain of ELA, contributing to a growing corpus of evidence-based multivariate methods for analyzing complex brain-behaviour relationships.

Connectivity between the cortex and bilateral amygdala are important brain circuits that are implicated in emotional processing and control. Although small, the association between ELA and cortico-amygdala FC dovetail with the broader developmental literature on the neural systems affected by adversity. The amygdala's involvement in threat detection and emotion regulation (Hariri et al., 2002, 2003), and its sensitivity to a range of exogenous influences is well documented (Gee, Gabard-Durnam, et al., 2013; Gee, Humphreys, et al., 2013; Herringa et al., 2016; Silvers, Lumian, et al., 2016). Amygdala FC has been shown to contribute to individual differences in emotion regulation (Berboth & Morawetz, 2021), experiences of emotional pain (Gandhi et al., 2020), and trait anxiety (Qin et al., 2014). Experiences of ELA, such as childhood neglect and maltreatment, have also been shown to alter amygdala function (Gale et al., 2004; Hariri et al., 2002; Hosseini-Kamkar et al., 2023) and FC with broader cortical networks (Cisler, 2017; Gee, Humphreys, et al., 2013; Wu et al., 2022).

The consensus across animal and human studies is that ELA contributes to premature maturation of cortico-amygdala FC and weaker cortico-amygdala FC in adults (Berboth & Morawetz, 2021; Colich, Rosen, et al., 2020; Kraaijenvanger et al., 2023; Liang et al., 2014). This may emerge as adaptive strategy, potentially offering proximal protection against immediate stressors in childhood at the cost of long-term mental and physical health outcomes (Belsky, 2019; Ellis et al., 2022; J. G. Miller et al., 2020; Parker et al., 2019). This view dovetails with evolutionary perspectives of accelerated development (Belsky, 2019; Ellis et al., 2009), and empirical evidence demonstrating that ELA instantiates an adult-like pattern of cortico-amygdala FC, which is associated with precocious menarche, early sexual debut, accelerated pubertal tempo, and cellular aging (Colich, Platt, et al., 2020; Colich, Rosen, et al., 2020; Petrican & Fornito, 2023; Prosperi & Chiarelli, 2023; Webster et al., 2014). However, this trend has not been consistently observed when ELA is separated into dimensions of threat or deprivation (Colich, Rosen, et al., 2020; McLaughlin et al., 2014).

While common trends in weakened cortico-amygdala FC are evident in ELA, it remains unclear whether personal histories of ELA contribute to individual differences in brain FC and if these differences lead to distinct behavioral adaptations. Indeed, finding multivariate intersubject variability in ELA and cortico-amygdala FC complements previous work, but demonstrates that individual experiences may contribute to disparate patterns of FC, which may not be fully manifest

using univariate group-level analyses. In line with a topological approach, these findings indicate that the ELA as a whole may have representational properties that are more meaningful than individual events or their purported dimensions.

One possible interpretation for why previous studies find an overall association between ELA and brain connectivity, but not individual subtypes, on cortico-amygdala FC is that efforts to distill experiences into constituent dimensions overlook the phenomenological complexity and interconnectedness of human experiences. For example, a child separated from their caregiver may initially perceive their loss as a threating experience, leading to emotion dysregulation and heightened vulnerability to stress (Hertzman, 2013). Over time, the absence of the caregiver leads to deprivation of expected stimuli like nurturance, warmth, and social support (McLaughlin et al., 2014). This scenario illustrates how a single event can "get under the skin" in multiple ways (Pollak & Smith, 2021). The lack of convergence may stem from individual variability that cannot be systematically controlled for (Pollak & Smith, 2021). A possible solution may be to relinquish classifications that carve nature at its joints – opting instead to embrace and leverage heterogeneity rather than discrete dimensions (Smith & Pollak, 2021).

The evidence supporting **Hypothesis 1** carries implications for advancing falsifiable hypotheses based on the topological approach, which hitherto has not been empirically explored (Pollak & Smith, 2021; Smith & Pollak, 2021). Here, a topological approach was used to compare the overall representational properties of ELA with whole-brain cortico-amygdala FC in multivariate spaces. The theory intuits that ELA is dynamic and individually constructed through numerous gene-environment interactions (Hertzman, 1999, 2013) that resist simple classification (Pollak & Smith, 2021; Smith & Pollak, 2021). Thus, the overall representation of ELA holds greater significance than its individual components.

The ELA literature remains at an impasse with respect to the quantification and measurement of ELA, which has generated debate and heterogeneity across research studies (McLaughlin et al., 2023). Here, a model-free approach was used to bypass the strict priors typically imposed by predefined models, allowing for a more flexible and open exploration of the data (E. S. Finn et al., 2020). Intersubject RDMs for ELA and brain FC were estimated from a variety of measures, and their comparison was made possible using a second-order isomorphism.

This technique provides a means to abstract pairwise representations of ELA and brain FC away from the idiosyncrasies inherent to the measurement of each (E. S. Finn et al., 2020; Kriegeskorte et al., 2008). These findings suggest that ELAs may interact in complex ways to shape how different brain circuits communicate, which can potentially influence emotion regulation and mental health outcomes; however further research is needed to clarify the direction of the association.

4.2 Individual differences in ELA generalize across resting-state scans

In line with **Hypothesis 2**, it was found that intersubject variability in ELA was associated with intersubject variability in cortico-amygdala FC across resting-state acquisitions. This association was observed bilaterally and across multiple imputed ELA datasets. Indeed, cross-validation in rs-fMRI is a recommended but overlooked step in computational neuroscience (Popal et al., 2019; Walther et al., 2016) which is important for establishing reproducibility and minimizing Type I error bias. The replicability of the findings across scans demonstrates that the observed relationship between ELA and brain connectivity are more likely to represent a meaningful, true effect, rather than a chance occurrence.

Both ICC and Mantel Test were used to establish an upper bound for the observed relationship between ELA and FC (Noble et al., 2021). Specifically, the intersubject correlation between ELA and FC was deemed valid only if it is less than the overall ICC and the intersubject correlation between RDMs obtained in runs 1 and 2. The results revealed a small yet significant correlation between bilateral cortico-amygdala RDMs across runs. Participant pairs maintained relatively stable dissimilarity patterns across consecutive runs, suggesting that the measurement was reproducible over short intervals.

ICC was estimated for individuals and averaged across the entire sample. The results indicated modest evidence of test-retest reliability, which is commensurate with almost a decade of evidence showing low test-retest reliability in FC across rs-fMRI datasets (Noble et al., 2019). Moreover, rs-fMRI has been shown to have low reliability within and across sessions (Honey et al., 2009). There are several possible explanations for this. First, research has identified the existence of up to twelve dynamic resting FC states, which exhibit age-related changes across

development (Hutchison & Morton, 2015). Depending on the specific FC measure, a scan length between 7 and 10 minutes is required to achieve an 80% reduction in these temporal dynamics (Tomasi et al., 2017). In the ABCD study, the duration of resting-state scans was 5 minutes which may not have been enough time to establish temporal stability. Taken together, the inherent variability in functional states and the low scan time may have contributed to the observed low test-retest reliability in FC across rs-fMRI datasets.

While reliability is a desirable psychometric property, efforts to promote it may inadvertently compromise validity (Noble et al., 2021). For example, denoising procedures such as motion correction, physiological noise reduction, and temporal filtering, have been shown to increase validity but reduce reliability. This is because noise regressors contain stereotyped signals (e.g., heartbeat, breathing) that are highly reproducible but introduce non-neural variability, thereby compromising validity (Noble et al., 2017, 2019). Therefore, reliability and validity should be considered as separate, but complimentary metrics for establishing the robustness of fMRI findings.

Importantly, the observed test-retest reliability between runs serves as an upper bound for the possible correlations in ELA and cortico-amygdala FC (Noble et al., 2021). Indeed, all correlations found for ELA and cortico-amygdala FC were below the test-retest threshold, and the overall ICC was larger than the correlation between RDMs. Thus, while there was low consistency across runs, the relationship between ELA and cortico-amygdala FC preserves its evidential value. This implies that individual variation in ELA is linked to unique signatures of cortico-amygdala FC, irrespective of other possible sources of variance such as mind-wandering, head motion, and attention.

Finally, an important feature of this study was the utilization of multiple imputation methods to address missingness in self-report data (Rubin, 1987). This multivariate approach uses available subject data to predict multiple plausible values for missing items, thereby mitigating potential biases and inaccuracies that can arise from incomplete datasets. This approach not only enhances the robustness and generalizability of the findings, but it effectively preserves statistical power that would otherwise be lost from methods like listwise deletion.

4.3 Limitations

Several limitations of this thesis should be noted. First, this analysis was both retrospective and cross-sectional, which limits the ability to draw causal inferences about the relationship between ELA and FC. For example, longitudinal studies demonstrate that cortico-amygdala FC exhibits significant age-related change across development, which cannot be addressed in a cross-sectional analysis. Future work should prioritize longitudinal and prospective measures to capture continuities and discontinuities associated with ELA (Gee, Gabard-Durnam, et al., 2013; Gee, Humphreys, et al., 2013; Hariri et al., 2003; Herringa et al., 2016; J. G. Miller et al., 2020; Silvers, Lumian, et al., 2016). It should be noted that prospective and retrospective measures exhibit low correspondence (see review by Baldwin et al., 2019), and there is evidence that retrospective reports may have stronger associations with mental health disorders (Patten et al., 2015). Therefore, future work should consider the integration of both measurement types (Kraaijenvanger et al., 2023; Patten et al., 2015).

The associations found in this study lack temporal and spatial specificity. For instance, each element of the intersubject FC RDM was derived from the correlation between one participant's FC profile—comprising the correlation between their average amygdala timeseries and 47 cortical ROIs—and another participant's unique FC profile. This method makes it impossible to localize the contribution of distinct ROIs in the observed relationship between ELA and cortico-amygdala FC. Additionally, time courses were averaged across voxels in each ROI, which obscures the finer-grained variability that may occur within each region. Future work should exploit a voxel-wise approach to enhance the spatial specificity of FC measures.

Furthermore, resting-state paradigms make it challenging to associate spontaneous fluctuations in brain synchrony with specific time-locked events. The observed associations in this study reflect general synchrony rather than specific interactions that occur in response to particular stimuli. Naturalistic paradigms, which leverage shared, time-locked stimuli, may mitigate these issues by making intersubject idiosyncrasies more interpretable (Chen et al., 2020; E. S. Finn et al., 2020; Hasson et al., 2008; Nastase et al., 2019).

ELA was broadly defined to encompass several risk domains across self and informant measures (Brieant et al., 2023; Kraaijenvanger et al., 2023; Smith & Pollak, 2021). Unlike cumulative risk ("lumping") models that aggregate risk factors or DMAP ("splitting") models that define dimensions of adversity, the topological approach recognizes the complexity and nuance of

individual experiences that cut across multiple domains (Pollak & Smith, 2021). While multivariate patterns of ELA were leveraged in this analysis to create the intersubject RDM, pairwise representations were effectively a comparison of one subject's cumulative ELA score with that of another subject, which deviates from a topological approach.

Finally, while a form of generalization, the within-subject cross-validation procedure was performed on resting-state acquisitions acquired consecutively. Therefore, the findings may not fully capture the variability and potential fluctuations in brain connectivity that could occur over longer intervals. Future studies should consider incorporating resting-state data collected over extended periods to better understand the stability and variability of cortico-amygdala FC as it relates to ELA. More advanced cross-validation techniques, such as k-fold cross validation, should also be considered to enhance the robustness and generalizability of the findings.

4.4 Conclusion

This study is the first to leverage IS-RSA to explore multivariate associations in whole brain cortico-amygdala FC with respect to ELA in a large preadolescent sample. In addition, this study used multiple imputation methods to address missingness in self-report data and cross-validation procedures to establish reproducibility across rs-fMRI acquisitions. By harnessing large-scale data and computational methods, it was found that subject-wise variability in ELA corresponded to subject-wise variability in cortico-amygdala FC, and that these associations demonstrated cross-sectional validity.

There are several implications of this work. By understanding a subject's ELA profile, it may be possible to predict certain aspects of their brain connectivity. This could be useful in identifying individuals who might be at higher risk for emotional and psychological issues. Furthermore, this study paves the way for future research and intervention strategies aimed at promoting resilience and positive developmental outcomes. Future research should consider using machine learning to identify how individual differences in ELA and brain connectivity may shape different developmental trajectories and emotional, mental, and behavioural outcomes. Taken together, these findings support cortico-amygdala FC as a potential biomarker in neuroimaging research and highlights the importance of multivariate methods for studying individual differences in ELA.

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Appendices

Appendix A. Yeo-7 Network Parcellation with Label and Component Names

Network	Label	Component
Dorsal attention		
Left	7Networks_LH_DorsAttn_Post	Posterior
	7Networks_LH_DorsAttn_FEF	Frontal eye fields
	7Networks_LH_DorsAttn_PrCv	Precentral ventral
Right	7Networks_RH_DorsAttn_Post	Posterior
	7Networks_RH_DorsAttn_FEF	Frontal eye fields
	7Networks_RH_DorsAttn_PrCv	Precentral ventral
Ventral attention		
Left	7Networks_LH_SalVentAttn_ParOper	Parietal operculum
	7Networks_LH_SalVentAttn_TempOcc	Temporal occipital
	7Networks_LH_SalVentAttn_FrOperIns	Frontal operculum insula
	7Networks_LH_SalVentAttn_PFCl	Lateral PFC
	7Networks_LH_SalVentAttn_Med	Medial
Right	7Networks_RH_SalVentAttn_TempOccPar	Temporal occipital parietal
	7Networks_RH_SalVentAttn_PrC	Precentral
	7Networks_RH_SalVentAttn_FrOperIns	Frontal operculum insula
	7Networks_RH_SalVentAttn_PFCv	Ventral PFC
	7Networks_RH_SalVentAttn_PFCl	Lateral PFC
	7Networks_RH_SalVentAttn_Med	Medial
Limbic		
Left	7Networks_LH_Limbic_OFC	Orbital frontal cortex
	7Networks_LH_Limbic_TempPole	Temporal pole
Right	7Networks_RH_Limbic_OFC	Orbital frontal cortex
	7Networks_RH_Limbic_TempPole	Temporal pole
Frontoparietal		
Left	7Networks_LH_Cont_Par	Parietal
	7Networks_LH_Cont_Temp	Temporal
	7Networks_LH_Cont_PFCd	Dorsal PFC
	7Networks_LH_Cont_PFCl	Lateral PFC
	7Networks_LH_Cont_OFC	Orbital frontal cortex
	7Networks_LH_Cont_PFCv	Ventral PFC
	7Networks_LH_Cont_pCun	Precuneus
	7Networks_LH_Cont_Cing	Cingulate
	7Networks_LH_Cont_PFCmp	Medial posterior PFC
Right	7Networks_RH_Cont_Par	Parietal
	7Networks_RH_Cont_Temp	Temporal
	7Networks_RH_Cont_PFCv	Ventral PFC
	7Networks_RH_Cont_PFCl	Lateral PFC
	7Networks_RH_Cont_pCun	Precuneus
	7Networks_RH_Cont_Cing	Cingulate
	7Networks_RH_Cont_PFCmp	Medial posterior PFC
Default		
Left	7Networks_LH_Default_Par	Parietal
	7Networks_LH_Default_Temp	Temporal
	7Networks_LH_Default_PFC	PFC
	7Networks_LH_Default_pCunPCC	Precuneus posterior cingulate cortex
	7Networks_LH_Default_PHC	Parahippocampal cortex
Right	7Networks_RH_Default_Par	Parietal
	7Networks_RH_Default_Temp	Temporal
	7Networks_RH_Default_PFCv	Ventral PFC

Appendix B. Parent Survey Items

ABCD Parent Adult Self Report Raw Scores Aseba (ASR)	
asr_q01_p	I am too forgetful
asr_q02_p	I make good use of my opportunities*
asr_q03_p	I argue a lot
asr_q04_p	I work up to my ability*
asr_q05_p	I blame others for my problems
asr_q06_p	I use drugs (other than alcohol, nicotine) for nonmedical purposes
asr_q07_p	I brag
asr_q08_p	I have trouble concentrating or paying attention for long
asr_q09_p	I can't get my mind off certain thoughts
asr_q10_p	I have trouble sitting still
asr_q11_p	I am too dependent on others
asr_q12_p	I feel lonely
asr_q13_p	I feel confused or in a fog
asr_q14_p	I cry a lot
asr_q15_p	I am pretty honest*
asr_q16_p	I am mean to others
asr_q17_p	I daydream a lot
asr_q18_p	I deliberately try to hurt or kill myself
asr_q19_p	I try to get a lot of attention
asr_q20_p	I damage or destroy my things
asr_q21_p	I damage or destroy things belonging to others
asr_q22_p	I worry about my future
asr_q23_p	I break rules at work or elsewhere
asr_q24_p	I don't eat as well as I should
asr_q25_p	I don't get along with other people
asr_q26_p	I don't feel guilty after doing something I shouldn't
asr_q27_p	I am jealous of others
asr_q28_p	I get along badly with my family
asr_q29_p	I am afraid of certain animals, situations, or places
asr_q30_p	My relations with the opposite sex are poor
asr_q31_p	I am afraid I might think or do something bad
asr_q32_p	I feel that I have to be perfect
asr_q33_p	I feel that no one loves me
asr_q34_p	I feel that others are out to get me
asr_q35_p	I feel worthless and inferior
asr_q36_p	I accidentally get hurt a lot, accident-prone
asr_q37_p	I get in many fights
asr_q38_p	My relations with neighbors are poor
asr_q39_p	I hang around people who get into trouble
asr_q40_p	I hear sounds and voices that other people think aren't there
asr_q41_p	I am impulsive or act without thinking

asr_q42_p	I would rather be alone than with others
asr_q43_p	I lie or cheat
asr_q44_p	I feel overwhelmed by my responsibilities
asr_q45_p	I am nervous or tense
asr_q46_p	Parts of my body twitch or make nervous movements
asr_q47_p	I lack self-confidence
asr_q48_p	I am not liked by others
asr_q49_p	I can do certain things better than other people
asr_q50_p	I am too fearful or anxious
asr_q51_p	I feel dizzy or lightheaded
asr_q52_p	I feel too guilty
asr_q53_p	I have trouble planning for the future
asr_q54_p	I feel tired without good reason
asr_q55_p	My moods swing between elation and depression
asr_q56a_p	Aches or pains (not stomach or headaches)
asr_q56b_p	Headaches
asr_q56c_p	Nausea, feel sick
asr_q56d_p	Problems with eyes (not if corrected by glasses)
asr_q56e_p	Rashes or other skin problems
asr_q56f_p	Stomachaches
asr_q56g_p	Vomiting, throwing up
asr_q56h_p	Heart Pounding or racing
asr_q56i_p	Numbness or tingling in body parts
asr_q57_p	I physically attack people
asr_q58_p	I pick my skin or other parts of my body
asr_q59_p	I fail to finish things I should do
asr_q60_p	There is very little I enjoy
asr_q61_p	My work performance is poor
asr_q62_p	I am poorly coordinated or clumsy
asr_q63_p	I would rather be with older people than with people of my own age
asr_q64_p	I have trouble setting priorities
asr_q65_p	I refuse to talk
asr_q66_p	I repeat certain acts over and over
asr_q67_p	I have trouble making or keeping friends
asr_q68_p	I scream or yell a lot
asr_q69_p	I am secretive or keep things to myself
asr_q70_p	I see things that other people think aren’t there
asr_q71_p	I am self-conscious or easily embarrassed
asr_q72_p	I worry about my family
asr_q73_p	I meet my responsibilities to my family*
asr_q74_p	I show off or clown
asr_q75_p	I am too shy or timid
asr_q76_p	My behavior is irresponsible
asr_q77_p	I sleep more than most other people during day and/or night

asr_q78_p	I have trouble making decisions
asr_q79_p	I have a speech problem
asr_q80_p	I stand up for my rights*
asr_q81_p	My behavior is very changeable
asr_q82_p	I steal
asr_q83_p	I am easily bored
asr_q84_p	I do things that other people think are strange
asr_q85_p	I have thoughts that other people would think are strange
asr_q86_p	I am stubborn, sullen, or irritable
asr_q87_p	My moods or feeling change suddenly
asr_q88_p	I enjoy being with people*
asr_q89_p	I rush into things without considering the risks
asr_q90_p	I drink too much alcohol or get drunk
asr_q91_p	I think about killing myself
asr_q92_p	I do things that may cause me trouble with the law
asr_q93_p	I talk too much
asr_q94_p	I tease others a lot
asr_q95_p	I have a hot temper
asr_q96_p	I think about sex too much
asr_q97_p	I threaten to hurt people
asr_q98_p	I like to help others*
asr_q99_p	I dislike staying in one place for very long
asr_q100_p	I have trouble sleeping
asr_q101_p	I stay away from my job even when I'm not sick or not on vacation
asr_q102_p	I don't have much energy
asr_q103_p	I am unhappy, sad, or depressed
asr_q104_p	I am louder than others
asr_q105_p	People think I am disorganized
asr_q106_p	I try to be fair to others*
asr_q107_p	I feel that I can't succeed
asr_q108_p	I tend to lose things
asr_q109_p	I like to try new things*
asr_q110_p	I wish I were of the opposite sex
asr_q111_p	I keep from getting involved with others
asr_q112_p	I worry a lot
asr_q113_p	I worry about my relations with the opposite sex
asr_q114_p	I fail to pay my debts or meet other financial responsibilities
asr_q115_p	I feel restless or fidgety
asr_q116_p	I get upset too easily
asr_q117_p	I have trouble managing my money or credit card
asr_q118_p	I am too impatient
asr_q119_p	I am not good at details
asr_q120_p	I drive too fast
asr_q121_p	I tend to be late for appointments

asr_q122_p	I have trouble keeping a job
asr_q123_p	I am a happy person*
asr_q124_p	In the past 6 months, about how many times per day did you use tobacco (including smokeless tobacco)?
asr_q125_p	In the past 6 months, on how many days were you drunk?
asr_q126_p	In the past 6 months, on how many days did you use drugs for nonmedical purposes (including marijuana, cocaine, and other drugs, except alcohol and nicotine)?
ABCD Parent Child Behavior Checklist Raw Scores Aseba (CBCL)	
cbcl_q25_p	Doesn't get along with other kids
cbcl_q37_p	Gets in many fights
cbcl_q38_p	Gets teased a lot
cbcl_q39_p	Hangs around with others who get in trouble
cbcl_q48_p	Not liked by other kids
ABCD Parent Demographics Survey	
demo_fam_exp1_v2	In the past 12 months, has there been a time when you and your immediate family experienced any of the following: Needed food but couldn't afford to buy it or couldn't afford to go out to get it?
demo_fam_exp2_v2	Were without telephone service because you could not afford it?
demo_fam_exp3_v2	Didn't pay the full amount of the rent or mortgage because you could not afford it?
demo_fam_exp4_v2	Were evicted from your home for not paying the rent or mortgage?
demo_fam_exp5_v2	Had services turned off by the gas or electric company, or the oil company wouldn't deliver oil because payments were not made?
demo_fam_exp6_v2	Had someone who needed to see a doctor or go to the hospital but didn't go because you could not afford it?
demo_fam_exp7_v2	Had someone who needed a dentist but couldn't go because you could not afford it?
demo_prnt_marital_v2	Are you now married, widowed, divorced, separated, never married or living with a partner?
ABCD Parent Family Environment Scale-Family Conflict Subscale Modified from PhenX (FES)	
fam_enviro1_p	We fight a lot in our family
fam_enviro2r_p	Family members rarely become openly angry*
fam_enviro3_p	Family members sometimes get so angry they throw things.
fam_enviro4r_p	Family members hardly ever lose their tempers*
fam_enviro5_p	Family members often criticize each other.
fam_enviro6_p	Family members sometimes hit each other
fam_enviro7r_p	If there is a disagreement in our family, we try hard to smooth things over and keep the peace*
fam_enviro8_p	Family members often try to one-up or outdo each other.
fam_enviro9r_p	In our family, we believe you don't ever get anywhere by raising your voice*
ABCD Family History Assessment Part 2	
famhx_ss_fath_prob_alc_p	father alcohol problem
famhx_ss_fath_prob_dg_p	father drug use problem
famhx_ss_fath_prob_dprs_p	father depression problem

famhx_ss_fath_prob_hspd_p	father hospitalized due to emotional/mental problem
famhx_ss_fath_prob_ma_p	father mania problem
famhx_ss_fath_prob_nrv_p	father nerves/nervous breakdown problem
famhx_ss_fath_prob_prf_p	father been to a doctor or counselor due to emotional/mental problem
famhx_ss_fath_prob_scd_p	father attempted or committed suicide
famhx_ss_fath_prob_trb_p	father trouble holds job/fights/police problem
famhx_ss_fath_prob_vs_p	father visions of others spying/plotting problem
famhx_ss_moth_prob_alc_p	mother alcohol problem
famhx_ss_moth_prob_dg_p	mother drug use problem
famhx_ss_moth_prob_dprs_p	mother depression problem
famhx_ss_moth_prob_hspd_p	mother hospitalized due to emotional/mental problem
famhx_ss_moth_prob_ma_p	mother mania problem
famhx_ss_moth_prob_nrv_p	mother nerves/nervous breakdown problem
famhx_ss_moth_prob_prf_p	mother been to a doctor or counselor due to emotional/mental problem
famhx_ss_moth_prob_scd_p	mother attempted or committed suicide
famhx_ss_moth_prob_trb_p	mother trouble holds job/fights/police problem
famhx_ss_moth_prob_vs_p	mother visions of others spying/plotting problem
ABCD Parent Diagnostic Interview for DSM-5 (KSADS)	
kbi_p_c_best_friend	Does your child have a best friend?*
kbi_p_c_bully	Does your child have any problems with bullying at school or in your neighborhood?
kbi_p_c_gay_problems	Has this caused any problems for you/your child with your family or with kids at school?
kbi_p_c_reg_friend_group	Does your child have a regular group of kids he or she hangs out with at school or in your neighborhood?*
kbi_p_c_trans_problems	Has this caused any problems for you/your child with your family or with kids at school?
kbi_p_conflict	In general, how do you and your child get along?
ksads_cdr_473_p	In the past two weeks, how often did your child get into physical fights with someone?
ABCD Parent Diagnostic Interview for DSM-5 (KSADS) Traumatic Events	
ksads_ptsd_raw_754_p	A car accident in which your child or another person in the car was hurt bad enough to require medical attention
ksads_ptsd_raw_755_p	Another significant accident for which your child needed specialized and intensive medical treatment
ksads_ptsd_raw_756_p	Witnessed or caught in a fire that caused significant property damage or personal injury
ksads_ptsd_raw_757_p	Witnessed or caught in a natural disaster that caused significant property damage or personal injury
ksads_ptsd_raw_758_p	Witnessed or present during an act of terrorism (e.g., Boston marathon bombing)
ksads_ptsd_raw_759_p	Witnessed death or mass destruction in a war zone
ksads_ptsd_raw_760_p	Witnessed someone shot or stabbed in the community
ksads_ptsd_raw_761_p	Shot, stabbed, or beaten brutally by a non-family member
ksads_ptsd_raw_762_p	Shot, stabbed, or beaten brutally by a grown up in the home
ksads_ptsd_raw_763_p	Beaten to the point of having bruises by a grown up in the home

ksads_ptsd_raw_764_p	A non-family member threatened to kill your child
ksads_ptsd_raw_765_p	A family member threatened to kill your child
ksads_ptsd_raw_766_p	Witness the grownups in the home push, shove or hit one another
ksads_ptsd_raw_767_p	A grown up in the home touched your child in their privates, had your child touch their privates, or did other sexual things to your child
ksads_ptsd_raw_768_p	An adult outside your family touched your child in their privates, had your child touch their privates or did other sexual things to your child
ksads_ptsd_raw_769_p	A peer forced your child to do something sexually
ksads_ptsd_raw_770_p	Learned about the sudden unexpected death of a loved one
ABCD Medical History	
medhx_6a	Has she/he ever been to a doctor for any of these things … Broken Bones
medhx_6b	...Sprains
medhx_6c	...Cuts or Scrapes
medhx_6d	...Stitches
medhx_6e	...Other Serious Wounds
medhx_6f	...Falls
medhx_6g	...Burns
medhx_6h	...High Fever
medhx_6i	...Head Injury
medhx_6j	...Knocked Unconscious
medhx_6k	...Bruises
medhx_6l	…Asthma Attack
medhx_6m	...Broken Teeth
medhx_6n	...Animal Bite
medhx_6p	...Seizure
medhx_6q	...Accidental Poisoning
medhx_6s	...Wound from knife or any other weapon
medhx_6t	...Other
ABCD Parent Neighborhood Safety/Crime Survey Modified from PhenX (NSC)	
neighborhood1r_p	I feel safe walking in my neighborhood, day or night*
neighborhood2r_p	Violence is not a problem in my neighborhood*
neighborhood3r_p	My neighborhood is safe from crime*

* Reverse coded

Note: Variables can be found at https://data-dict.abcdstudy.org/

Appendix C. Youth Survey Items

ABCD Youth Neighborhood Safety/Crime Survey Modified from PhenX (NSC)	
neighborhood_crime_y	My neighborhood is safe from crime.
Parental Monitoring Survey	
parent_monitor_q1_y	How often do your parents/guardians know where you are?*
parent_monitor_q2_y	How often do your parents know who you are with when you are not at school and away from home?*
parent_monitor_q3_y	If you are at home when your parents or guardians are not, how often do you know how to get in touch with them?*
parent_monitor_q4_y	How often do you talk to your parent or guardian about your plans for the coming day, such as your plans about what will happen at school or what you are going to do with friends?*
parent_monitor_q5_y	In an average week, how many times do you and your parents/guardians, eat dinner together?*
ABCD School Risk and Protective Factors Survey	
school_2_y	In my school, students have lots of chances to help decide things like class activities and rules*
school_3_y	I get along with my teachers*
school_4_y	My teacher(s) notices when I am doing a good job and lets me know about it*
school_5_y	There are lots of chances for students in my school to get involved in sports, clubs, or other school activities outside of class*
school_6_y	I feel safe at my school*
school_7_y	The school lets my parents know when I have done something well*
school_8_y	I like school because I do well in class*
school_9_y	I feel I'm just as smart as other kids my age*
school_10_y	There are lots of chances to be part of class discussions or activities*
school_12_y	In general, I like school a lot*
ABCD Children's Report of Parental Behavioral Inventory	
crpbi_parent1_y	First caregiver. Makes me feel better after talking over my worries with him/her*
crpbi_parent2_y	First caregiver. Smiles at me very often*
crpbi_parent3_y	First caregiver. Is able to make me feel better when I am upset*
crpbi_parent4_y	First caregiver. Believes in showing his/her love for me*
crpbi_parent5_y	First caregiver. Is easy to talk to*
crpbi_caregiver12_y	Makes me feel better after talking over my worries with them*
crpbi_caregiver13_y	Second caregiver. Smiles at me very often*
crpbi_caregiver14_y	Second caregiver. Is able to make me feel better when I am upset*
crpbi_caregiver15_y	Second caregiver. Believes in showing their love for me*
crpbi_caregiver16_y	Second caregiver. Is easy to talk to*
ABCD Youth Family Environment Scale-Family Conflict Subscale Modified from PhenX	
fes_youth_q1	We fight a lot in our family.
fes_youth_q2	Family members rarely become openly angry*
fes_youth_q3	Family members sometimes get so angry they throw things.
fes_youth_q4	Family members hardly ever lose their tempers*
fes_youth_q5	Family members often criticize each other.

fes_youth_q6	Family members sometimes hit each other.
fes_youth_q7	If there's a disagreement in our family, we try hard to smooth things over and keep the peace*
fes_youth_q8	Family members often try to one-up or outdo each other.
fes_youth_q9	In our family, we believe you don't ever get anywhere by raising your voice*
ABCD Youth Diagnostic Interview for DSM-5 Background Items 5 (KSADS-5)	
kbi_y_sex_orient_probs	Has this caused any problems for you with your family or with kids at school?
kbi_y_trans_prob	Has this caused any problems for you with your family or with kids at school?
ksads_bully_raw_26	Do you have any problems with bullying at school or in your neighborhood?

* Reverse coded

Note: Variables can be found at https://data-dict.abcdstudy.org/

Curriculum Vitae

Amira Hmidan

Education

2013-18	St. Francis Xavier University, Antigonish, Nova Scotia, Canada B.A. (Honours) in Psychology
2020-22	Western University, London, Ontario, Canada M.A. Counselling Psychology
2022-24	Western University, London, Ontario, Canada MSc. (Candidate) Clinical Science & Psychopathology

Honours/Awards

2024-27	Natural Sciences and Engineering Research Council (NSERC) Canada Graduate Scholarship - Doctoral Award, $120,000
2024	Ralph S. Devereux Award in Psychology, Western University, $1,800
2022	W.A. Townshend Gold Medal in Education
2021-22	NSERC Canada Graduate Scholarship- Masters Award, Western University, $17,500
2021, 22, 23	Ontario Graduate Scholarship, $15,000

Work Experience

2022-24	Teaching Assistant**,** Department of Psychology, Western University
2020-24	Graduate Student Researcher, Faculty of Education, Western University
2022-23	Temporary Psychometrist, Thames Valley District School Board

Publications

1. **Hmidan, A.,** Seguin, D., & Duerden, E. G. (2023). Media screen time use and mental health in school-aged children during the pandemic. *BMC Psychology*, *11*(1), 202. https://doi.org/10.1186/s40359-023-01240-0
2. Mckee, K., **Hmidan, A.,** Crocker, C., Lam, R., Meyer, J., Crockford, D., Trépanier, A., Aitchison, K., & Tibbo, P. (2021). Potential therapeutic benefits of cannabinoid products in psychiatric disorders: a systematic review and meta-analysis of randomized controlled trials. *Journal of Psychiatric Research*, *140*, 267-281. https://doi.org/10.1016/j.jpsychires.2021.05.044
3. **Hmidan, A.,** & Weaver, A. (2019). Sex dreams: Gender, erotophilia, and sociosexuality as predictors of dream content, valence, and frequency. *The Canadian Journal of Human Sexuality 28*(2), 177-189. https://doi.org/10.3138/cjhs.2019-0022

Poster presentations

1. Nandadasa, N., **Hmidan, A.,** & Lengyell, M. (2024). Teaching equity and cultural humility: A focus group analysis. A poster presentation given at the Society of Teaching and Learning in Higher Education (STLHE) Annual Conference, Niagara Falls, ON, Canada
2. **Hmidan, A.,** Nandadasa, N., & Lengyell, M. (2024). Teaching equity and cross-cultural humility. Oral presentation given at the Research on Teaching and Learning Symposium.

3. **Hmidan, A**., Seguin, D., Morton, B., & Duerden, E. (2021). The role of parent stress on children's screen time use and behavioural outcomes during the second wave of the pandemic. A poster presented at the Canadian Stress Research Summit, Toronto, ON, Canada
4. **Hmidan, A**., Seguin, D., Morton, J. B., & Duerden, G. E. (2021). Parent stress is associated with children's screen time use and behavioural outcomes during the second wave of the pandemic. Robert Macmillan Symposium in Education, London, ON, Canada
5. Mckee, K., **Hmidan, A.,** Crocker, C., Lam, R., Meyer, J., Crockford, D., Trépanier, A., Aitchison, K., & Tibbo, P. (2020). Potential Therapeutic Benefits of Cannabinoid Products in Mental Illness: A Systematic Review. Canadian Psychiatric Association
6. McKee, K., **Hmidan, A**., & Tibbo, P. (2019). Effectiveness of cannabinoid-based products for the treatment of mental health disorders in adulthood: A systematic review. Poster presented at Dalhousie Psychiatry Research Day, Halifax, N.S.
7. **Hmidan, A.,** & Weaver, A. (2018). Sex dreams: Gender, erotophilia, and sociosexuality as predictors of dream content, valence, and frequency. Poster presented at the Canadian Sex Research Forum, Toronto, ON