THE EFFECT OF TRAUMATIC STRESSFUL EVENTS ON SCHIZOTYPAL SYMPTOMS IN COMMUNITY-BASED US ADOLESCENTS

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A DISSERTATION

in

Nursing

Presented to the Faculties of the University of Pennsylvania

in

Partial Fulfillment of the Requirements for the

Degree of Doctor of Philosophy

2020

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DEDICATION

I dedicate my dissertation work to the memory of my dad who wanted his girl to “do things that can make you happy!”

I dedicate my dissertation work to my beloved mom for always being together with me through every high and low.

I also dedicate this dissertation to my many friends who have supported me throughout the doctoral program.

ACKNOWLEDGMENTS

Every moment in UPenn now becomes my cherish memory and will shine my future. I would like to acknowledge those who have helped me throughout my journey in UPenn.

I would like to express my sincere gratitude to my committee members who are more than generous with their expertise and precious time. A special thanks to Dr. Nancy Hodgson, my mentor and also the committee chairman, for her guidance and countless hours of reflecting, reading, encouraging, motivating through each stage of the process. Also, I am extremely grateful for Dr. Barbara Medoff-Cooper, for her strong dedication and continual support, advice, wisdom, and kind words that enabled me to push through this journey with confidence and feelings of accomplishment. I am also deeply grateful for Dr. Monica Calkins, for her wisdom and intelligence and commitment to academic excellence and reliable encouragement to consistently improve the quality of my research. I would like to thank my two readers: Dr. Peggy Compton and Dr. Sara Jacoby, for their insightful comments and encouragement, and also for the questions which incented me to widen my research from various perspectives.

I would like to thank Dr. Jianghong Liu, who started me out on my journey at Penn, for her intellectual contribution to this research.

I would like to thank my statistic advisors, Dr. Aryal Subashi and Professor Jesse Chittams at the School of Nursing's BECCA Lab; to thank my librarian, Dr. Sherry Morgan; to thank my research writing tutors, Professor Sheila Mayne at Penn ELP and

the professors at Marks Family Writing center, who provided incredible support for my dissertation work.

My sincere thanks go to Dr. Bridgette Brawner, Dr. Sarah Kagan, Dr. Amy Lisanti, who provided me an opportunity to join their research or teaching team and also provided support for my research. These precious experiences broaden my view of academia. My sincere thanks also go to all my professors who have taught me and provides constructive comments to me.

I am lucky to work with creative and passionate peers in the past three years. I would like to thank my peers, for the tremendous support they have provided for me, for the memorable time we were spending together in classes and in the DSO lounge, and for all the fun we have had during special days.

I would like to thank all my many relatives, friends, colleagues who have supported me throughout the doctoral program.

ABSTRACT

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There is undoubtedly a complex association between early life factors and schizotypal personality disorder (SPD) which represents as schizotypal symptoms in the adolescent population. To explore this relationship, this dissertation first starts with a systematic review of early life factors related to schizotypal symptoms. Twenty-four studies were identified following the PRISMA guideline. Three important clusters of early life factors found to be associated with schizotypal symptoms: prenatal and early postnatal factors, childhood trauma, and parental factors. Standardized measurement tools and well-designed longitudinal studies are needed to validate the associations between specific types or cumulative effects of early life factors and SPD. In addition, more research on the underlying mechanism connecting early life factors and SPD are needed.

Then, this dissertation utilized the Philadelphia Neurodevelopmental Cohort dataset to first examine the association between different types and cumulative traumatic stressful events (TSEs, the most studied early life factors) and schizotypal symptoms in longitudinal community-based US adolescents. More than half of the adolescents reported a childhood TSE. Significant effects were found for the specific TSE types on the three dimensions of schizotypal symptoms while controlling demographic and family history factors. However, no significant effects remained after further controlling for the symptomatic factors (i.e., psychosis spectrum symptoms, mood disorder, anxiety disorder, and behavior disorder). A dose-response effect of cumulative TSEs on

cognitive-perceptual symptoms was significant after further controlling for symptomatic factors. Finally, the mediation effects of executive function (EF) and social cognition (SC) were further explored in the association between cumulative TSEs and dimensional schizotypal symptoms. Only significant mediation effect of TSEs on cognitive-perceptual symptoms through executive function was found when adjusting for the demographic factors and family history factors. The dissertation findings call for more research to determine the roles of early life factors play in the development of SPD. It is important to consider confounds when examining associations between TSEs and schizotypal symptoms. Trauma-informed care to consider universal screenings of trauma in primary care may be particularly important. As executive function improvement program should be incorporated into interventions to reduce the burden of schizotypal symptoms in the adolescent population.

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CHAPTER ONE INTRODUCTION

Introduction

Schizotypal personality disorder (SPD), a chronic mental disorder manifested by significant discomfort in close relationships and cognitive distortions of behavior, affects about 4% of the US population (Pulay et al., 2009). Most individuals with SPD are characterized by three dimensions of schizotypal symptoms clusters: cognitive-perceptual symptoms, interpersonal symptoms, and disorganized symptoms (Venables & Raine, 2015). Although SPD is diagnosed in young adulthood, schizotypal symptoms have origins in adolescence, defined as the period between 10 and 24 years of age (Sawyer, Azzopardi, Wickremarathne, & Patton, 2018). Schizotypal symptoms in adolescence are associated with severe reductions in quality of life, significant disability and functional impairment and high rates of comorbidity with substance abuse disorder, mood disorder, anxiety, and psychotic and other personality disorders in adulthood (Brosey & Woodward, 2015; Cohen & Davis III, 2009; Korsgaard, Torgersen, Wentzel-Larsen, & Ulberg, 2016; Pulay et al., 2009).

To date, although the etiology of SPD is still unknown, there is a consistent agreement that SPD is a heritable condition, which arises from a complex combination of genetics and early life experiences (Caspi, Roberts, & Shiner, 2005; Morton et al., 2017). While genetic heritability of SPD has been estimated around 30% to 50% within families (Walter, Fernandez, Snelling, & Barkus, 2016), a large part of its variation has been attributed to environmental risk factors in early life, mainly including prenatal and postnatal factors, and traumatic stressful events. The early life of an individual has

several critical windows, including adolescence. Singular or multiple risk factors during the early life period are detrimental as the deficits can be severe and irreversible, leading to subsequent mental disorders (Krugers et al., 2017; Yam, Naninck, Schmidt, Lucassen, & Korosi, 2015). Thus, the identification of the specific early life factors that confer risk of SPD among adolescents should be regarded as a priority because some early life risk factors may be potentially amenable to early intervention or even prevention strategies. However, little is known about early life factors associated with the development of schizotypal symptoms, especially in adolescence.

Traumatic stressful events (TSEs) are the most studied early life factors in individuals with psychotic disorders and are also considered to be risk-modifying factors. Increased prevalence and long-term lingering effects of childhood TSEs are seen in individuals with schizotypal symptoms (Velikonja, Fisher, Mason, & Johnson, 2015). Generally, evidence supports the association between TSEs and schizotypal symptoms by a recent systematic review (Velikonja et al., 2015). However, the definition of childhood TSEs differed between studies due to the variance in the defined range of childhood and also little remains known about the association between specific subtypes of traumatic stressful events (such as assaultive events and non-assaultive events) and dimensions of schizotypal symptoms in a prospective perspective. In addition, few studies adjust for main confounding factors, such as sociodemographic factors, psychiatric family history, other early life factors and comorbid psychotic disorders when looking at trauma–schizotypy relationships.

Furthermore, in order to develop targets for preventive interventions, it is critical to identify mechanisms that underlie the strong link between TSEs and schizotypal symptoms as well as factors that buffer this link. The three-hit hypothesis (Barker, 2004) proposes that exposure to early life risk factors interacts with genetic factors to "prime" the brain, which leads to vulnerability as measured by changes in neuropsychological functioning; further stressors later in life may serve to convert the vulnerability into a mental disorder. A recent review paper suggests that exposure to childhood trauma is often associated with the poorer performance of executive function and deficits of social cognition in both individuals with a psychotic disorder and ultra-high risk for psychosis (Dauvermann & Donohoe, 2019). Research suggests potential mediation effects of neuropsychological function, especially executive function and social cognition, on the association of traumatic exposures and subsequent psychotic disorders (Buck, Healey, Gagen, Roberts, & Penn, 2016; MacKenzie et al., 2017). Thus, it is reasonable to propose that exposure to early life factors, especially traumatic stressful events, may have a significant detrimental effect on brain function reflected in executive dysfunction and social cognitive deficits in children, and thereby increase their risk for schizotypal symptoms.

Purpose of this dissertation

To fill the above-mentioned critical gaps, this dissertation starts with a systematic review of early life factors related to schizotypal symptoms and then explores the association between traumatic stressful events (the most studied early life factor) and schizotypal symptoms and its underlying mechanisms in a community-based sample of

US adolescents. With a better understanding of the association between childhood traumatic stressful events and schizotypal symptoms in adolescents, this dissertation provides an important foundation toward identifying early interventions for adolescents with schizotypal symptoms.

This dissertation aligns with the Research Domain Criteria (RDoC) (Insel et al., 2010), with its goal to understand the nature of mental health and illness in terms of varying degrees of dysfunctions in general psychological/biological systems. The anticipated findings will fill a critical gap in the literature related to the association between childhood traumatic stressful events and schizotypal symptoms in adolescents.

Background and significance

Characteristics and Consequences of Schizotypal Personality Disorder (SPD) in General Population and in Adolescents

Schizotypal personality disorder (SPD) first appeared in the American Psychiatric Association diagnostic nosology in 1980. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), SPD is defined as "a pervasive pattern of social and interpersonal deficits characterized by acute discomfort with and reduced capacity for close relationships, as well as by cognitive or perceptual distortions and eccentricities of behavior" (APA, 2013). These characteristics can be assessed in the general population using clinical interviews or psychometric self-report questionnaires, and have also been organized into positive and negative schizotypy (Dinn, Harris, Aycicegi, Greene, & Andover, 2002; Kwapil, Barrantes-Vidal, & Silvia, 2007) or three-dimensional symptoms (i.e. cognitive-perceptual symptoms, interpersonal symptoms, and disorganized

symptoms) (Ericson et al., 2009; Raine & Benishay, 1995). Positive schizotypy includes odd beliefs, unusual perceptual experiences, increased negative affect, and affective dysregulation, but without social disinterest or decreased positive affect, whereas negative schizotypy involves decreased positive affect and pleasure in daily life, and decreases in social contact and interest (Dinn et al., 2002; Kwapil et al., 2007). Cognitive-perceptual symptoms include ideas of reference, odd beliefs, unusual perceptual experience, and suspiciousness. Interpersonal symptoms include social anxiety and having no close friends. Disorganized symptoms include odd behavior and odd speech (Debbané & Barrantes-Vidal, 2015; Raine & Benishay, 1995). There is sufficient evidence to suggest that SPD is expressed along a continuum between high functioning within the general population to clinical cases of psychosis (Fonseca & Debbané, 2017; Van Os & Reininghaus, 2016). It is important to distinguish individuals with SPD from schizophrenia because their symptoms are quantitatively less severe than schizophrenia (Rosell, Futterman, McMaster, & Siever, 2014). While SPD displays symptoms similar to schizophrenia, most individuals with SPD do not transition to schizophrenia. Furthermore, SPD shares similar clinical features with anxiety disorder and borderline personality disorder such as discomfort in situations with unfamiliar people, and poor social relations (P. Cohen et al., 2008; Dickey et al., 2005; Giakoumaki et al., 2013).

SPD as a chronic neurodevelopmental disorder has lifetime prevalence in the general United States population estimated at approximately 4.0% (Pulay et al., 2009). The longitudinal features of SPD begin in childhood and adolescence, leading to severe reductions in quality of life and functional impairment in adulthood (Brosey &

Woodward, 2015; Cohen & Davis III, 2009). SPD also has shared clinical features with mood disorder, anxiety, and borderline personality disorders (Pulay et al., 2009). Other neurocognitive and behavioral outcomes in adolescents with SPD include developmental language delay (Nunn & Peters, 2001), motor dysfunction (Mittal, Tessner, Trottman, et al., 2007; Neumann & Walker, 2003), poor academic performance (Welham et al., 2010), and social difficulties (Cohen, Mohr, Ettinger, Chan, & Park, 2015; Mittal, Tessner, & Walker, 2007). Besides the above dysfunctions at the individual level, SPD is also associated with significant financial costs to the family, the healthcare system, social services and wider society (Knapp & Wong, 2020; Soeteman, Roijen, Verheul, & Busschbach, 2008). Consequently, it is important to identify amendable factors as early as possible that influence the onset of SPD.

Adolescence is a stressful period because adolescents are often experiencing physiologic and mental changes simultaneously. In this dissertation study, adolescence is defined as the period between 10 and 24 years of age, which aligns closely with contemporary patterns of adolescent growth and popular understanding of this life phase (Sawyer et al., 2018). SPD may first manifest in children and adolescents as attention problems, social anxiety, or interest in playing or working alone (APA, 2013). For example, in adolescents, bullying is considered a major stressful event which often heightens social anxiety and results in avoiding social interactions as much as possible, and consequently being labeled as “odd” or “eccentric.” While the dimensions of schizotypal symptoms may be present during adolescence, an SPD diagnosis can only be ascribed in early adulthood because adolescent personalities are considered not fully

developed until adulthood and the possible stigma associated with most psychiatric diagnoses may be detrimental to the adolescents. Given that diagnosis is not confirmed or treated until adulthood, the study of schizotypal symptom expressions in the adolescent population has a natural advantage as they are absent of the potential confounds of antipsychotic medication, hospitalization, chronicity of symptoms and length of illness. Preliminary evidence from the National Epidemiologic Survey on Alcohol and Related Conditions suggests that schizotypal symptoms prevalence rates in adolescents and young adults (18-29 years) are slightly higher than those in older age groups (above 30) (Pulay et al., 2009). Consequently, SPD risk remains under-identified and adolescents miss opportunities to successfully treat or moderate the impact of symptoms on the quality of their life at this critical developmental stage (Walsh, 1990).

Early Life Factors and Schizotypal Symptoms

Taking into account the early presentation of SPD and the likely benefits of early identification of symptoms of SPD, the research focus in SPD has shifted towards understanding SPD in the early developmental period. To date, little is known about the etiology of schizotypal symptoms as they are often treated as a by-product of research on early detection of psychosis (Debbané et al., 2015). The hypothesis suggests that schizotypal symptoms develop early in childhood, and their severity shaped through the interaction of inherited tendencies and environmental factors (Van Os, Kenis, & Rutten, 2010). SPD shares similar etiology to schizophrenia and therefore may share genetic vulnerability (Rado, 1953; Walter et al., 2016) while its expression has been argued to greatly depend on the environment, especially the early life experiences to which the

individual is exposed (Raine, 2006). The term "early life risk factors" describes a broad spectrum of adverse and stressful experiences (e.g., maltreatment, neglect, separation, parental loss, extreme poverty, domestic/community/school violence) during the first months of life, early and late childhood and adolescence that place an individual at risk for SPD, while the term has been recently extended by some authors to also include prenatal life events, such as parental age (Reynolds, Labad, Buss, Ghaemmaghami, & Räikkönen, 2013).

The literature also shows that genetic heritability of SPD is estimated to be around 30% to 50% within families (Rosell et al., 2014; Walter et al., 2016); this suggests a large part of the remaining variation has been attributed to environmental factors in early life. If these precursors in early life for the development of SPDs can be identified during adolescence, then treatment approaches aimed at early identification and prevention can be implemented. In addition, identification of early life risk factors for SPD can provide an opportunity to improve early detection and clinical outcomes of SPD through the development of targeted interventions and reduced chronicity and societal costs.

Research suggests strong links between prenatal factors and later mental health status; for example, Schwarze and colleagues (2013) explored prenatal factors on 100 patients with a DSM-IV diagnosis of another personality disorder, borderline personality disorder (BPD) with 100 matched controls. The results indicated that BPD patients were significantly more often exposed to adverse intrauterine conditions, such as tobacco exposure, maternal traumatic stress, familial conflicts, and partnership problems during pregnancy (Schwarze et al., 2013).

Parental behaviors, including neglect, and parent-child conflict, are also linked with adolescents' psychotic symptoms. A study examined differences in retrospectively reported parenting style in a group of referred adolescents with BPD features and healthy controls (Schuppert, Albers, Minderaa, Emmelkamp, & Nauta, 2012). The BPD group reported significantly less emotional warmth, more rejection and more overprotection from their mothers than the control group (Schuppert et al., 2012).

Traumatic stressful events and schizotypal symptoms

Traumatic stressful events related concepts

Exposure to trauma in early life has the potential to impact subsequent development across the life span. Several concepts are commonly used to study the exposure to trauma in early life, and include adverse childhood experiences, childhood trauma, stressors, and stressful events. The scope of these concepts varies depending on the measurement tool utilized.

The DSM-5 defines trauma as "exposure to actual or threatened death, serious injury or sexual violence" according to the American Psychological Association (2013, p. 271). Stressful events and stressors represent a broader category and can be associated with loss, work, relationships, one's environment, life transitions, medical or physical struggles, and perceived lack of achievement (APA, 2013). Researchers sometimes conflate the constructs of stressful and traumatic life events as traumatic stressful events (TSEs). TSEs in this dissertation cover an array of life time experiences which include a number of different types of adverse early life experiences, such as natural disasters or bad accidents; concern that someone close was hurt badly or killed; witnessing someone

getting killed, badly beaten, or die; seeing a dead body; and/or ever experiencing assault, including being attacked or badly beaten, threatened with a weapon; and/or sexually assaulted (Barzilay et al., 2019). Although exposure to TSEs confers risk of negative consequences regardless of the victim's age, TSEs exposure in adolescence is arguably more detrimental than later adulthood because of the risk of enduring changes during this sensitive period, when the brain is undergoing rapid development and differentiation. We will focus on TSEs in adolescence in the two data-based papers of this dissertation.

TSEs and schizotypal symptoms

Traumatic stressful events (TSEs) have been extensively investigated as major early life risk factors for the onset and course of psychosis (K. A. McLaughlin et al., 2012). According to the longitudinal study by Spauwen et al. (2006), TSEs increase the expression of psychotic symptoms in young people both high and low on psychosis (Spauwen, Krabbendam, Lieb, Wittchen, & Van Os, 2006). Steel and colleagues (2009) found that individuals who were categorized in the psychosis-prone group on the basis of their relatively high score on the schizotypal personality scale were more than six times more likely to have experienced physical abuse and four times more likely to have been sexually abused than those not in this group (Steel, Marzillier, Fearon, & Ruddle, 2009). TSEs are also found to be associated with schizotypal personality traits in a non-clinical sample (Kocsis-Bogár, Miklósi, & Forintos, 2013). However, few studies examine the association between specific subtypes of TSEs and dimensions of schizotypal symptoms in a prospective and longitudinal perspective, nor have most studies considered a dose-response effect of TSE in the adolescent population.

Furthermore, to distill the association between TSEs and schizotypal symptoms, several confounding variables should be taken into consideration. Depression is one such confounder; depressive symptoms are symptomatic factors associated with childhood trauma, especially emotional abuse and neglect, in schizophrenia (Şahin et al., 2013). Depression also overlaps with negative symptoms of schizophrenia (Chemerinski, Bowie, Anderson, & Harvey, 2008). In addition, one general population study in the United Kingdom showed that depression mediated the association between childhood sexual abuse and psychosis (Bebbington et al., 2011). Other possible symptomatic confounders include anxiety and substance use. Anxiety symptoms are also found to be associated with childhood trauma in patients with early psychosis (Duhig et al., 2015). And the National Epidemiologic Survey on Alcohol and Related Conditions study found that patients with SPD had higher rates of co-occurring substance use (Pulay et al., 2009), thus substance use can also represent as a symptomatic confounding variable.

Potential neuropsychological mechanisms which mediate the association between TSEs and schizotypal symptoms

People with schizotypal symptoms evidence disruptions in neurocognitive functioning (Stella G Giakoumaki, 2012, 2016). From a developmental perspective, exposure to traumatic events in early life, may impact neurological and cognitive development (De Bellis, 2001; Van der Kolk, 2005), and thereby leave adolescents vulnerable to develop schizotypal symptoms. Neurocognitive dysfunction may be considered as one possible neuropsychological mechanism linking TSEs and schizotypal symptoms. Specifically, executive functions (EFs) and social cognition are hypothesized to be affected by TSEs

exposure (Zou et al., 2013; Pine et al., 2005) and play a role in the development of schizotypal symptoms after TSEs exposure.

Emerging research has investigated the association between TSEs and cognitive impairments (Majer, Nater, Lin, Capuron, & Reeves, 2010), especially executive dysfunction (Zou et al., 2013). Executive dysfunction is defined as impairments in goal-directed behavior, including poor performance of cognitive flexibility, sustained attention, working memory, inhibitory control, and performance monitoring (Cornblath et al., 2019; Diamond, 2013). Research shows that exposure to childhood trauma is often associated with the poorer performance of executive function in healthy young adults (Lu et al., 2017) and individuals with ultra-high risk for psychosis (Üçok et al., 2015). It remains unclear to what extent TSEs affect cognitive ability that may, in turn, lead to psychosis, as there is also evidence to suggest that they are associated with impaired cognitive capacity in the general population.

In addition, exposure to traumatic environments interferes with the development of social cognition (SC) (Curtis & Cicchetti, 2011). SC is the ability to process social information, recognize expressions and emotions and interpret social situations (R. C. Gur & R. E. Gur, 2016). Children with the experience of TSEs appear more likely to develop an enhanced sensitivity to social cues that are reminiscent of the adults who abused them. Consequently, individuals who have been exposed to trauma may become more vigilant and distracted by threatening stimuli (Pine et al., 2005; Rokita, Dauvermann, & Donohoe, 2018a), thus failing to adequately process peripheral cognitive and social information, and evident in social cognitive dysfunction. Deficits in social

cognitive function are a hallmark feature of major psychiatric disorders such as schizophrenia, resulting in impaired social functioning (Henry, Von Hippel, Molenberghs, Lee, & Sachdev, 2016).

Little is known about whether these observed neuropsychological deficits could explain the functional changes which constitute the result of cognitive-perceptual anomaly, dysfunctional interpersonal relationships, and disorganized behaviors in adolescents. Exploring the evidence of the possible mechanism that underlies the relationship between TSEs and schizotypal symptoms might help us understand the etiology of schizotypal symptoms as well as psychotic disorders.

Conceptual framework

The conceptual framework of this dissertation is a modification of the three-hit model of vulnerability to stress-related mental disorders, which addresses gene-environment interactions during critical phases of perinatal and juvenile brain development (Barker, 2004; Daskalakis, Bagot, Parker, Vinkers, & de Kloet, 2013; Keshavan & Hogarty, 1999). The first hit (Hit 1), genetic predisposition and prenatal environment, represents the congenital genetic factors inherited from parents or de novo genetic mutations. The second hit (Hit 2) is adverse health environmental exposure during childhood and adolescence stage, or TSEs. The third hit (Hit 3) is adverse health environmental exposure during the later life stage. Hit 1 and Hit 2 may lead to child brain dysfunction of the neuronal circuits and vulnerability to mental disorders, while various factors alter gene expression and lead to phenotypes with differing susceptibility to Hit 3 in later life experiences.

The conceptual framework "Traumatic stressful events on adolescent neuropsychological vulnerability to schizotypal symptoms" focuses primarily on the second hit, where TSEs are the most important component. In this framework, *neuropsychological vulnerability* refers to the vulnerability and susceptibility, which is defined as the dynamic process characterized by diminished cognitive, interpersonal and behavioral capacity of an adolescent to anticipate, cope with, resist and recover from the impact of natural or human-caused risk factors in developmental stages (Addington et al., 2017; Das et al., 2016; Dickson et al., 2018; Eplov et al., 2010; Fischhoff, Downs, & De Bruin, 1998; Magaud et al., 2014; Ratheesh et al., 2017; Singham et al., 2017).

The conceptual model (see Figure 1.1) first indicates that risk factors in prenatal, postnatal and early life (childhood/adolescents) are major issues in increasing neuropsychological vulnerability. Research suggests that the risk factors here, including risks in different developmental stages, could work consequently to induce neuropsychological vulnerability. Lastly, the conceptual model depicts the consequences following neuropsychological vulnerability include schizotypal symptoms as one form of a continuum of psychosis. The three proposed theoretical propositions from this model are 1) Factors in early life period (TSEs in this dissertation) can act as antecedents and then increase the risk of schizotypal symptoms later on; 2) More specifically, traumatic stressful events during childhood and adolescent contributes to the development of schizotypal symptoms; 3) Neuropsychological vulnerability may mediate the relationship between TSEs and the development of schizotypal symptoms.

Parent Study for secondary data analysis

This dissertation was based on a secondary analysis using the Philadelphia Neurodevelopmental Cohort (PNC) dataset. The PNC study was designed to characterize clinical and neurobehavioral phenotypes of genotyped youths in order to elucidate the multiple factors that shape neurodevelopmental trajectories of mental disorders (Calkins et al., 2015, 2014).

The PNC study was an ongoing cohort study that employs repeated measures at baseline (Time 1) and every two years follow-up (Time 2, Time 3, and Time 4) among a community-based US population (Calkins et al., 2015, 2014). At baseline, participants were recruited from a pool (*N*= 50,293) of children previously genotyped as part of a genomic study at the Children's Hospital of Philadelphia healthcare network, which extended to over 30 clinical community sites in Pennsylvania, New Jersey, and Delaware, between November 2009 and December 2011. Potential participants (*N*= 13,598) from this pool were invited to the study if they met the inclusion and exclusion criteria in Table 1.1 based on electronic medical records review or follow-up phone contact. A sample of 9,498 participants completed the clinical assessments and a subset of participants (*N*=1,486) received neuroimaging at Time 1.

Recruitment for Time 2 participants in the PNC study was focused on obtaining longitudinal neuroimaging in participants with and without significant psychosis spectrum symptoms (PSS) at Time 1 (Calkins et al., 2017). PSS represents subclinical psychotic-like experiences and expressions which occur in childhood and PSS could be transient or persistent. From the subsample (*N*=1,486) who prior participate in

neuroimaging, 61% (*N*=910) could be reached for further screen and invitation to participate. A total of 464 participants completed study procedures at Time 2 (Calkins et al., 2017).

For all time points, after a complete description of the study, written informed consent was obtained for participants aged at least 18, and written assent and parental permission were obtained from children aged less than 18 and their parents/legal guardians. All procedures were approved by the University of Pennsylvania and the Children's Hospital of Philadelphia Institutional Review Boards (Calkins et al., 2017).

In this dissertation study, the Time 1 and Time 2 data contains ample data representing information of TSEs, neurocognitive function, schizotypal symptoms, and sociodemographic, parental psychopathology, child substance use, which can address the proposed research aims. One of the inclusion criteria for this dissertation is aged 10 to 24 years at Time 2 based on the definition of adolescents (Sawyer et al., 2018). The final analytic sample size of this dissertation study is 426. Figure 1.2 illustrates the study sample and study variables assessed at two-time points. The detailed information on the definition and measures of the variables are present in Table 1.3.

Chapter Aims and Hypothesis

The aims of this three-article structure dissertation are described below:

Chapter Two (Article One)

Aim. Chapter Two presented a systematic review of synthesizing the studies on the associations between various early life factors and schizotypal symptoms among adolescents.

Rationale. A systematic review is a review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyze data from the studies that are included in the review(Moher, Liberati, Tetzlaff, & Altman, 2009). The selected studies focused on adolescents aged 10 to 24 because schizotypal symptoms emerge during childhood and adolescence.

Chapter Three (Article Two)

Aim. Chapter Three investigated the longitudinal impact of different types of TSE on dimensional schizotypal symptoms controlling for the relevant confounding factors. This study also examined if there was a dose-response relationship between number of TSE and dimensional schizotypal symptoms. The confounding factors, which are either associated with TSEs or schizotypal symptoms, are controlled using analysis of covariance (ANCOVA), including age, gender, parental education (as a proxy of socioeconomic status), parental psychosis (as a proxy of genetic factors), parental substance use, parental suicide attempts, child depression, child anxiety disorder, and child behavioral disorder.

Hypothesis 1: Specific schizotypal symptoms ensue after exposure to different types of TSEs in adolescents after controlling potential covariates.

Hypothesis 2: Specific schizotypal symptoms ensue after exposure to cumulative TSEs in adolescents after controlling potential covariates.

Rationale. Evidence shows that only exposure to sexual abuse appears to play a role in the development of positive symptoms in adults with schizophrenia (Chae, Sim, Lim, Na,

& Kim, 2015). It is plausible, therefore, that exposure to a specific type of TSEs may lead to more present a dimension of schizotypal symptoms. At present, it is unclear to what extent that TSEs increases a person's risk of developing a distinct dimension of schizotypal symptoms in the adolescent population after controlling for the possible confounder variables.

Chapter Four (Article Three)

Aim. Chapter Four aims to explore the potential neuropsychological mechanisms which may mediate the association between cumulative TSEs and different dimensions of schizotypal symptoms among community-based U.S. adolescents.

Hypothesis 1: There are significant positive associations between TSEs and executive function and social cognition, and there are significant negative associations between executive function and social cognition and three dimensions of schizotypal symptoms;

Hypothesis 2: Executive function mediates the relationship between TSEs and schizotypal symptoms, such that higher numbers of TSEs will lead to executive dysfunction and, in turn, lead to the development of schizotypal symptoms;

Hypothesis 3: Social cognition mediates the relationship between TSEs and schizotypal symptoms, such that higher numbers of TSEs will lead to poor social cognition and, in turn, lead to the development of schizotypal symptoms.

Rationale. Individuals with schizotypy were found to have disruptions in both executive function and social cognition. In order to provide a more robust understanding regarding the link between TSEs and schizotypal symptoms, it is reasonable to argue that executive dysfunction and social cognition deficits may be served as neuropsychological

mediators linking TSEs and schizotypy. That is, TSEs may contribute to alterations in executive function /social cognition, which may lead to the development of schizotypal symptoms in adolescents. Further, different mediated pathways between TSEs and distinct dimensions of schizotypal symptoms are examined. It is worthy to investigate these pathways separately because failing to differentiate these dimensions could lead to conflicting results and which is likely due to the relative composition of these symptom dimensions in a given sample.

Chapter Five Overall Discussion

Aim. Chapter Five summarizes the main findings from this three-article structure dissertation, provided implications for practice, discussed its limitations, as well as directions for future research.

Summary

In sum, there is undoubtedly a complex relationship between early life factors and schizotypal symptoms or schizotypal personality disorder in the adolescent population. Chapter 1 overviews this three-paper dissertation study. Chapter 2 summarizes the current literature on the association between early life factors and SPD using a systematic review. Next, Chapter 3 utilizes the PNC data to focus on the most studied early life factor----TSEs, and test the longitudinal association between different types of TSEs and specific dimension of schizotypal symptoms in community-based US adolescents. Furthermore, using the same community sample, Chapter 4 explores the role neuropsychological functioning on the relationship between TSEs and schizotypal symptoms. Chapter 5 summarizes the overall findings and comments on future research.

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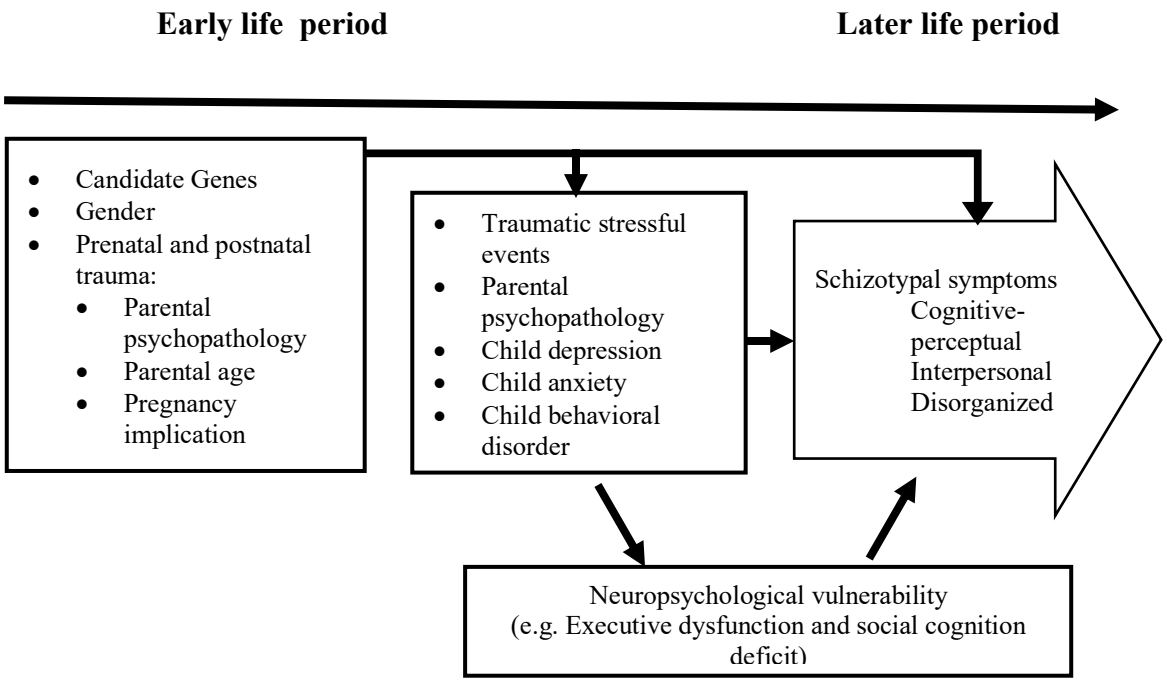

Figure 1.1 Conceptual Framework of Traumatic Stressful Events on Adolescent Neuropsychological Vulnerability to Schizotypal Symptoms

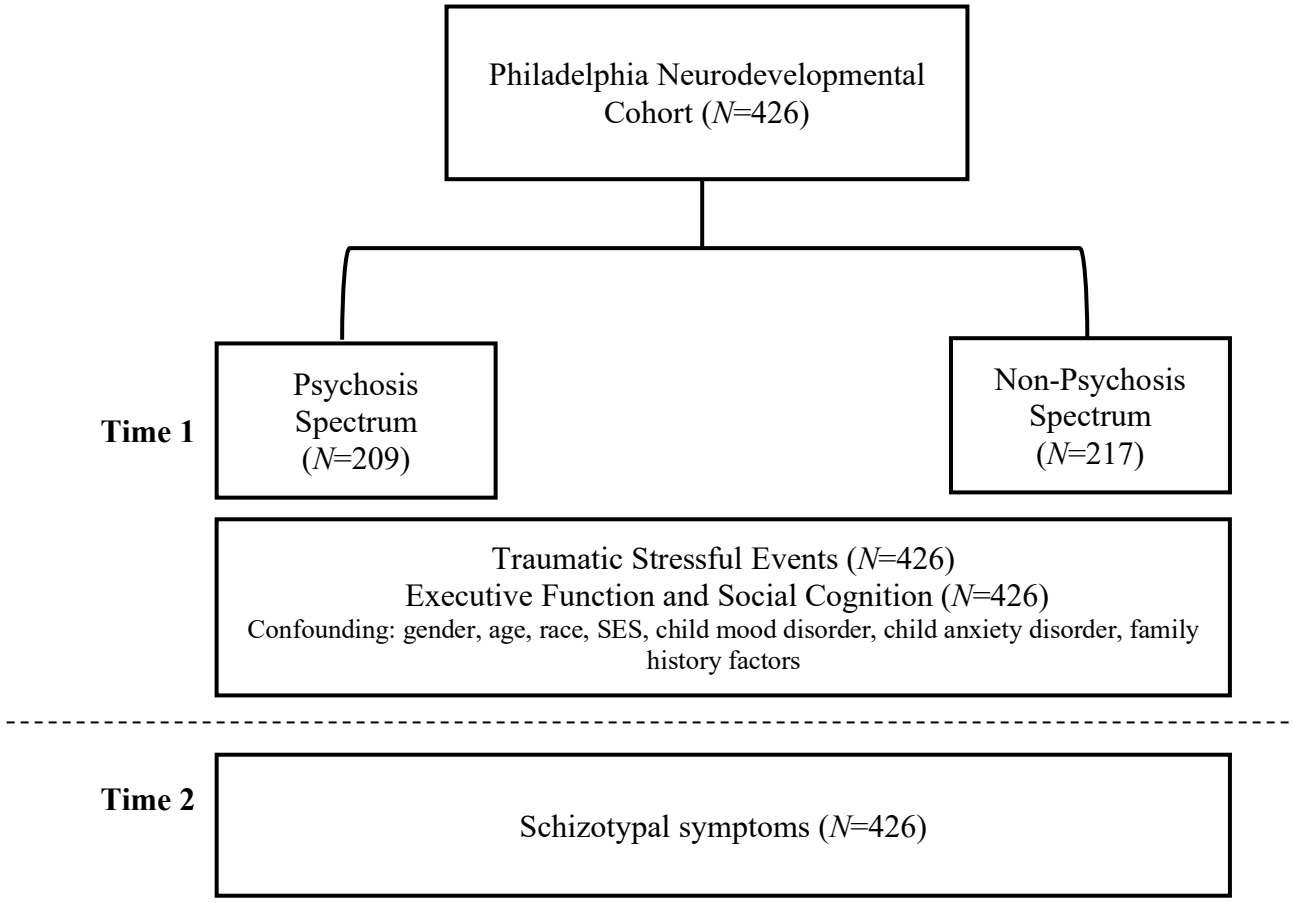

Figure 1.2 Study Sample and Study Variables Assessed at Two Time Points

Table 1.1 Inclusion and Exclusion Criteria of The Participants for Parent Study

Inclusion criteria	Exclusion criteria
(1) Aged 10~24 years at Time 2; (2) Ambulatory in stable health; (3) English proficiency; (4) Physically and cognitively capable of participating in an interview and performing the computerized neurocognitive battery;	(1) Significant physical conditions or developmental delay impairing motility or cognition (e.g., paresis or palsy, intellectual disability).

Table 1.2 Key Variables for Specific Aims

Aims	**Independent variable(s)**	**Dependent variable(s)**	**Possible moderator or mediator**	**Covariates**(T1)
Aim 1	Early life factors (prenatal, perinatal, postnatal, parental, childhood trauma or adversities)	Schizotypal symptoms		
Aim 2	1. Total score of traumatic stressful events(T1) 2. Assaultive events (including physical assault and sexual assault) (T1) 3. Non-assaultive events(T1)	1. Total score of schizotypal symptoms(T2) 2. Cognitive-perceptual symptoms(T2) 3. Disorganized symptoms(T2) 4. Interpersonal symptoms(T2)	1. Psychosis spectrum symptoms(T1)	1. Gender 2. Age 3. Race 4. Socioeconomic status 5. Family history factors 6. Child mood disorder 7. Child anxiety 8. Child behavioral disorder
Aim 3	1. Total score of traumatic stressful events (T1)	1. Cognitive-perceptual symptoms(T2) 2. Disorganized symptoms(T2) 3. Interpersonal symptoms(T2)	1. Executive function (T1) 2. Social cognition(T1) 3. Psychosis spectrum symptoms(T1)	1. Gender 2. Age 3. Race 4. Socioeconomic status 5. Family history factors 6. Child mood disorder 7. Child anxiety 8. Child behavioral disorder

Notes. T1, Time 1, baseline; T2, Time 2, two years follow up

Table 1.3 Definition and Measurement of the Variables, Level of Data, and Variable Operationalization

Variables	**Time**	**Conceptual Definition**	**Operational Definition**	**Measurement (Scoring, Reliability and Validity)**	**Levels of measurement for the final scoring**	**Notes**
Schizotypal symptoms	2	Schizotypal symptoms reflects a multidimensional personality trait determined by genetic and epigenetic or psychosocial factors and is expressed neurodevelopmentally across key dimensions which specify a phenotype that varies considerably in functional and clinical consequence (Cohen, Chan, & Debbane, 2018)	Schizotypal symptoms represent as three-dimensional factors: cognitive-perceptual (Ideas of reference, odd beliefs, unusual perceptual experience, suspiciousness), Interpersonal (social anxiety, no close friends, constricted affect), Disorganization (odd behavior and odd speech).	Schizotypal personality questionnaire (Raine,1991) includes 74 dichotomous questions(yes/no) with nine subscales (0~74). Items for each of three dimensions were summed for analysis. Cronbach 's α =.94 in current sample	Interval; Continuous;	Appendix a---- Schizotypal personality disorder questionnaire
Traumatic stressful events (TSEs)	1	The experience of an event by a child that is emotionally painful or distressful, which often results in lasting mental and physical effects. (NIMH)	Lifetime exposure to eight different traumatic events.	The TSE screen assessed lifetime exposure to eight traumatic events from the post-traumatic stress disorder section of the GOASSESS interview; Scoring: Sexual Assault TSE, Physical Assault TSE, Non-assaultive TSE (TSEs were categorized according to the above hierarchy for multiple endorsement).	Ordinal; Categorical;	Appendix b---- Traumatic stressful Life events questions;

				Cronbach 's α =.61		
Executive function (EF)	1	EF is necessary for regulation of goal-directed behavior, and encompasses cognitive processes including working memory, sustained attention, inhibition, task switching, and performance monitoring (Cornblath et al., 2019; Diamond, 2013).	ABF (abstraction/flexibility): Measures abstraction and concept formation, Tests for the ability to discover principles by hypothesis testing, with principle shifts after discovery is established (the ability to detect and adjust to changing rules).	Penn Conditional Exclusion Test (PCET): Based on the "Odd Man Out" paradigm, participants are asked to determine which particular object does not belong to a group of other objects.	Interval, 1)accuracy=number of correct responses, percentage) 2) response time=median response for correct times, continuous 3)Efficiency = Z-score (Accuracy) + Z-score (response time) * (-1)	This dissertation study utilizing the factor score of EF-CC. CC is complex cognition. And CC tests are not listed in this table.
			ATT (attention) Measures the ability to recognize numbers.	Penn Continuous Performance Test (PCPT): Participants are shown a series of configurations of red seven-segment displays (as on a digital clock display), and asked to press a space bar when the stimulus is a number (first half) or letter (second half).	Same as above	
			WM (working memory) Measures the ability	Short Letter N-Back (SLNB): participants are asked to pay attention to letters that flash	Same as above	

			to keep and refresh goal-related information.	on the computer screen one at a time, and to press the spacebar according to a specified principle.		
Social cognition	1	SC is the ability of processing social information, recognizing expressions and emotions and interpreting social situations. (R. C. Gur & R. E. Gur, 2016).	EMI (emotion identification) measures the ability to decode and correctly identify facial expressions of emotion.	The Penn Emotion Identification Test (ER40): Participants are shown 40 faces, one at a time, four female and four male faces for each emotion, and asked to determine whether the emotion expressed is happy, sad, angry, fearful, or neutral (no emotion).	Same as above	This dissertation study utilizing the factor score of SC.
			EMD (emotion Differentiation) measures the ability to decode the intensity of facial expressions of emotion.	The Penn Emotion Differentiation Test (PEDT): Participants are shown two faces at a time, both expressing the same emotion, and they select which of the two faces ex- presses the emotion more intensely. Differential intensity was obtained by morphing a neutral face to one of four emotions (happy, sad, angry, fearful). The test presents 40 such pairs.	Same as above	
			AGD (Age Differentiation)	The Penn Age Differentiation Test (PADT): Participants are shown two faces at a time,	Same as above	

			measures the ability to decode the age of a face.	both neutral, and asked to select which of the two faces is older. The stimuli were constructed from young faces morphed into old faces, providing graded levels of difficulty. The test presents 40 face pairs.	
Psychosis spectrum symptoms (PSS)	1	PSS represent a set of subclinical psychotic-like experiences and expressions (Calkins et al., 2017)	PSS encompass of positive sub-psychosis, positive psychosis, and negative/disorganized symptoms	Positive sub-psychotic symptoms in the past year were assessed with the 12-item assessor administered PRIME Screen-Revised (PS-R). Items were self-rated on a 7-point scale ranging from 0 (“definitely disagree”) to 6 (“definitely agree”). The participant then rated the duration of each endorsed symptom. Positive psychotic symptoms (lifetime hallucinations and delusions) were assessed using the Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS) psychosis screen questions, supplemented with structured questions to reduce false positives.	Dichotomous

				Negative/disorganized symptoms were assessed using six embedded assessor rated items from the Scale of Prodromal Symptoms (SOPS).	
Gender	1				Nominal; Dichotomous
Age	1				Interval; Continuous
Race	1		European American, African American and other		Nominal; 3 categories
Parental education	1		Father's years of education, mother's years of education		Continuous
Family history factors	1		An abbreviated version of the Family Interview for Genetic Studies (FIGS), administered to adult probands, screened for presence or absence of first-degree family history of psychosis, substance use, and suicide attempts or death.	To avoid influence of proband status on judgments about psychosis family history, presence/absence was coded by the first author based on FIGS data contained in a blinded file, without reference to proband status at either Time 1 or Time 2.	Ordinal, Dichotomous (presence/absence)
Child Depression/		The in-person interview based on the structured Schedule for Affective Disorders and			Dichotomous (presence/absence)

Anxiety/Behavioral disorder;	Schizophrenia for School-Age Children (GOASSESS) evaluated lifetime history of clinical symptoms on mood disorder, anxiety disorder.

Notes: Time=1, baseline; Time=2, two years follow up

Appendix A

Schizotypal personality disorder questionnaire (CAT-SPQ, 74-item)

The response format is "yes/no." All Items endorsed "yes" score 1 point.

Ideas of Reference

1.Do you sometimes feel that things you see on the TV or read in the newspaper have a special meaning for you?

10. I am aware that people notice me when I go out for a meal or to see a film.

19. Do some people drop hints about you or say things with a double meaning?

28. Have you ever noticed a common event or object that seemed to be a special sign for you?

37. Do you sometimes see special meanings in advertisements, shop windows, or in the way things are arranged around you?

45. When shopping does you get the feeling that other people are taking notice of you?

53. When you see people talking to each other, do you often wonder If they are talking about you?

60. Do you sometimes feel that other people are watching you?

63. Do you sometimes feel that people are talking about you?

Excessive Social Anxiety

2. I sometimes avoid going to places where there will be many people because I will get anxious.

11. I get very nervous when I have to make polite conversation.

20. Do you ever get nervous when someone is walking behind you?

29. I get anxious when meeting people for the first time.

38. Do you often feel nervous when you are in a group of unfamiliar people?

46. I feel very uncomfortable in social situations involving unfamiliar people.

54. I would feel very anxious if I had to give a speech in front of a large group of people.

71. I feel very uneasy talking to people I do not know well.

Odd Beliefs or Magical Thinking

3. Have you had experiences with the supernatural?

12. Do you believe in telepathy (mind-reading)?

21. Are you sometimes sure that other people can tell what you are thinking?

30. Do you believe in clairvoyance (psychic forces, fortune telling)?

39. Can other people feel your feelings when they are not there?

47. Have you had experiences with astrology, seeing the future, UFOs, ESP, or a sixth sense?

55. Have you ever felt that you are communicating with an- other person telepathically (by mind-reading)?

Unusual Perceptual Experiences

4. Have you often mistaken objects or shadows for people, or noises for voices?

13. Have you ever had the sense that some person or force is around you, even though you cannot see any- one?

22. When you look at a person, or yourself in a mirror, have you ever seen the face change right before your eyes?

31. I often hear a voice speaking my thoughts aloud.

40. Have you ever seen things invisible to other people?

48. Do everyday things seem unusually large or small?

56. Does your sense of smell sometimes become unusually strong?

61. Do you ever suddenly feel distracted by distant sounds that you are not normally aware of?

64. Are your thoughts sometimes so strong that you can almost hear them?

Odd or Eccentric Behavior

5. Other people see me as slightly eccentric (odd).

14. People sometimes comment on my unusual mannerisms and habits.

23. Sometimes other people think that I am a little strange.

32. Some people think that I am a very bizarre person.

67. I am an odd, unusual person.

70. I have some eccentric (odd) habits.

74. People sometimes stare at me because of my odd appearance.

No Close Friends

6. I have little interest in getting to know other people.

15. I prefer to keep myself to myself.

24. I am mostly quiet when with other people.

33. I find It hard to be emotionally close to other people.

41. Do you feel that there is no one you are really close to outside of your immediate family, or people you can confide In or talk to about personal problems?

49. Writing letters to friends is more trouble than it is worth.

57. I tend to keep in the background on social occasions.

62. I attach little Importance to having close friends.

66. Do you feel that you cannot get "close" to people?

Odd Speech

7. People sometimes find it hard to understand what I am saying.

16. I sometimes jump quickly from one topic to another when speaking.

25. I sometimes forget what I am trying to say.

34. I often ramble on too much when speaking.

42. Some people find me a bit 68. vague and elusive during a conversation. 73.

50. I sometimes use words in unusual ways.

58. Do you tend to wander off the topic when having a conversation?

69. I find it hard to communicate clearly what I want to say to people.

72. People occasionally comment that my conversation Is confusing.

Constricted Affect

8. People sometimes find me aloof and distant.

17. I am not good at expressing my true feelings by the way I talk and look.

26. I rarely laugh and smile.

35. My "nonverbal" communication (smiling and nodding during a conversation) is not very good.

43. I am poor at returning social courtesies and gestures.

51. I tend to avoid eye contact when conversing with others.

68. I do not have an expressive and lively way of speaking.

73. I tend to keep my feelings to myself.

Suspiciousness

9. I am sure I am being talked about behind my back.

18. Do you often feel that other people have it in for you?

27. Do you sometimes get concerned that friends or coworkers are not really loyal or trustworthy?

36. I feel I have to be on my guard even with friends.

44. Do you often pick up hid- den threats or put-downs from what people say or do?

52. Have you found that It is best not to let other people know too much about you?

59. I often feel that others have it in for me.

65. Do you often have to keep an eye out to stop people from taking advantage of you?

Appendix B

Traumatic stressful life events Survey questions

Have ever experienced any of the following events?

(a) a natural disaster;

(b) thought they or someone close to them was going to be killed or hurt badly;

(c) been attacked by somebody or badly beaten;

(d) been forced to do something sexual (including but not limited to rape);

(e) been threatened with a weapon;

(f) been in bad accident;

(g) seen or heard somebody get killed, hurt badly, or die;

(h) been upset by seeing a dead body or seeing pictures of the dead body of somebody they knew well.

CHAPTER TWO EARLY LIFE FACTORS OF SCHIZOTYPAL PERSONALITY DISORDER: A SYSTEMATIC REVIEW

Abstract

Background and objective: Schizotypal personality disorder (SPD) affects 4% general population in the US. The identification of the specific early life risk factors that confer risk to SPD in adolescents (ages 10 to 24 years old) has become a major focus of clinical research on schizophrenia-spectrum disorder. This systematic review aims to identify and summarize possible early life events associated with the onset of SPD in the adolescent population.

Methods: This review was conducted following PRISMA guidelines. A systematic search of PubMed, PsycINFO, Psychiatry online, Scopus, Web of Science, EMBASE, and CINAHL databases was conducted using relevant keywords. Studies were included if: (1) mean sample age of the target individuals were < 24 years old; (2) include one or more early life factors; (3) include measurement of schizotypal symptoms or SPD; 4) early life factors were modeled as independent variables, and schizotypal symptoms or SPD was modeled as a dependent variable for longitudinal studies. Data were extracted using a standardized form following PRISMA guidelines. The quality of the studies was assessed using the criteria of the Newcastle–Ottawa Quality Assessment Scale (NOS).

Results: Twenty-four studies met the criteria for inclusion in this review. Early life factors in the development of SPD were grouped into three important clusters: (1) prenatal and early postnatal factors (9 studies; pregnancy and birth complication, parental age, prenatal androgen/estrogen levels, maternal influenza or cold weather during

gestation); (2) childhood trauma (9 studies; maternal separation, living with parent/s with mental disorders and psychosocial adversity) and (3) parental factors (6 studies). Based upon the Newcastle–Ottawa Quality Assessment Scale (NOS), the overall quality of the studies was assessed as moderate.

Conclusion: This systematic review is the first to summarize the research on the impact of early life environmental factors and SPD in the adolescent and young adult population. As some early life factors are sometimes modifiable to prevention, more research is needed to determine the roles of these early life factors play in the development of SPD. Finally, these findings may serve to inform possible future interventions for SPD, such as parenting interventions and early adversity interventions.

Keywords: schizotypal personality disorder, prenatal, postnatal, parental, childhood trauma, adversity, adolescent, young adulthood

Summations

- This systematic review is the first to summarize the research on the impact of early life environmental factors and SPD in the adolescent and young adult population. It shows an association between three clusters of early life factors and SPD: prenatal and early postnatal factors; childhood trauma; and parental factors.
- Most of the included studies are limited due to the assumption that a single type of early life factor can be considered as a single influence on the development of SPD. More research is needed to evaluate the effect of multiple and/or cumulative early life factors on SPD.
- More research is needed to determine the independent roles these early life factors played in the development of SPD by controlling for the effects of select covariates.

Limitations

- Articles published in languages other than English were not included and therefore some relevant studies may have not been considered.
- Heterogeneity in the methods of the included studies precludes the utility of meta-analysis to determine the relative contribution of each factor under study.
- This review focused on the environmental influence during early life and did not investigate possible genetic factors, which cannot be discounted.

Introduction

Schizotypal personality disorder (SPD) is a complex mental disorder classified both as a personality disorder (Bateman, Gunderson, & Mulder, 2015) and as part of the schizophrenia spectrum disorder (APA, 2013). SPD has a lifetime prevalence of 0.6% - 4.6% in the general population (APA, 2013; Lenzenweger, Lane, Loranger, & Kessler, 2007). The complexity and the high prevalence of SPD pose serious challenges in its management and it brings severe consequences for the patient with SPD. SPD's adverse effects are not only limited to the patients but also affect their relatives and society at large (Gustavsson et al., 2011). The costs of SPD include direct costs such as treatment for the SPD, and indirect costs such as loss of capacity for work due to the disorder (Mangalore & Knapp, 2007; Soeteman et al., 2008).

SPD typically emerges in late adolescence and manifests as identifiable schizotypal symptoms (APA, 2013; Ettinger et al., 2015). Cognitive-perceptual symptoms or positive schizotypy include ideas of reference, odd beliefs, unusual perceptual experience, and suspiciousness; interpersonal symptoms or negative schizotypy include social anxiety, no close friends, constricted affect; disorganized symptoms include odd behavior and odd speech (APA, 2013; Debbané & Barrantes-Vidal, 2015; Ettinger et al., 2015; Raine & Benishay, 1995).

To date the etiology of SPD is unknown, although research suggests the severity of SPD is shaped through the interaction of inherited tendencies and environmental factors (Kahn et al., 2015; van Os et al., 2010). Conceptualized according to a three-hit hypothesis of disease vulnerability and resilience proposed by the British epidemiologist

Dr. David J. Barker, the first hit for SPD is genetic predisposition and prenatal environment, the second hit is the early life environment, and the third hit involves various factors altering gene expression and leading to phenotypes with differing susceptibility to later life experiences and exposures (Barker, 2004; Daskalakis et al., 2013; Keshavan & Hogarty, 1999). The first and second hit may lead to offspring brain dysfunction of neuronal circuits and vulnerability to the SPD.

Schizotypal symptoms have been considered to indicate genetic vulnerability for schizophrenia (Rado,1953) while these symptoms have been argued to greatly depend on the environment, especially the early life experiences to which the individual is exposed (Raine et al. 1995). Literature also shows that genetic heritability for SPD is estimated to be between 30% to 50% within families (Rosell et al., 2014; Walter et al., 2016), indicating that a large part of the remaining variation can be attributed to environmental factors in early life. If these early life precursors of SPDs are identified during adolescence and early adulthood, then treatment approaches aimed at early identification and prevention can be implemented. In addition, identification of early life risk factors for SPD can provide an opportunity to improve early detection and clinical outcomes of SPD through the development of targeted interventions and to reduce chronicity and societal costs.

Appreciating the early presentation of SPD and the likely benefits of early intervention, research focus in SPD has shifted towards examining SPD or schizotypal symptoms in the early developmental period. In recent years, various early life factors have been examined for their association with SPD. One recent review has reported the

association between childhood trauma and SPD, which has a large age range from 6 to 95 (Velikonja et al., 2015); thus, it is difficult to compare findings in a young age group with findings in an older age group. As SPD emerges mainly between late adolescence and young adulthood, adolescence for this review is defined from 10 to 24 (Sawyer et al., 2018) to obtain a better understanding of how early life factors affect the development of SPD.

Research is needed to identify early life factors that can be targeted in prevention and intervention efforts to improve the mental health outcomes among the adolescent population. To date, no comprehensive synthesis covering all potentially important early life factors that are associated with the development of SPD has been reported. The purpose of this systematic review is to synthesize literature on the above-mentioned early life factors associated with the development of SPD.

Methods

Search Strategy

A systematic literature search was performed according to the PRISMA guideline (Moher et al., 2009) for relevant empirical studies in the electronic databases PubMed, PsycINFO, Psychiatry Online, Scopus, Web of Science, EMBASE, and CINAHL. In addition, forward and backward searches of the reference lists of relevant studies were examined for additional information. Keywords related to the early life correlated factors and schizotypy were used (see Supplement 2.1 for detailed search strategy). The search covered studies available as of June 1, 2019 and was limited to studies published in English.

Inclusion and Exclusion Criteria

Studies considered in the present review were selected based on the following inclusion criteria: (1) an original quantitative research paper; (2) published in a peer-reviewed journal; (3) mean sample age of the target individuals < 24 years old or having data available for individuals age < 24 years old; (4) include one or more early life factors; (5) include schizotypal traits or schizotypal personality disorder (using standardized or non-standardized measure, assessing either a single schizotypal trait or multidimensional schizotypy); (6) For longitudinal studies, early life factors were modeled as independent variables, and schizotypal personality disorder was modeled as a dependent variable.

Studies were excluded if (1) only qualitative data was used and (2) the focus was on parents diagnosed with SPD and their child did not have SPD. The first author conducted data extraction and quality assessment. The senior author reviewed the data extraction and also was involved in discussions about the extraction of the data to ensure the rigor of the analysis.

Data Extraction

The data extraction protocol was following the PRISMA guideline (Moher et al., 2009). After abstracts were screened, full-text records were appraised, and the following information was extracted: author/year, study location, study design, sample recruited and characteristics, measures used for early life factors and outcomes, results relevant to this review, strengths, and limitations.

Quality Assessment

This review used the criteria of the Newcastle–Ottawa Quality Assessment Scale (NOS) to assess the quality of observational studies (included in Supplement 2.2). A quality score is calculated based on three major components in reporting of sample selection, comparability and outcome. The quality scale scores 0-8 stars for cross-sectional studies and 0-9 stars for longitudinal studies. The more stars indicate a higher quality study (Herzog et al., 2013; Wells et al., 2014). The Cochrane Non-Randomized Studies Methods Working Group considers the NOS one of the best tools available for the assessment of non-randomized studies (Reeves, Deeks, & Higgins, 2008).This review also evaluated the level of evidence of each study based on the methodological quality of their design, validity, and applicability using an evidence based practice toolkit (Ackley, 2008), and provided the strength of recommendation of the included studies.

Results

Literature Search

The literature search yielded 5,165 records, with 1,824 identified for review after removing duplicates. Titles and abstracts were screened for inclusion/exclusion criteria by the author and 1,625 were excluded. The full text of the remaining studies (N=199) was screened for eligibility. Five extra records were also identified through backward and forward tracking. A total of twenty-four articles were included based on the inclusion criteria to examine the relationship between early life factors and schizotypal personality disorder. The details of the selection procedure and the reason for excluding articles at each stage are displayed in the PRISMA diagram (Figure 2.1).

Study Characteristics

The main characteristics of reviewed studies are presented in Table 2.1. All studies were published between 1994 and 2018, with eight of 24 being published in the past five years. The sample size of these studies ranged from 78 to 9,942. Among these studies, 14 were cross-sectional studies utilizing retrospective data, and ten were longitudinal studies with prospective data. There were eight studies from the United States, and the remaining papers were from the Mauritius (3), United Kingdom (2), Greece (2), Canada (2), Spain (1), New Zealand (1), China (1), Italy (1), Israel (1), Switzerland (1) and Finland (1). Two studies sampled only males and five studies sampled primarily females (more than 70%). Six studies did not report racial/ethnic demographics. Seven out of the 24 studies took a dimensional approach to the measurement of SPD measures, while all the other 16 used the total score of the SPD measures. The measurement tools (see Supplement 2.3) varied across the included studies, including three different clinical interviews, more than seven different kinds of psychometric self-report questionnaires, and also survey items related to SPD symptoms.

All the included studies were rated as being of good quality cross-sectional studies (mean NOS stars= 5), or longitudinal cohort studies (mean NOS stars= 6.1) (see Table 2.2a and Table 2.2b). Six included a comparable control group, and ranked as Level III evidence while the remaining were ranked as Level IV evidence (see Table 2.2a and Table 2.2b), indicating that the overall quality of the included studies was satisfactory.

Due to the low number of studies retrieved, the heterogeneity of measures in these studies, the variability of sample's characteristics that are studied, and the different confounders that are controlled for in statistical analyses, it was not possible to synthesize

the evidence for formal meta-analyses on the association between the early life factors and SPD. Therefore, a narrative synthesis of the included studies was conducted.

Prenatal and Early Postnatal Factors

Nine studies were identified examining the association between several prenatal and early postnatal factors and schizotypy. Prenatal and early postnatal factors include season of birth (four cross-sectional studies), influenza (two longitudinal studies), birth complications (one study), parental age (one study), and prenatal androgen/estrogen levels (one study).

Season of birth and influenza are the prenatal factors occurring during developmental windows prior to birth. Major findings suggest that winter birth and exposure to influenza may be associated with a higher schizotypy score. Four cross-sectional studies examined the link between season of birth and schizotypy and yielded inconsistent results. Three out of four reported winter/spring birth increase the risk of schizotypy in all the studied population (Bolinskey, Iati, Hunter, & Novi, 2013; Reid & Zborowski, 2006) or only in males (Mimarakis, Roumeliotaki, Roussos, Giakoumaki, & Bitsios, 2018), while one out of four found no relationship between schizotypy and birth seasons (Cohen & Najolia, 2011). Two longitudinal studies reported significant findings that exposure to influenza during the fifth (Venables, 1996) or sixth (Machón et al., 2002) month of pregnancy was associated with SPD symptoms.

Other prenatal and early postnatal factors, such as birth complications, parental age, and prenatal androgen/estrogen levels, were examined as independent risk factors for SPD in three studies. In a sample of undergraduates, high SPD symptoms were

significantly associated with retrospectively recalled pregnancy and birth complications, in particular breathing problems or need for oxygen, artificial induction of labor, and breech birth (Bakan & Peterson, 1994). Another study in a sample of undergraduates found that older paternal age and younger maternal age predicted greater cognitive-perceptual schizotypy, but did not predict interpersonal and disorganized schizotypy (Grattan et al., 2015). As a proxy for prenatal androgen/estrogen levels, one study reported larger the 2nd and 4th finger digit ratios (2D:4D) in the SPD group than controls among white males (Walder, Andersson, McMillan, Breedlove, & Walker, 2006).

Childhood Trauma

Childhood trauma was examined in nine studies included in this review. A broad types of childhood trauma was inspected including parental separation (two studies), childhood abuse and neglect (one study), living with parent(s) with mental disorders (four studies) and psychosocial adversity other than parental separation (three studies). The results in general suggest that exposure to these trauma types is associated with SPD.

Two longitudinal studies found significant positive associations between parental separation at a younger age and higher schizotypy expressions at their twenties (Anglin, Cohen, & Chen, 2008) (Wong, Raine, & Venables, 2018) and both emphasized early maternal separation from caregivers may predict elevations in SPD symptoms.

A longitudinal study using only a female sample showed positive correlations between emotional abuse/sexual abuse/physical neglect and SPD. This study aggregated SPD into Cluster A personality disorder (including SPD, schizoid personality disorder and paranoid personality disorder), and it reported that only emotional abuse in childhood

was related to Cluster A personal disorder (Scheffers, Van Vugt, Lanctôt, & Lemieux, 2019).

Four studies, including one longitudinal (Rössler et al., 2007) and three cross-sectional studies (Cella et al., 2013; Cheng, Huang, Liu, & Liu, 2011; Hans et al., 2009), highlighted that living with a parent experiencing a mental disorder during early life period could increase the risk for the development of schizotypy based on both genetic and environmental factors.

Three longitudinal studies examined psychosocial adversity, operationalized as lower family socioeconomic status and poor household function, as a potential risk factor for schizotypy. Measuring psychosocial adversity as a continuous variable, two of the three studies reported consistent results that the experience of psychosocial adversity was significantly associated with higher levels of SPD symptoms (Anglin et al., 2008; P. Cohen et al., 2008) and the other longitudinal study reported psychosocial adversity at age 3 was found to be related to interpersonal and disorganized schizotypy at age 23 (Venables & Raine, 2012).

Parental Factors

Six studies, including four cross-sectional and two longitudinal studies, were identified examining the association between various parental behaviors and schizotypy. A majority of the studies focused on parenting behaviors such as parental bonding (Berry, Band, Corcoran, Barrowclough, & Wearden, 2007; Giakoumaki et al., 2013; Meins, Jones, Fernyhough, Hurndall, & Koronis, 2008); parental antipathy (Sheinbaum et al., 2015); maternal verbal abuse (Johnson et al., 2001); and harsh maternal punishment and poor

maternal/paternal supervision of the child (Johnson et al., 2006). These six studies yield slightly different results depending on specific behaviors and their measurement. Three cross-sectional studies used the parental bonding instrument as the measurement of parental behavior, and two indicated that paternal care, maternal care, paternal overprotection, and paternal protection are consistently associated with schizotypy symptoms (Berry et al., 2007; Giakoumaki et al., 2013).One found only maternal care could predict schizotypy (Meins et al., 2008). Other parental behaviors, such as parental antipathy, maternal verbal abuse, and other problematic parental behavior during child-rearing years (e.g. harsh maternal punishment, poor maternal/paternal supervision of the child), were also found to have a significant association with SPD (Johnson et al., 2006, 2001; Sheinbaum et al., 2015).

Discussion

The present review systematically collates and appraises 24 studies on early life factors and their association with schizotypal personality disorder in adolescence and young adulthood. This systematic review is the first to summarize the research on the impact of early life environmental factors and the development of SPD in the adolescent and young adult population. The evidence supports an association between three clusters of early life factors and SPD: (1) prenatal and early postnatal factors, including influenza exposure, pregnancy complications, prenatal androgen/estrogen levels, and paternal age; (2) childhood trauma, including maternal separation, living with a parent or parents with mental disorders, and broader psychosocial adversity; (3) the parental factors, including disturbances in early parental bonding/attachment.

All studies used observational designs and nine longitudinal studies provide information on temporal order in the increased risk of the onset of SPD when exposed to early life factors in terms of the temporal ordering of the exposure and outcome. The majority of studies were rated as methodologically moderate in quality. The evidence base for an association between childhood trauma and SPD, as well as for an association between parental factors and SPD, is stronger than the evidence for an association between prenatal and early postnatal factors and SPD in adolescents and young adults. Many of the studies in this review had an over-representation of mothers. Hence, although our findings reflect the role of parental factors in general, they may be largely driven by the role of maternal factors and should be interpreted with that caveat in mind.

There is variability in the measures of early life factors, which makes it difficult to determine the relative contribution of each factor under study. Most of the studies reviewed here used non-standard or nonspecific measures for early life factors. For example, studies used dates of birth to determine if the mother's gestation occurred within prenatal influenza season (Machón et al., 2002; Venables, 1996), or simply used birth season as a proxy for prenatal influenza exposures as cold weather may promote viral infections (Bolinskey et al., 2013; Cohen & Najolia, 2011; Mimarakis et al., 2018; Reid & Zborowski, 2006). In these studies, Cohen and Najolia (2011) did not find an association between birth season and SPD, but other studies confirm this association. Therefore, it is difficult to evaluate the association between gestational influenza and SPD as this inconsistency may be due to different season definitions or geographic differences in the sample location.

Another example of limitations related to measurement are the assessments of psychosocial adversities, which were synthesized objectively by an aggregation of demographic variables including household income, material resources, education and occupation (Anglin et al., 2008; P. Cohen et al., 2008, Venables & Raine, 2012). Psychosocial adversity is a complex construct and these indicators are not exhaustive (Braveman et al., 2005); additional factors that were not considered include related neighborhood and family characteristics, such as exposure to violence, toxins and parental care (Adler & Rehkopf, 2008; Braveman et al., 2005; Krieger, Williams, & Moss, 1997). An alternative index of psychosocial adversity might yield different results in the future. Furthermore, psychosocial adversities may generate early physiological and cognitive deficits, such as low birth-weight, and slow cognitive development during infancy, childhood, and adolescence, which compound long-term adverse consequences (Conroy, Sandel, & Zuckerman, 2010). More robust research employing standardized measurement of psychosocial adversity is needed to support its relationship with SPD.

Interpretation is further limited by the various and multiple measures used to identify the dependent variable, schizotypy. Four studies used structured clinical interviews to diagnose SPD, and the remainder defined schizotypal symptoms using either self-reports standardized questionnaires or unstandardized questions. The variability of measurements limited the comparisons between studies and also limited the generalization of the findings.

As noted, schizotypal symptoms are often measured in a dimensional approach, including cognitive-perceptual symptoms or positive schizotypy, interpersonal symptoms

or negative schizotypy and disorganized symptoms (APA, 2013; Ettinger et al., 2015; Kwapil, Barrantes-Vidal, & Silvia, 2007); However, only seven out of the included studies took a dimensional perspective, with the remainder reducing to a total score as the index of schizotypal symptoms directly based on the variability of schizotypy measures. Limited evidence shows early life factors associated with different dimensions of schizotypy in the adolescent population. For example, positive schizotypy was associated with influenza exposure and cold weather (Machón et al., 2002; Venables, 1996), and also older paternal age (Grattan et al., 2015), while negative schizotypy was associated with living with a parent with a mental disorder (Hans et al., 2009) and psychosocial adversity (Venables & Raine, 2012); parental care was associated with both positive and negative schizotypy (Berry et al., 2007). Unfortunately, the great majority of studies relied upon a total schizotypy score; thus, more research is needed to validate the specific effect of early life factors on dimensions of schizotypal symptoms.

This review demonstrates that researchers have studied a broad range of early life factors which associated with SPD development. Limited evidence (one study for each factor) was found for certain prenatal factors including pregnancy complications, prenatal androgen/estrogen levels, and paternal age. None of the studies examined the risk factors of parental stress during pregnancy, maternal smoking, head injury and the development of SPD. According to the three-hit hypothesis, the prenatal factors usually interact with genetic factors during this crucial phase in the formation of the nervous system. These hits, together with the second hit, can cause subtle abnormalities that are not immediately expressed, which leave the individual vulnerable to SPD later in life after experiencing a

third hit (Barker, 2004). Longitudinal research is necessary to investigate the three-hit hypothesis as it relates to SPD.

The division of childhood trauma from parental factors is somewhat arbitrary as these two concepts can be used interchangeably due to overlapping definitions in measurement tools. In general, the literature suggested SPD had a stronger link with both childhood trauma and parental factors. Findings on the association between maternal separation before age 5 and SPD (Anglin et al., 2008) are consistent with prior research that linked parental separation to higher odds of developing schizophrenia when compared to other diagnostic groups (Cannon & Mednick, 1993). Other studies have linked separation from parents in childhood to increased risk for personality disorders (Kantojarvi et al. 2008), especially if an individual was separated before the age of 5 (M. Lahti et al., 2012). Although it is hypothesized that parental separation is more related to personality disorder than schizophrenia (Gibbon et al. 2009), this type of trauma is a risk factor for a range of psychopathologies that occurs in later life. For example, separation from a parent may represent a chronic stressor that underpins insecure attachment (Woodward, Fergusson, & Belsky, 2000). In this conceptualization, separation alters sensitivity to stress, both of which heighten the likelihood of mental illness in adolescence (Daskalakis et al., 2013). In addition, exposure to parental separation was significantly associated with lower attachment to parents in adolescence and more negative perceptions of maternal and paternal care and protection during childhood (Woodward, Fergusson, & Belsky, 2000). The risk of developing personality pathology is partly heritable, and this review consistently demonstrated that children of parents with psychiatric problems were

more likely to have SPD (Cella et al., 2013; Cheng et al., 2011; Hans et al., 2009; Rössler et al., 2007). The underlying mechanism is unclear, but a reasonable explanation derived from the three-hit hypothesis (Barker, 2004) may be: 1) children inherited a genetic disposition that makes them more vulnerable to other early life stressors; and 2) the child experiences an environmental trigger that onsets schizotypal symptoms.

This review has identified the limits to the efficacy of the studies that used a single type of early life factors as the predictor for the subsequence of SPD. To examine the association between specific early life factors and SPD, researchers should consider either controlling the potential confounders or providing a comparable control group, and also consider the individual differences in a broader developmental perspective when interpreting the findings. Individuals may experience early life trauma differently, and may lead to different outcomes (Luyten, Vliegen, Van Houdenhove, & Blatt, 2008), thus considering individual differences may help to fully understand and integrate the associations between the early life factors and SPD. In addition, there is insufficient evidence in this review to synthesize the interaction between different early life factors, and also the interaction between early life factors and genetic factors in the included studies. Thus, more research is needed to investigate the gene-environment interaction in SPD. These design features and considerations are necessary because SPD is thought to act in interaction with several different factors, including genetic factors, early life factors, and other environmental considerations (van Os et al., 2010).

Nevertheless, these findings suggest the value of considering intervention in the family environment in childhood schizotypy research. For example, one study provided possible

parent training to reduce the influence of negative parental behaviors on SPD (Johnson et al., 2001). This idea was also supported by evidence that parent training has been a successful intervention component for parents that have a child with a developmental disorder (Chanen & McCutcheon, 2013; McConachie & Diggle, 2007; Miklowitz et al., 2014). For example, parent training leads to increased parental knowledge of the disorder, enhanced parent-child interaction, and facilitates the resilience of children and in turn improving symptoms in children.

Strengths and Limitations

The current review used a methodologically rigorous and systematic approach to collating and synthesizing the literature. The search strategy enabled screening of a large number of studies with no limits on publication date. Evidence was synthesized from several thousand people in longitudinal studies, representing populations in different countries. More than half of the studies recruited in narrow age ranges around the early twenties which is the age group of SPD onset (APA, 2013, Pulay et al., 2009). Most of the studies used college and community samples which could be tested for associations between early life factors and SPD without important confounding factors, such as medication effects.

However, this systematic review should be considered in light of several limitations. First, articles published in languages other than English were not included and therefore some important studies were not included. Second, a meta-analysis of the findings was not conducted due to the heterogeneity of risk factors and measurement used in the studies. With more consistent methods, a meta-analysis may add additional information

about the differential impact of each risk factor. Third, this review focused on environmental influences during early life, but did not consider the important role genetic factors also play in the development of SPD.

Implications for the Future Research

Future research should address the methodological limitations identified in this review. More research is needed to reveal the causal effects underlying described association, the causal role of early life factors remains to be determined by well-designed longitudinal studies. More research is needed to evaluate the effect of multiple and/or cumulative early life factors on SPD rather than a single type of early life factors. Future research is needed to validate the associations between these factors and SPD by going beyond self-report measurements and using the highest quality level of assessments, and capturing a larger scope of the early life factors, such as physical assaultive, sexual assaultive and witness violence that have high prevalence in a nationally representative sample of adolescents aged 12 to 17 (Finkelhor, Turner, Shattuck, & Hamby, 2013).

In addition, studying these potential early life factors may be of use to both healthcare workers and policymakers, and findings of this review may introduce a new opportunity for preventative interventions in early life. They may determine early prevention strategies and find possible solutions to modify these early life factors in order to offer the best hope of reducing the burden of SPD in the general population. Future research may also consider testing the effectiveness of parent training intervention in the population with SPD. Preventative strategies are more feasible than genetic interventions and can also help identify families who would most benefit from tailored environmental

intervention. If future research can more clearly identify the environmental causes of dimensions of SPD, clinicians may then be able to make more informative choices about which therapies are most appropriate for their patients.

Conclusion

This systematic review provides valuable clarifications of early life factors, including prenatal and postnatal factors, psychosocial adversity, childhood trauma, and parental factors, that may increase the risk for an individual to develop SPD. As early life factors are amendable to prevention, more research is needed to determine the roles these early life factors play in the development of SPD. The findings may inform the critical components of interventions to prevent the onset of schizotypal symptoms.

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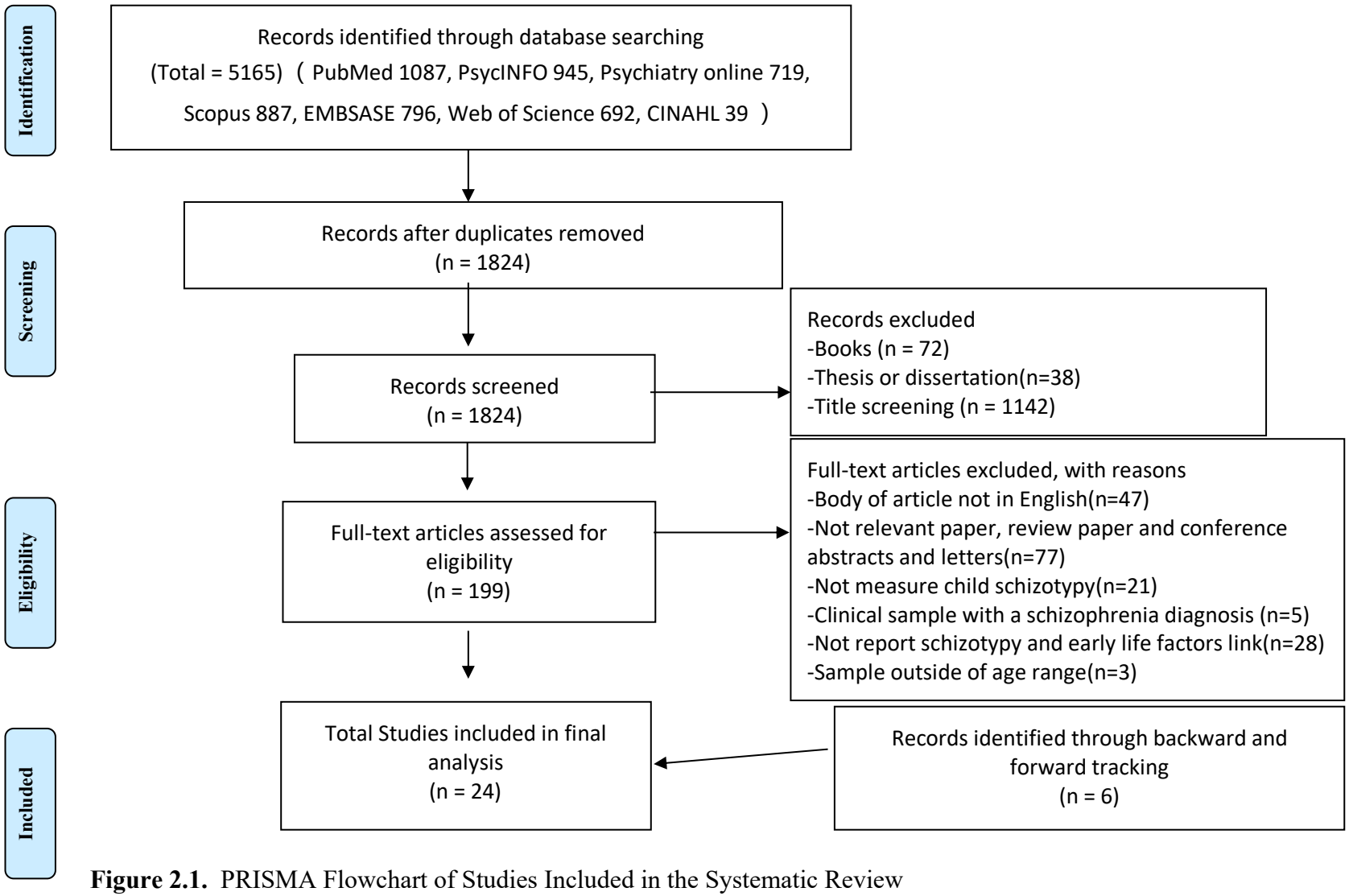

Figure 2.1. PRISMA Flowchart of Studies Included in the Systematic Review

Table 2.1 Table of Evidence for the Included Studies

	Author (year, study location)	Study design	Sample recruited, including sample size, % male, ethnicity, age range/mean age(years)	Measure of early life factor	Measure of schizotypy	Results	Strengths	Limitations
Prenatal and postnatal factors (9)	Bakan and Peterson (1994), Canada	Cross-sectional study, retrospective data	University undergraduates, *N*=499,34.3% male, ethnicity NR, age NR	pregnancy and birth complications Questionnaire (PBCS),20items	Rust inventory of schizotypal Cognitions(Rust, 1987, 1988);26 items	Individuals in the upper decile of schizotypy scores report more pregnancy and birth complication than the remaining individuals.	1. Use a large size of non-psychotic sample	1. The sample consist of university students and thus does not represent the general population. 2. Self-reported SPD may not be the same as DSM diagnosis. 3. Self-report the PBCS data may not be accuracy as medical record and maternal reports.
	Bolinskey et al. (2013), United States	Cross-sectional study, retrospective data	College students, *N*=84, (Schizotypy=42, Controls=42),16.7% male Mixed (Caucasian, African American, Hispanic) 18~23	Season of birth: Dec. through Mid-Mar (winter)	Chapman psychosis proneness scales (CPPS)(Chapman, Chapman, & Raulin, 1978; M. Eckblad & Chapman, 1983; M. L. Eckblad, Chapman, Chapman, & Mishlove, 1982);105items	The individuals in schizotypy group was more likely to be born in winter than were the individuals in control group. Odds ratio (OR) is 3.75, 95%confidence interval (CI) = 1.36~10.36	1. Using a matched comparison sample	1. Use a relatively small sample size 2. Most of the sample are female.
	Cohen et al. (2011), United States	Cross-sectional study, retrospective data	Undergraduate students, *N* =3485, Schizotypy=203(39% male) Controls=3282(36% male) Mixed (Caucasian, African American, Hispanic and "other")	Season of birth:December.22-March.21(Winter), March.22-June.21(Spring), June.22-September.21(Summer), September.22-December.21(Fall).	Schizotypal Personality Questionnaire(SPQ), the full version (n = 1130), (Raine, 1991); the brief version (n = 1110)(Raine & Benishay, 1995); or a revised brief version (n =1680),(Cohen,	Winter birth was dramatically high in individuals who reported both schizotypy and a history of psychiatric hospitalization and/or schizophrenia diagnosis. No statistically significant difference	1. Use a large sample size 2. Use a reasonable control group 3. Use a self-report for history of psychiatric hospitalization and /or receiving	1. Aggregation of three different versions of SPQ may have introduced unintended noise into analysis

		Schizotypy:19.07±1.52 Controls:19.29±2.30		Matthews, Najolia, & Brown, 2010); On average,42 items answered by each individual	was found across either season between individuals with extreme schizotypy score and those without schizotypy. OR=1.06, 95% CI=0.76–1.5, *p*= 0.735)	a diagnosis of schizophrenia	
Grattan et al. (2015) study 1, New Zealand	Cross-sectional study, retrospective data	Undergraduates (*N* = 500) final sample in study 1 is 436(25.2% male) Mixed (New Zealand European, and Maori, Chinese, Indian, Pacific Island, and others) 17~55, mean 20.3±3.3	Paternal age and maternal age	Schizotypal Personality Questionnaire(SPQ),(Raine, 1991; Wuthrich & Bates, 2005) ,74 items	Older paternal age and younger maternal age predicted more cognitive-perceptual schizotypy (Beta=0.13 and 0.19, respectively), but not predict interpersonal and disorganized schizotypy.	1. Take SPD in a dimensional perspective.	1. Participant reported their parents age 2. Most of the sample are female.
Machón et al. (2002), Finland	Longitudinal study, prospective data	Finnish men from military service (*N* =4490, 2339 exposed/ 2151controls, all male) 2309 out of 2339 exposed/ 2065 out of 2151controls for further analysis Not specified, all born in greater Helsinki. 19~20	Exposure to Influenza epidemic based on birth date	2-7-8 code profile on the Minnesota Multiphasic Personality Inventory(Merritt & Balogh, 1984, 1990; Meyer, 1993; Nakano & Saccuzzo, 1985)	A significantly higher proportion of 6th month (calculated on a 10-month pregnancy) exposed subjects had upper quartile schizotypy scores as compared to their controls. (p<0.003)	1. Provide a time-order correlation between influenza and SPD. 2. Use a large sample size. 3. Pair the exposed and the control group	1. The SPD measurement captured more positive schizotypy. 2.Only male sample.
Mimarakis et al. (2018), Greece	Cross-sectional study, retrospective data	High school pupils (*N* =445, 43% male) Mixed (Greek origin, Albanian origin and others) 17~22(18±1.10)	Season of birth: May to November December to April	Schizotypal Traits Questionnaire (STQ),(Claridge & Broks, 1984),37 items	Total schizotypy, Magical thinking (Beta=0.82, 95% CI=0.01–1.62, *p*= 0.047), Paranoid ideation (Beta=1.22, 95% CI=0.40–2.04, *p*= 0.004) was significantly predicted by winter-birth only in male after adjusted covariates;	1. Take SPD in a dimensional perspective. 2. This is the first report that examined the relationship of winter- birth, urbanicity and immigrant status, with positive schizotypy in late adolescence	1. Use self-report of SPD. 2. The SPD measurement captured more positive schizotypy.

	Reid and Zborowski. (2006), United States	Cross-sectional study, retrospective data	Undergraduate students (*N* =452, 24.6% male) Mixed (White, Black, Hispanic, Asian, American-Indian and "other") 21.31±5.05	Season of birth：December.21-March.20(Winter), March.21-June.20(Spring), June.21-September.20(Summer), September.21-December.20(Fall).	Perceptual Aberration-Magical Ideation (PER-MAG) scale (Chapman &Chapman, 1980,1987); 65 items	PER-MAG scores are higher in Winter/Spring births than in summer/fall birth(p=0.01); OR=0.94, 95% CI=0.62–1.41, p=0.766	1. Three division of the year was utilized: 12 months, 4 seasons, and two half years.	1. PER-MAG scale only capture the positive schizotypy. 2. Most of the sample are female.
	Walder et al. (2006), United States	Cross-sectional study, retrospective data	Adolescents with SPD diagnosis (*N*=34,64.7% male) and normal controls (*N*=44, 61.4% male) Mixed (White/Caucasian, African-American, Asian-American, and other) Schizotypy:14.09±1.69 Controls:14.20±1.94	2D:4D----Dividing 2D (tip of middle finger to tip of index finger) by 4D (tip of middle finger to tip of ring finger)	Structured interview for DSM-IV Personality(SIDP-IV),(Pfohl, Blum, & Zimmerman, 1997)	Among White/Caucasian males right 2D:4D was significantly larger in SPDs than controls.	1. Provide an SPD diagnosis 2. Provide a control group	1. Small sample size;
	Venables. (1996), Mauritius	Longitudinal study, prospective data	A birth cohort from Mauritius Child Health Project (N=771,52.5% male) Mixed (Muslims, Hindus, Tamils and African) 15.09~19.76 (17.06 ±0.95)	Maternal exposure to influenza or cold weather (For each participant, using his or her birthdate, the mean median environmental temperature for each of the three trimesters of the mother's pregnancy was calculated.)	Schizotypy questionnaire (Venables, Wilkins, Mitchell, Raine, & Bailes, 1990), 30items	Women's exposure to influenza in 5th month of gestation (calculated on a 9-month pregnancy) is associated with an elevation of positive schizotypy score in their offspring. (*N*=213， p=0.017)	1. Provide a time-order correlation between influenza and SPD. 2. Provide three control groups for women's exposure to influenza in three trimesters. 3. Take SPD in a dimensional perspective.	1. Small sample size of control group for women's exposure to influenza in the third trimester.
Childhood Trauma (9)	Anglin et al. (2008), United States	Longitudinal cohort study, prospective data	Random sampled from general population (Baseline *N* = 776, 51% male) Mixed (91%Caucasian, 8% African American and other)	Mothers provided self-report data about early separations for at least 1 month in 1975 and at follow-up in 1983; Psychosocial adversity was measured as a	The Children in the community self-report (CIC-SR) schizotypal personality disorder(SPD) symptom scale(Crawford et al., 2005),16 items	Individuals with separation before age 5 showed a significant increase in average SPD symptoms at age 20 of entire sample (β = 2.03, S.E. = 1.05, p < 0.05), after controlled gender and SES.	1. Mother report the early separation 2. Provide a time-order correlation between maternal separation and SPD.	1. Small sample exposed to separation; 2. The absence of externally assessed childhood temperament during infancy

		in 1983 (N =756; mean age = 13.7, SD = 2.6 years), 1985–1986 (N =746; mean age = 16.1, SD = 2.8 years), 1991–1993 (N =749: 717 with complete information; mean age = 22.0, SD = 2.7 years), and 2001–2004 (N =678; mean age = 33.1, SD = 2.8 years)	standardized sum of standardized measures of years of maternal and paternal education, occupational status and family income.		Individuals from family with psychosocial adversity reported significantly higher levels of SPD symptoms.		which could serve as a confounder.
Cella et al. (2013), Italy	Cross-sectional	1023 high school students, 506 males (49.5%) and 517 females (50.5%). Mean age in the sample was 17.3 years (SD 1.3 years) Italian	Family history of psychosis, including. hallucinations, psychotic-like beliefs and paranoids thinking	Oxford-Liverpool Inventory of Feelings and Experiences(O-LIFE)(Mason & Claridge, 2006), 43 items	"True" schizotypy class (22%) showed an overall higher level of item endorsement across schizotypal dimensions, and positive association with psychological distress and family history of psychosis. OR = 3.45 (95%CI=2.11 – 5.65)	1. Representative sample of similar age group students in the same context	1. Self-report of schizotypal features and family history
Cheng et al. (2010), China	cross-sectional	9892 high school students from Beijing Chinese <19	Parent Personality disorder—(Personality Diagnostic Questionnaire ,fourth edition) (PDQ-4), Parent ages, Family type, parental relationship, parental education and occupation	Students reported PDQ-4≥42 were invited to diagnostic interviews using international personality disorder examination.	Parents' SPD score correlates students' SPD score. Parents of cluster A-PD students scored higher in PDQ and were more likely to be cluster A-PD cases than controls' parents after controlling family income, parental relationship and parental rearing behavior (OR=18.79father/9.81mother)	1. Provider a diagnosis for SPD. 2. Provide a comparable control group	1.Very small sample size of SPD
Cohen et al. (2008), United States	Longitudinal Cohort study, prospective data	778 mothers and children were interviewed in their homes at baseline (male percentage not reported)	Psychosocial adversity was measured as a standardized sum of standardized measures of years of maternal and paternal	Self-reported Personality disorder symptoms (Crawford et al., 2005)	Psychosocial adversity had robust modest independent effects on both SPDs over the entire age span despite substantial cumulative effects of trauma	1. Provide a time-order correlation between psychosocial adversity and SPD.	1.Self-report of schizotypy measure. 2. No control group.

		Mixed (91%Caucasian, African American, Asian) offspring ages in 1983: 13.7± 2.6 ; in 1985: 16.1±2.8 ; in 1991: 22.0± 2.7; in 2001: 33.1± 2.9	education, father's occupational status, mother's occupational status and family income.		history, stressful recent life events, IQ, poor parenting, and comorbid symptoms	2. Considered the potential covariates related to psychosocial adversity	
Hans et al. (2009), Israel	Cross sectional	*N*=114, (a) 39 young people in which at least one biological parent had schizophrenia, (b) 39 young people in which at least one parent had a major lifetime non-schizophrenic mental disorder (affective disorder or personality disorder), and (c) 36 young people in which neither parent had diagnosable mental illness. Israeli 12~22	Parents with or without mental disorder, prenatal developmental disruption	Nine questions from Semi-Structured Kiddie Interview for Personality Syndromes	Interpersonal schizotypal symptoms were more prevalent in the schizophrenia offspring group than in the no mental illness offspring group.	1. Provide three parent diagnosis groups 2. Take SPD in a dimensional perspective	1.Small sample size of each group 2.It's hard to distinguish the possible association between adolescent schizotypal symptoms and specific types of nonschizophrenia parental mental illness
Rossler et al. (2007), Switzerland	Longitudinal study, prospective data	Representative sample from general population (Baseline N=372) Swiss Baseline age 19(male)/20(female), follow-up at 21,23, 28, 30, 35 and 41	Life events list according to the Holmes–Rahe scale (Holmes & Rahe, 1967)	SCL-90-R (Derogatis, 1977), including paranoid ideation and psychoticism	Problems and conflicts with parents as well as chronic physical or mental disorders in parents contributed to schizotypal signs	1. Provide a time-order correlation. 2. SCL90- R captured schizotypal signs, including odd interpersonal beliefs and paranoid ideation. SCL90-R is not commonly used for SPD.	1. Self-report SCL90-R may lead to recall bias.

Scheffers et al. (2019), Canada	Longitudinal study, prospective data	Clinical setting, Montreal Longitudinal study on adolescent girls (Baseline N=182, all female) Canada First wave and sixth wave (N=125) mean age =19.41	Childhood trauma questionnaire (CTQ, Bernstein & Fink, 1998)	Personality Diagnostic Questionnaire 4+ (PDQ-4+)	Emotional abuse was significantly related to schizotypal ($\beta = .18$, $p < 0.05$)	1. Provide a time-order correlation between childhood trauma and SPD.	1. Only focus on females.
Venables et al. (2012), Mauritius	Longitudinal study, prospective data	A birth cohort from Mauritius Child Health Project (final sample N=815, 51.4% male) Mixed (Indian, 68.5%; Creole (African origin), 25.7%; and Chinese, English, or French origin) Age 3 and Age 23	SES (Psychosocial adversity): The adversity index was created by adding 1 point for each of the variables, which were as follows: uneducated father, uneducated mother, semiskilled father or father in unskilled occupation, single-parent status, separation from parents, large family size, poor health of mother, teenage mother, and overcrowded home	Schizotypal Personality Questionnaire (Raine, 1991) ,74items	Psychosocial adversity at age 3 was found to be related to interpersonal And disorganized schizotypy, which is mediated by performance IQ.	1. Provide a time-order correlation between psychosocial adversity and SPD. 2. Take SPD in a dimensional perspective.	1.Measure of psychosocial adversity is based on the data collected at age 3 which could not also reflect the variability from age 2 to age 23.
Wong et al. (2018), Mauritius	Longitudinal study, prospective data	A birth cohort from Mauritius Child Health Project (N=1794,51.8% male), home alone children (N=34, 64.7%male); Mixed (68.3% Indian (Hindu, Tamil, Muslim), 25.7% Creole, 1.8% Chinese, and 3.8% other (English or French descent) Baseline age: 3 Follow up: 11, 17, and 23 years	The child's guardianship was first assessed by a social worker who visited the home when the child was aged 3. Then the mothers or caregivers attend a subsequent interview	Schizotypy at age 11 years were measured using Child Behavior Checklist (CBCL) (Achenbach et al., 1987) Schizotypy at age 17 years were measured using the Schedule for Attitudes and Experiences (SAE), which was a self-report schizotypy measure with subscales measuring cognitive-perceptual, interpersonal deficits,	Home alone children showed higher scores on schizotypal personality at 23 years compared to the other groups.	1. Provide a time-order correlation. 2. Provide a comparable control group	1. Small sample of home alone children.

					and disorganized features (Venables, 1989, 1996; Venables and Raine, 2015). Schizotypy at age 23 years were measured using SPQ, 74 items.			
Parental factors (6)	Berry et al. (2007), United Kingdom	Cross-sectional study, retrospective data	University students (*N* =304, 43.5% male) White British (72%) 18~53, median age of the sample was 21 years	maternal and paternal versions of the Parental Bonding Instrument(PBI)(Parker, 1979), 25 items;	Oxford-Liverpool Inventory of Feelings and Experiences scale(O-LIFE),(Mason, Claridge, & Jackson, 1995)	Maternal care and paternal care were negatively associated with schizotypy subscales, while maternal overprotection and paternal overprotection were positively associated with schizotypy subscales.	1. Take SPQ in a dimensional analysis.	1.Self-report of PBI and schizotypy measure.
	Giakoumaki et al. (2013), Greece	Cross-sectional study, retrospective data	Male army conscripts (*N*=324, all male) NR 18~28(20.84± 2.62)	PBI(Parker, 1979)),25 items	Schizotypal Traits Questionnaire(STQ)(Claridge & Broks, 1984), 37 items	Significant correlation was found between PBI measures and schizotypy. 9.1% (Adjusted R^2: 8.5%) of the ‘‘Schizotypy’’ variance was significantly predicted by high maternal overprotection (Beta = 0.20; t = 3.38, P < 0.001) and low paternal care (Beta = –0.17; t = –3.00, P < 0.003)	1. Take PBI in a dimensional analysis.	1. Only male sample. 2. Self-report of PBI and schizotypy measure.
	Johnson et al. (2001), United States	Longitudinal study, prospective data	Representative community sample, mothers and their offspring （*N*= 793, offspring 51% male） NR in 1975: 5.6, ±2.8； in 1983: 13.7± 2.7； in 1985: 16.3±2.8； in 1991: 22.1± 2.7	Childhood verbal abuse was obtained from maternal interview questions.	The parent and youth versions of the diagnostic interview schedule for Children （DISC-I） (Costello et al. 1984), Personality Diagnostic Questionnaire (Hyler et al., 1988)	Childhood verbal abuse was associated with SPD during adolescence and early adulthood (F= 12.28, p < 0.005) after adjusting for offspring age, parental education, parental psychiatric disorder, physical abuse, sexual abuse	1. Representative community-based sample. 2. Provide a time-order correlation between childhood verbal abuse and SPD. 3. Considered the potential covariates.	1. Maternal report of verbal abuse may lead to reporting bias and recall bias.

Johnson et al. (2006), United States	Longitudinal study, prospective data	593 families with 122respindents met the DSM-IV diagnostic criteria for one or more Personality disorder at a mean age of 22 or 33(male percentage not reported) Ethnicity NR in 1975: 5.6, ±2.8 ; in 1983: 13.7± 2.8 ; in 1985: 16.3±2.8 ; in 1991: 22.1± 2.7; in 2001: 33.1± 2.9	Personality Diagnostic Questionnaire (Hyler et al., 1988), parent and offspring version of the Cornell Parent Behavior Inventory(Devereux, Bronfenbrenner, & Rodgers, 1969) the child's report of Parental Behavior Inventory(Schaefer, 1965)	The Personality Diagnostic Questionnaire and the Structured Clinical Interview for DSM-III-R Personality Disorders(First et al., 1995)	Problematic and aversive parental behavior during child rearing may be associated with elevated risk for offspring SPDs at the mean age of 22 years.	1. Representative community-based sample. 2. Provide a time-order correlation between problematic parental behavior and SPD.	1. Only maternal report the parental behaviors may lead to reporting bias.
Meins et al. (2008), United Kingdom	Cross-sectional study, retrospective data	Undergraduate students (*N* =154,43.5% male) Ethnicity NR 17~42(20.6± 2.98)	PBI(Parker, 1979),25 items	Schizotypal Personality Questionnaire (Raine, 1991) ,74items	Paranoia and negative schizotypal traits were predicted by perceived parental care.	1. Take SPD in a dimensional perspective.	1. Small sample size may not have enough power to address the current research question.
Sheinbaum et al. (2015), Spain	Cross-sectional study, retrospective data	Undergraduate students *N* =214, 22% male) Ethnicity NR 21.4 ± 2.4	The Childhood experience of Care and abuse (CECA) interview to assess childhood care	The structured clinical interview for DSM-IV Axis-II Disorders(SCID-II)(First & Gibbon, 2004)	Both parental antipathy and role reversal (poor childhood care) were associated with schizotypal PD traits after controlling the depression symptom.	1. Provide SPD diagnosis using validated interview. 2. Provided a comparable control group.	1.Most of the sample is female.

Note. NR = not reported. SES=socio-economic status=psychosocial adversity. SPD = schizotypal personality disorder

Table 2.2a Newcastle-Ottawa Quality Assessment Scale for Cross-Sectional Studies (Herzog et al., 2013)

	Selection				Comparability*	Outcome			
Study (First author)	**Representativeness of the sample[a]**	**Sample size[b]**	**Non-respondents[c]**	**Ascertainment of the exposure (risk factor)[d]**	**Based on the study design and analysis**	**Assessment of the outcome[d]**	**Statistical test[e]**	**Total stars (8)**	**Levels of Evidence**
Bakan, et al., 1994		X		X		X	X	4/8	Level IV
Berry et al., 2007		X	X	X		X	X	5/8	Level IV
Bolinskey et al., 2013	X	X		X	X	X	X	6/8	Level III
Cella et al.,2013	X	X		X		X	X	5/8	Level IV
Cheng et al.,2010	X	X		X	X	X	X	6/8	Level III
Cohen et al., 2011		X	X	X	X	X	X	6/8	Level III
Giakoumaki et al., 2013		X		X	X	X	X	5/8	Level IV
Grattan et al., 2015, study 1		X	X	X		X	X	5/8	Level IV
Hans et al.,2009		X		X	X	X	X	5/8	Level IV
Meins et al., 2008		X		X	X	X	X	5/8	Level IV
Mimarakis et al., 2018		X		X	X	X	X	5/8	Level IV
Reid et al., 2006		X		X		X		3/8	Level IV
Sheinbaum et al., 2015		X		X	X	X	X	5/8	Level III
Walder et al., 2006		X		X	X	X	X	5/8	Level IV

[a] Truly representative of the average in the target population (all subjects or random sampling), somewhat representative of the average in the target population (non-random sampling), selected group of users.

[b] Justified and satisfactory.

[c] Comparability between respondents and non-respondents' characteristics is established, and the response rate is satisfactory.

[d] Independent blind assessment, record linkage, self-report.

[e] The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p-value).

* A maximum of 2 points can be allotted in this category. The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.

Table 2.2b Newcastle-Ottawa Quality Assessment Scale for Longitudinal Studies (Wells et al., 2014) (*http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp*)

Study (First author)	Selection				Comparability*	Outcome			Total stars (9)	Levels of Evidence
	Representativeness of the exposed cohort[a]	Selection of the non-exposed cohort[b]	Ascertainment of exposure[c]	Presence of outcome of interest at start of the study	Based on the study design and analysis	Assessment of the outcome[d]	Length of follow-up[e]	Adequacy of follow up of cohorts[f]		
Anglin et al., 2008	X	X	X		X	X	X	X	7/9	Level III
Cohen et al., 2008	X		X		X	X	X	X	6/9	Level IV
Johnson et al., 2001	X		X	X	X	X	X	X	6/9	Level IV
Johnson et al., 2006	X		X	X	X	X	X	X	6/9	Level IV
Machón et al., 2002	X	X	X	X	X	X			6/9	Level IV
Rossler et al., 2007	X		X		X	X	X	X	6/9	Level IV
Scheffers et al. (2019)	X		X		X	X	X	X	6/9	Level IV
Venables et al., 2012	X		X	X	X	X	X		6/9	Level IV
Venables. 1996	X	X	X		X	X			5/9	Level IV
Wong et al., 2018		X	X	X	X	X	X		6/9	Level III

[a] Truly/somewhat representative of the general population, selected group of users.
[b] Drawn from the same community as the exposed cohort or from a different source.
[c] Use of validated questionnaire.
[d] Doctor's diagnosis or objective measurements, parent/self-reported doctor's diagnosis, parent/self-report.
[e] Was follow-up long enough for outcomes to occur?
[f] Complete follow up - all subjects accounted for, subjects lost to follow up unlikely to introduce bias - small number lost, i.e. > 80 % follow up, description provided of those lost proving a non-selective loss to follow up.
[*] A maximum of 2 points can be allotted in this category. Either exposed and non-exposed individuals must be matched in the design and/or confounders must be adjusted for in the analysis. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability.

Supplement 2.1

Systematic Review Search strategy

	Keywords
the early life factors	"prenatal", "perinatal", "neonatal", "postnatal", "postpartum", "fetal", "uteri", "pregnancy", "birth", "obstetric", and "gestation"; "childhood", "parent*," "paternal", "maternal" and "father", "mother", "parent-child relationship", "famil*"; "adversity", "trauma", "maltreatment", "abuse", "neglect"
schizotypy / SPD	"schizotyp*", "social anhedonia", "magical ideation", "social isolation", "interpersonal deficit", "odd", "eccentric".

Supplement 2.2

Newcastle-Ottawa Scale Adapted for Cross-sectional Studies

Selection: (Maximum 5 stars)
1) Representativeness of the sample:
a) Truly representative of the average in the target population. * (all subjects or random sampling)
b) Somewhat representative of the average in the target population. * (non-random sampling)
c) Selected group of users.
d) No description of the sampling strategy.
2) Sample size:
a) Justified and satisfactory. *
b) Not justified.
3) Non-respondents:
a) Comparability between respondents and non-respondents' characteristics is established, and the response rate is satisfactory. *
b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory.
c) No description of the response rate or the characteristics of the responders and the non-responders.
4) Ascertainment of the exposure (risk factor):
a) Validated measurement tool. **
b) Non-validated measurement tool, but the tool is available or described.*
c) No description of the measurement tool.
Comparability: (Maximum 2 stars)
1) The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.
a) The study controls for the most important factor (select one). *
b) The study control for any additional factor. *
Outcome: (Maximum 3 stars)
1) Assessment of the outcome:
a) Independent blind assessment. **
b) Record linkage. **
c) Self report. *
d) No description.
2) Statistical test:
a) The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value). *
b) The statistical test is not appropriate, not described or incomplete.

Newcastle-Ottawa Scale adapted for Cohort studies

Note: A study can be given a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Selection:

1) Representativeness of the exposed cohort

a) Truly representative ***(one star)***

b) Somewhat representative ***(one star)***

c) Selected group

d) No description of the derivation of the cohort

2) Selection of the non-exposed cohort

a) Drawn from the same community as the exposed cohort ***(one star)***

b) Drawn from a different source

c) No description of the derivation of the non exposed cohort

3) Ascertainment of exposure

a) Secure record (e.g., surgical record) ***(one star)***

b) Structured interview ***(one star)***

c) Written self-report

d) No description

e) Other

4) Demonstration that outcome of interest was not present at start of study

a) Yes ***(one star)***

b) No

Comparability

1) Comparability of cohorts on the basis of the design or analysis controlled for confounders

a) The study controls for age, sex and marital status ***(one star)***

b) Study controls for other factors (list) _____ ***(one star)***

c) Cohorts are not comparable on the basis of the design or analysis controlled for confounders

Outcome

1) Assessment of outcome

a) Independent blind assessment ***(one star)***

b) Record linkage ***(one star)***

c) Self report

d) No description

e) Other

2) Was follow-up long enough for outcomes to occur

a) Yes ***(one star)***

b) No

Indicate the median duration of follow-up and a brief rationale for the assessment above:_____

3) Adequacy of follow-up of cohorts

a) Complete follow up- all subject accounted for ***(one star)***
b) Subjects lost to follow up unlikely to introduce bias- number lost less than or equal to 20% or description of those lost suggested no different from those followed. ***(one star)***
c) Follow up rate less than 80% and no description of those lost
d) No statement

Supplement 2.3
Measurement of Schizotypy Summary of the Included Studies.

Interviews	Standardized questionnaires	Items related to SPD symptom
1. Structured interview for DSM-IV Personality (SIDP-IV) (Pfohl, Blum, & Zimmerman, 1997) 2. The diagnostic interview schedule for Children（DISC-I）(Costello et al. 1984) 3. The structured clinical interview for DSM-III-R /DSM-IV Axis-II Disorders (SCID-II)(First & Gibbon, 2004; First et al., 1995)	1. The Rust Inventory of Schizotypal Cognitions (RISC)(Rust, 1987, 1988) 2. The Chapman psychosis proneness scales (CPPS) (Chapman, Chapman, & Raulin, 1978; M. Eckblad & Chapman, 1983; M. L. Eckblad, Chapman, Chapman, & Mishlove, 1982) 3. The Schizotypal Personality Questionnaire (SPQ) (Raine, 1991) 4. Schizotypy questionnaire (Venables, Wilkins, Mitchell, Raine, & Bailes, 1990) 5. the Oxford–Liverpool Inventory of Feelings and Experiences (O-LIFE)(Mason et al., 1995)	1. Items from Minnesota Multiphasic Personality Inventory (MMPI) (Merritt & Balogh, 1984, 1990; Meyer, 1993; Nakano & Saccuzzo, 1985), 2. Items from CBCL(Achenbach et al., 1987) 3. Items from SCL-90-R (Derogatis, 1977) 4. Items from semi-structured interview questions.

CHAPTER THREE ASSOCIATION BETWEEN TRAUMATIC STRESSFUL EVENTS AND SCHIZOTYPAL SYMPTOMS AMONG COMMUNITY-BASED U.S. ADOLESCENTS

Abstract

Background: Traumatic stressful events (TSEs), especially during early life, are one of the most studied environmental risk factors for the subsequent development of the schizotypal symptoms. However, the specificity of trauma exposure and cumulative effect on schizotypal symptoms remains unclear. This study aims to investigate how specific types and cumulative effects of TSEs relate to specific dimensions of schizotypal symptoms among a community-based sample of US adolescents.

Objectives: To investigate how specific types of childhood traumatic stressful events relate to specific dimensions of schizotypal symptoms among a community-based sample of U.S. adolescents, and to examine if there is a dose-response relationship between number of TSEs and specific dimensions of schizotypal symptoms.

Methods: Secondary analyses were conducted on data from 426 adolescents (51.6% female) collected in the Philadelphia Neurodevelopmental Cohort study. Assessments included demographic and family history information, TSEs and mental health symptomatic symptoms, including anxiety, depression, and behavioral disorder. Evidence of schizotypal personality was completed approximately two years later.

Results: More than half of the adolescents experienced at least one type of TSE in childhood. Adolescents with assaultive TSEs reported approximately 1.5 times higher

endorsement rates of all three dimensions of schizotypal symptoms when compared to non-assaultive TSEs, after the controlling for demographic and family history factors. No statistical significance was found after further controlling symptomatic confounders (e.g., psychosis spectrum symptoms, mood disorder, anxiety disorder, and behavior disorder). There was a dose-response effect of cumulative TSE on cognitive-perceptual symptoms after controlling for all the relevant confounders.

Conclusions: Trauma-informed care to consider universal screenings of trauma in primary care may be particularly important given the high prevalence of TSEs reported. After adjusting for all important confounders, there was negligible evidence for association between trauma types and dimensional schizotypal symptoms. More compelling evidence established for the association between cumulative TSEs and cognitive perceptual symptoms. The findings highlight the importance of considering cumulative effect of TSEs and confounds when examining associations between TSEs and schizotypal symptoms.

Introduction

Traumatic stressful events (TSEs), such as being exposed to natural disasters, witnessing unsetting events, and experiencing physical or sexual assault, are among the most intensively studied environmental risk factors for the development of schizophrenia-spectrum disorder (Barzilay et al., 2019; Belbasis et al., 2018; Gearon, Kaltman, Brown, & Bellack, 2003). The milder manifestation on the continuum of schizophrenia-spectrum disorder, known as schizotypal symptoms, often has origins in adolescence, defined as ages 10 to 24 in this study (Sawyer et al., 2018). Adolescents who experience TSEs are at increased risk for the development of schizotypal symptoms, and these symptoms are associated with poorer global functioning, comorbid psychological difficulties, and increased disability (Gore et al., 2011). Investigating the association between TSEs and schizotypal symptoms, especially in adolescents, could provide information on the etiology of schizophrenia-spectrum disorder. Understanding the role of TSEs is also essential to provide effective trauma-focused intervention.

Emerging literature explores the association between TSEs and increased schizotypal symptoms in adolescents (Bendall, Jackson, Hulbert, & McGorry, 2007; Johnson et al., 2006, 2001; Sheinbaum et al., 2015). Most of these studies are based on cross-sectional design, thus, there are no time cues in cross-sectional studies to indicate the sequence of TSEs and schizotypal symptoms, introducing the issue of reverse causality (Bendall et al., 2007). That is, schizotypal symptoms may lead to increased TSEs exposure. In addition, most of the studies focus on a single type of trauma. Therefore, there is a need

for longitudinal studies to provide stronger evidence for a causal role and the impact of different types of TSEs on subsequent schizotypal symptoms.

Schizotypal symptoms are often measured in a three dimensional approach, including cognitive-perceptual or positive symptoms, interpersonal or negative symptoms, and disorganized symptoms (Barrantes-Vidal, Grant, & Kwapil, 2015a; Raine & Benishay, 1995). A few studies have examined the specific contribution of TSE type on the three dimensions of schizotypal symptoms in adult populations. Research shows that childhood abuse (emotional, physical, and general) is only associated with the positive schizotypal dimension, whereas neglect is associated with both positive and negative schizotypal dimensions (Van Dam et al., 2015). However, the nature of the association between specific types of TSEs and each dimension of schizotypal symptoms requires validation in adolescents. Moreover, adolescents who are confronted with one trauma are at increased risk for experiencing a number of TSEs (Finkelhor, Ormrod, & Turner, 2007). Thus, this study also examines the association between total number of TSEs and the three dimensions of schizotypal symptoms.

Studies describing the association of TSEs with schizotypal symptoms have often relied on the adult recollection of childhood TSEs, which can be inaccurate (Hardt & Rutter, 2004), especially in psychiatric patients. Studies conducted among community-based adolescents can avoid recall bias (Newbury et al., 2018) and also provide more accurate information about trauma experiences. It is noteworthy that the study of schizotypal symptoms during adolescence is a relatively recent field. Therefore,

adolescents need to be the subject of more systematic research in order to better interpret the relationship between TSEs and schizotypal symptoms.

In addition, few studies have directly measured and controlled for important potential covariates that may either be associated with schizotypal symptoms (Brosey & Woodward, 2015; Cohen & Davis III, 2009; Korsgaard et al., 2016; Pulay et al., 2009) or have confounding effects on adverse outcomes associated with TSEs (Doidge, Higgins, Delfabbro, & Segal, 2017). These confounding variables include demographic factors (age, gender, race, SES), and family historical factors (any of a family member having psychosis, suicide or substance use). Covariate variables such as psychosis spectrum symptoms (PSS), anxiety disorder, mood disorder, and behavioral disorder, are known to increase risk of both TSEs and schizotypal symptoms (Barzilay et al., 2019; Calkins et al., 2017). Many longitudinal studies, aiming to identify independent risk factors for psychosis, include baseline psychotic symptoms as covariates (Gage, Hickman, & Zammit, 2016; Jones, Calkins, Scott, Bach, & Gur, 2017; Mustonen et al., 2018). For example, Mustonen's research (2018) controlled baseline prodromal symptoms when examining the association between adolescent cannabis use and subsequent psychosis. The interplay between symptomatic factors, TSEs, and schizotypal symptoms among adolescents has not yet been explored. Controlling all possible confounders in the study will help researchers draw more robust conclusions about the etiological relevance of TSEs in the pathway to schizotypal symptoms.

To address the gaps in prior research, the present study utilizes data from a longitudinal study of community-based adolescents in two-year intervals. The aim is to

investigate the longitudinal impact of different types of TSEs on the three dimensions of schizotypal symptoms. This study also examines if there is a dose-response relationship between cumulative TSEs and the dimensional schizotypal symptoms. The study takes into account demographic factors, family history factors, and symptomatic factors as covariate factors to test the robustness of the findings. The two main research hypotheses are (1) There are significant association between specific types of TSEs and the three dimensions of schizotypal symptoms respectively, regardless of whether the relevant covariate factors are controlled for; and (2) There are significant association between total number of TSEs and the three dimensions of schizotypal symptoms respectively, regardless of whether the relevant covariate factors are controlled for.

Methods

Parent study and sample

This study uses secondary analysis of data. Participants are from the Philadelphia Neurodevelopmental Cohort (PNC), which is a unique dataset with neuroimaging, genetic, detailed clinical, and neurocognitive measures on a representative US community population. The study design and procedures have been described in detail elsewhere (Calkins et al., 2015, 2014). The Time 1 and Time 2 data in the PNC cohort study will be used in this study. Briefly, the PNC at Time 1 had a large community sample of 9,498 individuals aged 8 to 21 years. At Time 2, a neuroimaging eligible subset of 1,486 was identified for a two-year follow-up based on the screening of either positive or negative for psychosis spectrum symptoms. Among this neuroimaging eligible

subset, a total of 464 individuals aged 10 to 23 completed the schizotypal personality questionnaire and will be included in the study.

Informed Consent

Participants over 18 years of age provided written consent. Parental permission and written assent were obtained for participants under 18 years old. The institutional review boards at the University of Pennsylvania and Children's Hospital of Philadelphia approved the study procedures.

Measures

Traumatic stressful events (TSEs)

TSEs were assessed at Time 1, using questions on lifetime exposure to eight traumatic events. Participants were asked if they had ever experienced any of the following situations: (a) a natural disaster; (b) thought that they or someone close to them was going to be killed or hurt badly; (c) been attacked by somebody or badly beaten; (d) been forced to do something sexual (including but not limited to rape); (e) been threatened with a weapon; (f) been in a bad accident; (g) seen or heard somebody get killed, hurt badly, or die; and (h) been upset by seeing a dead body or seeing pictures of the dead body of somebody they knew well. Two types of TSEs were calculated: assaultive TSEs included endorsement of being attacked, badly beaten or threatened with a weapon, and being sexually forced; and non-assaultive TSEs included all other endorsements. Participants who endorsed in both categories were assigned to assaultive TSE as a priority. Total TSEs score was calculated by a count of endorsed items of TSEs, ranging from 0 to 8 (Barzilay et al., 2019). The Cronbach's alpha is .61 in this study.

Schizotypal symptoms

Schizotypal symptoms were evaluated using the Schizotypal Personality Questionnaire (SPQ) (Raine, 1991). The SPQ is a 74-item yes/no self-report inventory developed to characterize the schizotypal symptoms and is among the most widely studied scales quantifying schizotypal traits (Raine, 1991). It contains three subscales: cognitive-perceptual (33 items), interpersonal (25 items), and disorganization (16 items). Cognitive-perceptual symptoms include ideas of reference, odd beliefs, unusual perceptual experience, and suspiciousness; interpersonal symptoms include social anxiety, no close friends, and constricted affect; disorganized symptoms include odd behavior and odd speech. Summing the relevant items created the dimension scores and an SPQ total score, where a higher number denoted more schizotypal symptoms in dimensions and total. The endorsement rate of dimensional/total symptoms was then calculated by dimensional/total score over its corresponding number of items, and a higher endorsement rate indicated more endorsed symptoms. Eight additional infrequency items, which were modeled after the infrequency scale of the personality research form, were interspersed among SPQ items to assess random or careless responding (Moore, Calkins, Reise, Gur, & Gur, 2018). Participants were removed from the analysis if they endorsed three or more of the eight infrequency items. SPQ has been found to be reliable and valid in the original study (Cronbach's alpha = .91) (Raine, 1991). In the current study, the Cronbach's alpha was .94 for the SPQ and 0.85-0.91 for the three dimensions of SPQ.

Covariate measures

All measures are assessed at Time 1. Demographic information included age, gender (0 = male, 1 = female), and race (White, Black, other). Father's educational year and mother's educational year were used as the proxy of the socioeconomic status (SES) of the family. Higher father and mother education year indicated a higher SES of the family.

Family history information, including presence/absence of psychosis, presence/absence of suicide attempt or death, and presence/absence of substance use in any of a family member, were obtained through an abbreviated version of the Family Interview for Genetic Studies (Calkins et al., 2015).

Psychosis spectrum symptoms were assessed using three screening tools, PRIME-Screen Revised (PS-R), Scale of Prodromal Syndromes (SOPS), and psychosis screen questions from the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS). The detailed measures are described elsewhere (Calkins et al., 2014, 2017). In the present study, a binary variable was used to indicate with or without PSS. The enrichment of the PSS sample in the present study ensures an examination of the widest possible range of schizotypal symptoms as research found that participants in the PSS group were substantially more likely to show follow-up schizotypal symptoms than those in the non-PSS group (Calkins et al., 2017).

The in-person interview based on the structured Schedule for Affective Disorders and Schizophrenia for School-Age Children (GOASSESS) evaluated lifetime history of clinical symptoms on mood disorder, anxiety disorder, and behavior disorder at Time 1 (Calkins et al., 2015). In this study, three dichotomous variables were used to indicate whether or not participants had any mood/anxiety/behavioral disorder.

Power analysis

Power analysis was conducted using PASS 19.0. Sample size for analysis of covariance is 58 to investigate whether a set of two independent variables can predict the outcome with a target value *r*-squared of .1 while the value of *r*-squared for the other 13 controlled variables is assumed to be estimated as .2. The sample size is similar with the minimum recommendation for non-experimental studies (Bujang, Sa'at, & Bakar, 2017). Thus, this study with a sample size of 426 achieved sufficient power to test the association between trauma types (assaultive TSEs and non-assaultive TSEs) and different dimension of schizotypal symptoms while controlling for important covariates.

Statistical analyses plan

First, we generated descriptive statistics for all variables and assessed the distribution of baseline measures. The descriptive analyses included means and standard deviations for continuous outcomes and contingency tables with proportions for categorical data. Cronbach's alpha was examined for the reliability of all the measurements in this study. The sample contained a much higher proportion of adolescents with PSS than would occur in a random sample of the general adolescent population. To address this, this paper compared descriptive statistics for the adolescents with PSS to descriptive statistics for the typically developing adolescents (non-PSS group).

Second, bivariate analyses were carried out to identify if there were any covariates that could be influencing schizotypal symptoms. *T*-Tests were performed to compare means of continuous variables among categorical predictors; *Chi-square* tests were conducted to compare proportions among categorical variables; the Pearson or point-biserial

correlation coefficients were computed to assess the association between studied variables. Furthermore, multicollinearity tests were done to determine whether predictors were highly correlated. Myers (1990) has suggested that a variance inflation factor (VIF) value greater than 10 is a cause for concern.

Then, the effects of the specific type of TSEs or cumulative TSEs on the three-dimension scores of schizotypal symptoms were analyzed using analysis of covariance (ANCOVA). Each dimension of schizotypal symptoms served as the dependent variable, respectively. TSE types or TSEs total score were independent variables, while the other variables served as covariates. Two models were built up for each ANCOVA analysis. The first model examined the effect of specific traumatic type or TSEs total on the three dimensions of schizotypal symptoms while controlling demographic and family history variables that may confound the effects. The second model further added symptomatic factors that may confound the effects. Although the dependent variables (schizotypal symptoms) have slightly skewed distributions rather than normal distributions, ANCOVA methods are robust against slight violations of normality (Tabachnick, Fidell, & Ullman, 2007). Sensitivity analyses consisting of square root transformations were performed to validate those analyses.

The two-sided significance level set at *alpha* =.05. Analyses were performed using RStudio (Version 1.2.5033).

Results

Thirty-eight participants were removed because they endorsed three or more of the eight infrequency items in SPQ resulting in a total of 426 adolescents included in the

study. There were no missing data in age, gender, race, participant education, TSEs items, and SPQ items. Family history factors had missing values. Listwise deletion was used to handle missing data as missing proportions of family history factors were 8.5%.

Table 3.1 shows descriptive analysis for demographic characteristics for the whole study sample as well as trauma specific subgroups and PSS subgroups. The average sample age at Time 2 was 17.2 (SD = 3.15). The sample was 51.6% female, and comprised of 43.7% White, 46.5% Black and 9.9% other races. The average educational years of the father and mother were 13.8 and 14.4, respectively. Comparing assaultive TSEs, non-assaultive TSEs to no trauma groups, adolescents who were older, male, black race, and fewer parental educational years tend to experience more assaultive or non-assaultive TSEs. Girls experienced relatively higher non-assaultive TSEs while boys experienced more assaultive trauma; Black adolescents experienced relatively more TSEs than White adolescents, especially assaultive trauma. Percentages of adolescents with the characteristics of older age, male gender, black race and fewer years of parental education were higher in the PSS group than the non-PSS group.

Table 3.2 shows TSEs prevalence in whole sample and PSS groups. More than half of the sample (54.2%) had reported having one TSE. Around 2.3% of the sample reported sexual assaultive experiences, and 6~7% of the sample reported physical assaultive experiences, including being attacked or threatened with a weapon. Almost three out of ten adolescents reported non-assaultive trauma, including "witnessing someone getting killed, badly beaten or die, and seeing a dead body." The prevalence of TSEs in the PSS group (70.8%) was higher than the non-PSS group (38.2%). More specifically,

adolescents in the PSS group experienced more trauma events, except natural disaster and bad accident, than the non-PSS group.

Table 3.3 provides family history and symptomatic characteristics for the whole study sample as well as trauma specific subgroups and PSS subgroups. In the whole sample, the percentages of having a family history of psychosis, suicide, and substance use were 2.3%, 6.8%, and 19.2%, respectively, and the percentages of having met the criteria of mood disorder, anxiety disorder, and behavior disorder were 15.7%, 39.4%, and 38.0%, respectively. The percentages of having a family history and satisfying a clinical diagnosis were higher in assaultive or non-assaultive groups comparing to the no trauma group, and also higher in the PSS group comparing to the non-PSS group.

Table 3.4 presents the correlations between types of TSEs and three dimensional schizotypal symptoms. Trauma types were moderately related to each other (r = .32), assuming co-occurrence of TSEs experiences. All dimensional schizotypal symptoms were moderately associated with one another (r varied from .53 to .63). The TSEs total score had a weak to moderate relationship with dimensional schizotypal symptoms (r varied from .15 to .33), while both assaultive and non-assaultive TSEs had a weak association with dimensional schizotypal symptoms (r varied from .08 to .18).

Table 3.5 shows the results of the ANCOVA analysis of TSE types and the three dimensions of cognitive-perceptual, interpersonal, and disorganized symptoms. Both assaultive and non-assaultive TSEs had significant effects on three dimensions of schizotypal symptoms when controlling demographic, and family history characteristics. Adolescents who were exposed to assaultive TSEs had increased endorsement rates of

cognitive-perceptual, interpersonal, and disorganized symptoms that were .11, .09, and .14, respectively compared to the 'no trauma' group, while adolescents who were exposed to non-assaultive TSEs had increased endorsement rates of .07, .06, and .08, respectively compared to the 'no trauma' group. After further controlling symptomatic characteristics (e.g., psychosis spectrum symptoms, mood disorder, anxiety disorder, and behavior disorder), the estimated effects of trauma types on endorsement rates of dimensional schizotypal symptoms dramatically dropped from 11-14% to 3-4% for assaultive TSEs and from 6-8% to 1-2% for non-assaultive trauma, and did not hold statistical significance.

Considering the effect of the cumulative TSEs, Table 3.6 shows the results of the ANCOVA analysis of TSEs total score and cognitive-perceptual, interpersonal, and disorganized symptoms. When controlling demographic, and family history characteristics, the effects of cumulative trauma on all dimensional schizotypal symptoms were statistically significant. The effect of cumulative trauma remained statistically significant on cognitive-perceptual symptoms while additionally controlling symptomatic factors, although the estimated effect decreased when considering effects of the presence of psychosis spectrum symptoms. The effect of cumulative trauma on interpersonal and disorganized symptoms were no longer significant while further controlling for the symptomatic factors.

The models, which included all the studied variables, explained about 19% to 27% variance of the dimensional schizotypal symptoms. The presence of symptomatic factors, including psychosis spectrum symptoms, child mood disorder, child anxiety disorder and

child behavior disorder, are strong indicators for the development of all dimensions of schizotypal symptoms, and they explained about 9~13% of the variance (ΔR^2 ranges from 9%~13%).

Given the drop in significance following the introduction of psychosis spectrum symptoms, mood disorder, anxiety disorder, and behavior disorders, the multicollinearity between study variables were checked through examination of VIF and determined to be acceptable as no variable had a VIF higher than 2. The ANCOVA analysis using square root transformation of three-dimension of schizotypal symptoms resulted in similar findings as reported above.

Discussion

The present study utilized data collected from community-based U.S. adolescents to investigate the specific impact of traumatic types on dimensional schizotypal symptoms noted two-years following initial data collection. This study also tested the cumulative effects of traumatic stressful events (TSEs) on dimensional schizotypal symptoms. Overall, the study found more than half of the adolescents experienced at least one type of TSE. After adjusting for demographic and family history factors, adolescents with assaultive TSEs reported higher (about 1.5 times) endorsement rates of all three dimensions of schizotypal symptoms than non-assaultive TSEs. Although statistical significance was not found in the effect of specific TSE types on different dimensions of schizotypal symptoms when controlling all the relevant confounders, our findings still showed that one additional assaultive TSE can increase 3%-4% endorsement rate on schizotypal symptoms, and one additional non-assaultive TSE can increase 1-2%

endorsement rate on schizotypal symptoms. These findings suggested a relationship between TSE type and the development of dimensional schizotypal symptoms. Furthermore, there was a dose-response effect of cumulative TSEs on cognitive-perceptual symptoms after controlling for the relevant confounding factors, such that demographic factors, family history factors, and symptomatic factors.

The prevalence of TSEs was notable (54%) in the current sample, yet was a bit lower than those (62%) observed in a nationally representative sample of U.S. adolescents because the measurement tools for types of TSEs did not fully map with each other and the current study did not examine other common traumatic types, such as childhood maltreatment in a family context (K. A. McLaughlin et al., 2013). Conversely, the prevalence of TSEs was higher (54%) in the current sample than the prevalence reported (43.2%) in the original baseline sample (Barzilay et al., 2019). That is to be expected given that the sample at Time 2 oversampled adolescents with PSS which had a relatively higher prevalence of TSEs than the normal controls. The number of trauma experiences increased with age and black adolescents had experienced a higher number of assaultive TSEs than white adolescents. These findings align with the opinions that late adolescence is a relatively vulnerable period for experiencing potentially traumatic events (K. McLaughlin, Brent, & Hermann, 2018) and that there are also racial disparities in trauma exposure (López et al., 2017).

This study found assaultive TSEs to have a relative higher impact on each of the three dimensional schizotypal symptoms, compared to non-assaultive TSEs. Adolescents with assaultive TSEs in our study were mainly physical assaultive cases; our study found a

significant effect of assaultive TSEs on schizotypal symptoms after controlling for demographic and family history factors, but the significance no longer existed after controlling symptomatic factors. A recent research utilizing a 35-year study of a longitudinal birth cohort examined the impact of two types of trauma--sexual assault and physical assault, on psychotic experiences (Bell, Foulds, Horwood, Mulder, & Boden, 2019). It reported that both sexual assault and physical assault had increased rates of psychotic experiences after controlling the demographic factors, but only sexual assault, not physical assault, had increased rates of psychotic experiences by further controlling anxiety and depression symptoms (Bell, Foulds, Horwood, Mulder, & Boden, 2019). In addition, our longitudinal analysis was conducted in a two-year interval, and the mean age of our sample at Time 2 was 17.2, when early manifestation of dimensional schizotypal symptoms typically emerge (APA, 2013; P Fusar-Poli, Carpenter, Woods, & McGlashan, 2014; Linscott & Van Os, 2013). The null findings related to TSE types may also suggest that the effect of TSE types on dimensional schizotypal symptoms could emerge later in development.

This study also found the significant association between TSEs and cognitive-perceptual symptoms when the traumatic exposure was increasing after adjusting all covariates. This dose–response effect has been reported in other studies (Darnell, Flaster, Hendricks, Kerbrat, & Comtois, 2019; Layne et al., 2014).

Nurses, clinicians, and other health professionals would benefit from understanding the outcomes of this research. More community-based approaches should be considered to improve practices around trauma screening and treatment. Psychiatric nurses and other

mental health professionals need to be cognizant of the link between TSEs and schizotypal symptoms among adolescents and be particularly sensitive to the adolescent population with TSEs in the assessment and the treatment of them. Universal screenings are needed for differential types of trauma in childhood, particularly in high risk groups such as Black males. In addition, psychological interventions to reduce cognitive-perceptual symptoms and trauma-informed care to prevent recurrent trauma may be particularly important given the negative impact of schizotypal symptoms on adolescents.

Strengths and Limitations

The current study has several advantages. First, the findings added to the extremely limited body of evidence on early life factors, especially childhood trauma, for schizotypal symptoms among the adolescent population. Second, the longitudinal design of the current study established causality of the effects of TSEs on schizotypal symptoms as the temporal order of the variables that were assessed was known. Third, this study controlled for a number of relevant confounders to establish the unique contribution of TSEs on schizotypal symptoms. Fourth, the measures using both adolescent self-report and caregiver report for adolescents under 17 years old could provide a more complete picture of the experiences and symptoms of adolescents.

Despite the above advantages, these findings must be viewed with caution. First, this study utilized secondary data; only 5% of the original Time 1 sample were followed up at Time 2, which was not enough information to address the representatives of the Time 2 sample. Compared to the original Time 1 sample, the current sample has an older age (mean 14.2 in the original sample vs mean 15.2 in the current sample), higher portion of

black adolescent population (32.9% in the original sample vs 46.5 in the current sample), and similar gender portion (Calkins et al., 2015). Second, this study was not applicable for studying the specific contribution of physical assault and sexual assault separately due to the low portion of reported sexual assaultive experiences (only 10 participants). Third, TSEs measures had only three categories of trauma, which were used to assess post-traumatic experiences. The more general traumatic experiences, such as child abuse and child neglect, which are also considered important risk factors for schizotypal symptoms (Velikonja et al., 2015), should be assessed using a comprehensive measurement.

Conclusion

Evidence was found to support the specific types of TSEs on dimensional schizotypal symptoms, and the results hold when adjusting for demographic and family history factors, but the significance do not hold when further adjusting for symptomatic factors. This study establishes an initial dose-response relationship of TSEs on cognitive-perceptual symptoms in a community-based population. Overall, these results should raise a clinical concern. Given the high prevalence of TSEs reported, universal screenings are needed for differential types of childhood trauma. The findings call for community-based approaches that aim to reduce trauma exposure and promote adolescents, family, and community resilience. Future research with larger samples of adolescents and comprehensive assessments of TSEs should be used to elucidate the nature of specific trauma types on adolescent schizotypal symptoms.

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Table 3.1 Demographic Characteristics in Whole Sample, Trauma Groups and Psychosis Spectrum Symptoms (PSS) Groups

	Whole sample (n=426)	Trauma groups			p_{trauma_groups}	PSS groups		$p_{PSSvsNonPSS}$
		Assaultive (n=53)	Non Assaultive (n=178)	No Trauma (n=195)		PSS (n=209)	Non PSS (n=217)	
Age at Time 1 (years)								
Mean (SD)	15.2 (3.01)	16.7 (2.53)	15.3 (2.63)	14.6 (3.28)	<0.001	15.5 (2.59)	14.9 (3.34)	<.0.05
Age at Time 2 (years)								
Mean (SD)	17.2 (3.15)	18.9 (2.60)	17.4 (2.71)	16.6 (3.48)	<0.001	17.6 (2.68)	16.8 (3.52)	<0.05
Sex								
Male	206 (48.4 %)	31 (58.5 %)	82 (46.1 %)	93 (47.7 %)	0.274	97 (46.4 %)	109 (50.2 %)	0.489
Female	220 (51.6 %)	22 (41.5 %)	96 (53.9 %)	102 (52.3 %)		112 (53.6 %)	108 (49.8 %)	
Race								
White	186 (43.7 %)	8 (15.1 %)	80 (44.9 %)	98 (50.3 %)	<0.001	66 (31.6 %)	120 (55.3 %)	<0.001
Black	198 (46.5 %)	41 (77.4 %)	85 (47.8 %)	72 (36.9 %)		116 (55.5 %)	82 (37.8 %)	
Other	42 (9.9 %)	4 (7.5 %)	13 (7.3 %)	25 (12.8 %)		27 (12.9 %)	15 (6.9 %)	
Father Education (years)								
Mean (SD)	13.8 (2.54)	12.8 (2.07)	13.8 (2.48)	14.2 (2.65)	<0.001	13.3 (2.22)	14.4 (2.70)	<0.001
Mother Education (years)								
Mean (SD)	14.4 (2.34)	13.6 (2.33)	14.2 (2.31)	14.7 (2.32)	<0.01	14.0 (2.19)	14.7 (2.43)	<0.01

Table 3.2 TSES Prevalence in Whole Sample and Psychosis Spectrum Symptoms (PSS) Groups

	Whole sample (n=426)	**PSS (n=209)**	**Non PSS (n=217)**	$p_{PSSvsNonPSS}$
Sexually forced	10 (2.3 %)	9 (4.3 %)	1 (0.5 %)	<0.05
Attacked or badly beaten	26 (6.1 %)	22 (10.5 %)	4 (1.8 %)	<0.001
Threatened with a weapon	31 (7.3 %)	25 (12.0 %)	6 (2.8 %)	<0.001
Experienced natural disaster	15 (3.5 %)	8 (3.8 %)	7 (3.2 %)	0.941
Thought that s/he or someone close to him/her could be killed or hurt badly	63 (14.8 %)	52 (24.9 %)	11 (5.1 %)	<0.001
Experienced a bad accident	43 (10.1 %)	26 (12.4 %)	17 (7.8 %)	0.157
Witnessed someone getting killed, badly beaten, or die	110 (25.8 %)	76 (36.4 %)	34 (15.7 %)	<0.001
Saw a dead body	124 (29.1 %)	84 (40.2 %)	40 (18.4 %)	<0.001
TSE total score Mean (SD)	0.99 (1.21)	1.44 (1.36)	0.55 (0.85)	<0.001
TSE type				
No Trauma	195 (45.8 %)	61 (29.2 %)	134 (61.8 %)	<0.001
Non Assaultive	178 (41.8 %)	104 (49.8 %)	74 (34.1 %)	
Assaultive	53 (12.4 %)	44 (21.0 %)	9 (4.1 %)	

Notes. PSS = psychosis spectrum symptoms.

Table 3.3 Family History and Adolescent Psychopathological Symptoms in Whole Sample, Trauma Groups and Psychosis Spectrum Symptoms (PSS) Groups

	Whole sample (n=426)	Trauma groups			$p_{traumagroups}$	PSS groups		$p_{PSSvsNONPSS}$
		Assaultive (n=53)	Non Assaultive (n=178)	No Trauma (n=195)		PSS (n=209)	Non PSS (n=217)	
Any Family Psychosis	10 (2.3 %)	6 (11.3 %)	3 (1.7 %)	1 (0.5 %)	<0.001	10 (4.8 %)	0 (0.0 %)	<0.01
Family Suicide attempts or death	29 (6.8 %)	6 (11.3 %)	12 (6.7 %)	11 (5.6 %)	0.325	19 (9.1 %)	10 (4.6 %)	0.0914
Missing	9 (2.1%)	2 (3.8%)	3 (1.7%)	4 (2.1%)		6 (2.9%)	3 (1.4%)	
Family Substance Use	82 (19.2 %)	10 (18.9 %)	39 (21.9 %)	33 (16.9 %)	0.514	51 (24.4 %)	31 (14.3 %)	<0.05
Missing	36 (8.5%)	3 (5.7%)	14 (7.9%)	19 (9.7%)		17 (8.1%)	19 (8.8%)	
Any Mood Disorder	67 (15.7 %)	18 (34.0 %)	37 (20.8 %)	12 (6.2 %)	<0.001	64 (30.6 %)	3 (1.4 %)	<0.001
Any Anxiety Disorder	168 (39.4 %)	27 (50.9 %)	90 (50.6 %)	51 (26.2 %)	<0.001	128 (61.2 %)	40 (18.4 %)	<0.001
Any Behavior Disorder	162 (38.0 %)	31 (58.5 %)	82 (46.1 %)	49 (25.1 %)	<0.001	127 (60.8 %)	35 (16.1 %)	<0.001

Notes. PSS = psychosis spectrum symptoms.

Table 3.4 Bivariate Correlation Matrix of Specific Traumatic Stressful Events with Dimensional Schizotypal Symptoms in Whole Sample

	Whole sample (n = 426)				
	1	(1a)	(1b)	2	3
1 TSEs total					
(1a) Assaultive TSEs	0.47**				
(1b) Non-Assaultive TSEs	0.61**	0.32**			
2 Cognitive-Perceptual	0.33**	0.18**	0.10*		
3 Interpersonal	0.19**	0.11*	0.10*	0.57**	
4 Disorganized	0.15**	0.10*	0.08	0.63**	0.53**

Notes. TSEs: Traumatic Stressful Events

**Correlations were significant at $p<.01$ (two-tailed). * Correlations were significant at $p<.05$ (two-tailed).

Table 3.5 ANCOVA of TSE Types and Dimensional Schizotypal Symptoms

	Cognitive-perceptual symptoms						**Interpersonal symptoms**						**Disorganized symptoms**					
	Model One			**Model Two**			**Model One**			**Model Two**			**Model One**			**Model Two**		
	B	*SE*	*p*	*B*	*SE*	*p*	*B*	*SE*	*p*	*B*	*SE*	*p*	*B*	*SE*	*p*	*B*	*SE*	*p*
Non-Assaultive TSEs	0.07	0.02	**0.002**	0.02	0.02	0.330	0.06	0.02	**0.007**	0.02	0.02	0.344	0.08	0.03	**0.008**	0.01	0.03	0.625
Assaultive TSEs	0.11	0.03	**0.001**	0.03	0.03	0.311	0.09	0.04	**0.014**	0.03	0.04	0.330	0.14	0.05	**0.003**	0.04	0.05	0.334
Age at Time 1	-0.00	0.04	0.940	-0.01	0.04	0.704	-0.09	0.04	**0.038**	-0.09	0.04	**0.025**	-0.05	0.05	0.382	-0.05	0.05	0.303
Female	-0.00	0.02	0.847	-0.01	0.02	0.490	0.01	0.02	0.502	0.00	0.02	0.837	0.01	0.03	0.814	-0.00	0.03	0.897
Race-Black	0.07	0.02	**0.003**	0.06	0.02	**0.009**	0.06	0.03	**0.024**	0.05	0.02	**0.048**	0.01	0.03	0.840	-0.02	0.03	0.573
Race-Other	0.07	0.04	**0.048**	0.03	0.04	0.441	0.06	0.04	0.131	0.03	0.04	0.412	0.11	0.05	**0.031**	0.05	0.05	0.328
Father education	-0.01	0.01	**0.015**	-0.01	0.00	**0.027**	-0.01	0.01	**0.014**	-0.01	0.00	**0.027**	-0.00	0.01	0.624	0.00	0.01	0.924
Mother education	0.01	0.01	0.177	0.01	0.01	0.095	-0.00	0.01	0.942	-0.00	0.01	0.925	0.01	0.01	0.083	0.01	0.01	0.080
Family psychosis history	0.15	0.07	**0.023**	0.08	0.06	0.188	0.08	0.07	0.251	0.02	0.06	0.745	0.09	0.09	0.306	0.02	0.08	0.837
Family suicide history	0.00	0.04	0.991	-0.01	0.04	0.852	0.02	0.04	0.607	0.02	0.04	0.636	0.12	0.05	**0.020**	0.11	0.05	**0.027**
Family substance use history	0.04	0.03	0.144	0.02	0.02	0.477	0.03	0.03	0.197	0.02	0.02	0.382	0.06	0.03	0.071	0.04	0.03	0.225

PSS		0.10	0.02	**<0.001**		0.05	0.03	**0.038**		0.16	0.03	**<0.001**
Child mood disorder		0.08	0.03	**0.005**		0.03	0.03	0.268		0.01	0.04	0.778
Child anxiety disorder		0.04	0.02	0.078		0.09	0.02	**<0.001**		0.08	0.03	**0.007**
Child behavioral disorder		0.03	0.02	0.184		0.02	0.02	0.517		0.03	0.03	0.378
Observations	390	390			390	390			390	390		
R^2 / R^2 adjusted	0.147 / 0.123	0.275 / 0.246			0.125 / 0.100	0.220 / 0.189			0.081 / 0.055	0.218 / 0.187		

Notes. TSEs: Traumatic Stressful Events; B: beta coefficient of variable in the model; SE: standard error of a variable in the model. Reference group for TSEs is "no trauma group", and White, non-Hispanic for race.

Table 3.6 ANCOVA of Cumulative TSES and Dimensional Schizotypal Symptoms

	Cognitive-perceptual symptoms						**Interpersonal symptoms**						**Disorganized symptoms**					
	Model One			**Model Two**			**Model One**			**Model Two**			**Model One**			**Model Two**		
	B	*SE*	*p*	*B*	*SE*	*p*	*B*	*SE*	*p*	*B*	*SE*	*p*	*B*	*SE*	*p*	*B*	*SE*	*p*
Cumulative TSEs	0.05	0.01	**<0.001**	0.03	0.01	**<0.001**	0.03	0.01	**0.001**	0.01	0.01	0.217	0.04	0.01	**0.003**	0.00	0.01	0.699
Age at Time 1	-0.02	0.04	0.623	-0.03	0.04	0.424	-0.09	0.04	**0.033**	-0.09	0.04	**0.023**	-0.04	0.05	0.439	-0.05	0.05	0.361
Female	-0.01	0.02	0.727	-0.01	0.02	0.491	0.01	0.02	0.593	0.00	0.02	0.889	-0.00	0.03	0.996	-0.01	0.03	0.799
Race-Black	0.06	0.02	**0.010**	0.05	0.02	**0.020**	0.05	0.03	**0.033**	0.05	0.02	0.051	0.01	0.03	0.841	-0.01	0.03	0.634
Race-Other	0.07	0.04	0.051	0.03	0.03	0.355	0.05	0.04	0.161	0.03	0.04	0.429	0.10	0.05	**0.041**	0.04	0.05	0.355
Father education	-0.01	0.00	**0.013**	-0.01	0.00	**0.026**	-0.01	0.01	**0.013**	-0.01	0.00	**0.026**	-0.00	0.01	0.579	0.00	0.01	0.953
Mother education	0.01	0.01	0.120	0.01	0.00	0.072	-0.00	0.01	0.972	-0.00	0.01	0.937	0.01	0.01	0.081	0.01	0.01	0.080
Family psychosis history	0.14	0.06	**0.028**	0.07	0.06	0.226	0.08	0.07	0.232	0.02	0.06	0.720	0.11	0.09	0.221	0.03	0.08	0.732
Family suicide history	-0.01	0.04	0.739	-0.01	0.04	0.686	0.01	0.04	0.719	0.02	0.04	0.678	0.12	0.05	**0.027**	0.11	0.05	**0.027**
Family substance use history	0.04	0.02	0.071	0.02	0.02	0.308	0.04	0.03	0.146	0.02	0.02	0.349	0.06	0.03	0.057	0.04	0.03	0.244
PSS				0.09	0.02	**<0.001**				0.05	0.03	**0.039**				0.17	0.03	**<0.001**
Child mood disorder				0.08	0.03	**0.008**				0.03	0.03	0.270				0.01	0.04	0.726

Child anxiety disorder		0.04	0.02	0.086		0.09	0.02	**<0.001**		0.08	0.03	**0.007**
Child behavioral disorder		0.03	0.02	0.256		0.01	0.02	0.527		0.03	0.03	0.360
Observations	390	390			390	390			390	390		
R^2 / R^2 adjusted	0.192 / 0.171	0.296 / 0.270			0.127 / 0.104	0.220 / 0.191			0.075 / 0.050	0.217 / 0.187		

Notes. TSEs: Traumatic Stressful Events; B: beta coefficient of variable in the model; SE: standard error of a variable in the model. Reference group for TSEs is “no trauma group”, and White, non-Hispanic for race.

CHAPTER FOUR THE MEDIATING ROLE OF EXECUTIVE DYSFUNCTION AND SOCIAL COGNITION DEFICITS AMONG ASSOCIATION BETWEEN TRAUMATIC STRESSFUL EVENTS AND SCHIZOTYPAL SYMPTOMS IN COMMUNITY-BASED US ADOLESCENTS

Abstract

Background: Certain individuals who were exposed to traumatic stressful events (TSEs) exhibit schizotypal symptoms subsequently. The underlying mechanism is yet to be clear. Evidence suggests an independent association among TSEs, poor performance of executive function (EF) or social cognitive (SC) deficits, and schizotypal symptoms.

Objective: This study explored the possible mediating role of executive dysfunction or and social cognitive deficits between TSEs and dimensional schizotypal symptoms.

Method: Secondary data analyses of a community-based sample of 426 US adolescents were conducted. Adolescents completed measures of TSE, EF and SC at Time 1, and they completed measures of schizotypal symptoms two-years later (Time 2). Demographic, family history, and symptomatic factors were also collected at Time 1.

Results: There were significant mediation effects of EF on the relationship between TSEs and cognitive-perceptual schizotypal symptoms when adjusting for demographic factors; however, this mediation effect was no longer significant when adding symptomatic factors. No mediation effect of EF or SC was found in the association between TSEs and interpersonal schizotypal symptoms. No mediation effect of EF or SC was found in the association between TSEs and disorganized symptoms.

Conclusion: The results suggest a mediating effect of EF on the connection between TSEs and cognitive-perceptual schizotypal symptoms. Early intervention to teach

compensatory strategies through either traumatic environmental modification or cognitive behavior training to mitigate the effects of EF impairments might be helpful for the improvement of adolescents with cognitive-perceptual symptoms. More research is needed to explore the mechanisms between TSEs and schizotypal symptoms.

Introduction

Traumatic stressful events (TSEs), including physical assault, sexual assault, and non-assaultive trauma, are risk factors for schizophrenia spectrum disorders (Barzilay et al., 2019; Belbasis et al., 2018; Gearon et al., 2003). Schizophrenia spectrum disorders can be explained by the schizotypy construct which states as schizotypal symptoms in adolescence (APA, 2013; Barrantes-Vidal, Grant, & Kwapil, 2015b). These symptoms have three dimensions: cognitive-perceptual, interpersonal, and disorganized symptoms (Venables & Raine, 2015), and if they go untreated, they may persist into adulthood and cause significant impairment (Skodol, Johnson, Cohen, Sneed, & Crawford, 2007). Furthermore, the period of adolescence ages 10 to 24 (Sawyer et al., 2018) is a dynamic neuropsychological maturation phase of rapid cognitive and social changes (Rapee et al., 2019; Ullsperger & Nikolas, 2017). Due to this developmental plasticity, it is possible that exposure to TSEs might impair brain function (E. McCrory, De Brito, & Viding, 2010; Van der Kolk, 2005), thereby leaving adolescents vulnerable to developing symptoms of psychotic disorders, such as schizotypal symptoms. Given that schizotypal symptoms have a negative impact on the individual's global functioning and mental health (Gore et al., 2011), examining the underlying neuropsychological mechanisms linkingTSEs and schizotypal symptoms can provide informative insight for the developmental trajectory of schizophrenia spectrum disorder.

Adolescence is thought to be a crucial time period for the development of later psychotic disorders (Laurens et al., 2019; Oshima et al., 2010). Thus, by studying the underlying mechanisms of the link between TSEs and schizotypal symptoms specifically

in the adolescent population, there will be fewer confounding effects, such as illness chronicity, treatment medication, or long-term hospitalizations.

TSEs have been reported to be associated with schizotypal symptoms in non-clinical adult populations (Sheinbaum, Kwapil, & Barrantes-Vidal, 2014) as well as in adolescents (Wong et al., 2018). The association of TSEs on schizotypal dimensions, however, has not been fully understood. Traumatic experiences peak during adolescence, with about 70-80% of U.S. adolescents (ages 10–21 years) reporting exposure to at least one type of TSE, such as physical violence and sexual abuse (Fairbank, 2008; Nooner et al., 2012). Traumatic events and other adverse childhood experiences rarely occur in isolation (Finkelhor et al., 2007). Focusing on cumulative TSEs rather than a discrete traumatic event will contribute to the existing literature on the association between TSEs and dimensional schizotypal symptoms.

TSEs contribute to functional alterations of brain regions such as the posterior cingulate cortex (PCC), and the dorsomedial prefrontal cortex (dmPFC), which are essential for effective executive function (EF) and social cognition (SC) (Quidé et al., 2017). From the traumatic perspective, one possibility is that TSEs in early life alter neuropsychological function, with negative effects on cognitive, emotional, and social growth, leading to cognitive-perceptual symptoms, interpersonal symptoms, and disorganized symptoms in later life. However, few studies have examined the possibility that EF or SC mediates, in part, the association between trauma exposure and the subsequent development of schizotypal symptoms.

EF is necessary for regulation of goal-directed behavior, and it encompasses cognitive processes including task switching/flexibility, sustained attention, working memory, inhibitory control, and performance monitoring (Cornblath et al., 2019; Diamond, 2013). TSEs are associated with poorer EF, which is referred to as executive dysfunction among adolescents in the general population (Polak, Witteveen, Reitsma, & Olff, 2012). Executive dysfunction has been not only observed in both adolescents with schizotypal personality disorder (Diforio, Walker, & Kestler, 2000) as well as in healthy adults exhibiting schizotypal traits (Louise et al., 2015). Moreover, executive dysfunction has also been found in patients with psychotic disorders with a history of childhood abuse (MacKenzie et al., 2017; Üçok et al., 2015). Research suggests a potential mediation effect in which traumatic exposures alter the brain structure in regions responsible for EF, thus contributing to cognitive and behavioral deficits of a psychotic disorder (MacKenzie et al., 2017).

SC encompasses a set of various social skills including the ability to infer others' mental states, to recognize expressions and emotions, and to interpret social situations (Adolphs, 2001; Gur & Gur, 2016). Relations between TSEs and SC have been demonstrated among adolescents in both the general population and those with psychiatric disorders (Barzilay et al., 2019; Venta, Hatkevich, Mellick, Vanwoerden, & Sharp, 2017). Poorer SC was observed in those exposed to childhood neglect as compared to those not exposed to childhood adversities (Garcia et al., 2016). Deficits of SC also were found in young adults with more schizotypal symptoms (Aghvinian & Sergi, 2018; Quidé et al., 2018). The exposure to traumatic stressful events may cause

deprivation of early social interactions, and social cognitive deficits may facilitate the development of psychotic disorders (Buck et al., 2016; Van Os et al., 2010).

Little is known on how the association between TSEs and executive function or between TSEs and social cognition influence the development of schizotypal symptoms among the adolescent population. The aim of this study is to understand the potential neuropsychological mechanisms that explain the association between cumulative TSEs and dimensional schizotypal symptoms, among community-based U.S. adolescents.

Factors identified in the extant literature that may predispose a person to both TSEs and schizotypal symptoms are included in this study as confounders. These factors include demographic factors, such as age, gender, race, and socioeconomic status (SES); family history factors, such as psychosis, suicide attempts, and substance use reported by ; and symptomatic factors, such as psychosis spectrum symptoms, child mood disorder, child anxiety disorder, and child behavioral disorder. The three main hypotheses are (1) There are significant associations among TSEs, the three dimensions of schizotypal symptoms, EF, and SC; (2) EF mediates the relation between TSEs and three dimensions of schizotypal symptoms respectively: higher number of TSEs will lead to executive dysfunction and, in turn, lead to higher endorsement rates of dimensional schizotypal symptoms; and (3) SC mediates the relation between TSEs and three dimensions of schizotypal symptoms respectively: higher number of TSEs will lead to poor social cognition and, in turn, lead to higher endorsement rates of dimensional schizotypal symptoms.

Methods

Participants

Participants in this study were from the Philadelphia Neurodevelopmental Cohort (PNC). The PNC is a study containing neuroimaging, genetic, detailed clinical, and neurocognitive data on a representative of the US urban population. The study design and procedures have been described in detail elsewhere (Calkins et al., 2015, 2014). Briefly, the PNC at Time 1 had a large final community sample of 9,498 individuals aged 8 to 21 years. A neuroimaging eligible subset of 1,486 was identified for a two-year follow-up at Time 2 based on screening results of participants having either positive or negative signs for psychosis spectrum symptoms (PSS). A sample of 464 individuals had completed Time 2 measurements, who were the analytic sample in this study.

The institutional review boards at the University of Pennsylvania and Children's Hospital of Philadelphia approved the study protocol. Participants over 18 years provided written consent, and parental permission and written assent were obtained for participants under 18 years old.

Measures

Traumatic Stressful Events (TSEs)

TSEs at Time 1 were assessed using eight items to probe 1) lifetime exposure to natural disasters; 2) bad accidents; 3) concern that someone close was hurt badly or killed; 4) witnessing someone getting killed, badly beaten, or die; 5) seeing a dead body; and/or 6) ever experiencing assault, including being attacked or being badly beaten; 7)

being threatened with a weapon; and/or 8) sexually assaulted. The total TSE score was calculated by a count of endorsed TSEs, ranging from 0 to 8 (Barzilay et al., 2019).

Schizotypal Symptoms

Schizotypal symptoms at Time 2 were evaluated using the Schizotypal Personality Questionnaire (SPQ). The SPQ was a self-report measure, covering 74 items with a Yes/No format. The measure was originally developed to assess schizotypal personality disorder according to the DSM-III-R (Raine, 1991). Tallying the relevant items created three-dimension scores (cognitive-perceptual, 33 items; interpersonal, 25 items; and disorganized, 16 items) and an SPQ total score. The total SPQ score ranges between 0 and 74; cognitive-perceptual, interpersonal, and disorganized dimension ranges from 0 to 33, from 0 to 25, from 0 to 16, respectively. The endorsement rate of dimensional/total symptoms was then calculated by dimensional/total score over its corresponding number of items, where a higher endorsement rate denotes more schizotypal symptoms in each dimension and the total. The measure has high internal reliability (Cronbach *alpha*=0.91) (Raine, 1991). In the current study, the Cronbach's alpha was .94 for the SPQ and 0.85~0.91 for the three dimensions of SPQ.

Executive function (EF)

Executive function at Time 1 was evaluated using the Penn Computerized Neurocognitive Battery (Gur et al., 2012, 2010). Executive function is one of the five neurobehavioral domains in this battery. The EF domain includes three tests measuring abstraction and mental flexibility, attention, and working memory, respectively. Each test provides age-corrected z-scores for both accuracy and speed. The complex cognition

(CC) domain in this battery, which measures nonverbal reasoning ability and spatial ability, has a high correlation with the EF domain. A general EF-CC factor score was generated through exploratory factor analysis to capture the information of the above tests (Moore, Reise, Gur, Hakonarson, & Gur, 2015). In this study, the EF-CC accuracy factor score was used in subsequent analysis, with higher positive factor score indicating better performance than the mean average.

Social Cognition (SC)

Social cognition at Time 1 was administered as one domain in the Penn computerized Neurocognitive Battery (Gur et al., 2012, 2010), which includes three tests: emotion identification, emotion intensity differentiation, and age differentiation. Each test provides age-corrected z-scores for both accuracy and speed. Internal consistency was established with acceptable to high Cronbach alpha coefficients on both accuracy and speed (Gur et al., 2010). A general SC factor score was also produced through exploratory factor analysis to capture the information of the above three tests (Moore et al., 2015). In this study, the SC accuracy factor score was used in the analysis, with higher positive factor score indicating better performance than the mean average.

Brief test information for both EF and SC are detailed elsewhere (Gur et al., 2010).

Measures for Covariates

All the relevant covariates were tested at Time 1. Demographic factors included age, gender (0 = male, 1 = female), and race (White, Black, other). Years of education for the father and the mother were used as a proxy for socioeconomic status (SES).

Family history factors, including presence/absence of psychosis, presence/absence of suicide attempt or death, and presence/absence of substance use in any of a family member, were obtained through an abbreviated version of the Family Interview for Genetic Studies (Calkins et al., 2015).

Detailed measures of psychosis spectrum symptoms (PSS) are described elsewhere (Calkins et al., 2014, 2017). The present study used a binary variable to indicate whether the participants had PSS. The in-person interview based on the structured Schedule for Affective Disorders and Schizophrenia for School-Age Children (GOASSESS) evaluated lifetime history of clinical symptoms of mood disorder, anxiety disorder, and behavioral disorder at Time 1 (Calkins et al., 2015). In this study, three dichotomous variables were used to indicate whether or not participants had any mood/anxiety/behavioral disorder.

Power analysis

The minimum recommended sample size for mediation analysis using a percentile bootstrap method ("mediation" package in R) is 558 (Fritz & MacKinnon, 2007). Thus, the mediation analyses in the current study are exploratory.

Data analyses

Thirty-eight participants were removed because they endorsed three or more of the eight infrequency items in the SPQ. Thus, the analytic sample size was 426 for descriptive and correlation analyses, and 390 for mediation analyses due to 36 missing cases in family history information. First, we calculated the descriptive statistics for all the variables. Means and confidence intervals were provided for continuous variables and frequencies and percentages for categorical variables. *T*-Tests were performed to

compare means of continuous variables and *Chi*-square tests were conducted to compare proportions, respectively.

Then, a Pearson correlation analysis was used to ensure that independent variables (IV) (i.e. TSE total score), dependent variables (three DVs) (i.e., cognitive-perceptual symptoms, interpersonal symptoms, and disorganized symptoms), and hypothesized mediators (M) (i.e., EF or SC) were directly associated.

Next, mediation analyses were conducted for each DV. When independent variables IV, DV, and M were associated, the mediation effects of EF and SC were examined, respectively. Mediation models also adjusted for relevant covariates to validate the mediation analyses. Thus, three models were tested: an unadjusted model, a demographic and family history factors adjusted model, and an all covariates adjusted model. Mediation analyses were performed using the "mediation" package in R (Tingley, Yamamoto, Hirose, Keele, & Imai, 2014). The average direct effect (ADE) and average causal mediation effect (ACME) in the "mediation" package reflect direct and indirect (i.e. mediated) effects of EF/SC on schizotypal symptoms. In addition, a non-parametric bootstrapping procedure was conducted to yield more robust estimates of the indirect effects with 1,000 bootstrap samples (Preacher & Hayes, 2008).

Only family history factors had missing values. Listwise deletion was used to handle missing data as missing proportions of family history factors were 8.5%. *P* values less than .05 are considered statistically significant (tested 2-sided). All the analyses were considered exploratory and conducted in RStudio (Version 1.2.5033).

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Results

Demographic characteristics are presented in Table 4.1. Participating adolescents had a mean age of 17.5 years (SD = 3.17) at Time 2. The sample was 52% male, and comprised of 44% White, 46% Black, and 10% other races. Parental average education years were 14, demonstrating that parents had high school graduation and some college education on average.

Table 4.2 displays descriptive characteristics of TSEs, dimensions of schizotypal symptoms, and EF and SC, and also correlation coefficients between them. The average number of exposures to traumatic events per adolescent was .99 (54% of adolescents experienced at least one TSE event). The current sample showed approximately a 30% endorsement rate for all three dimensions of schizotypal symptoms. The positive correlations between TSEs and dimensions of schizotypal symptoms were significant, and TSEs had a moderate correlation with cognitive-perceptual symptoms (r = .33), while TSEs had a small correlation with interpersonal symptoms and disorganized symptoms (r = .19 and .15). The negative correlations between TSEs and EF (r = -.23) and social cognition (r = -.15) were also significant but small. The small negative correlations were only significant between EF and cognitive-perceptual symptoms (r = -.24), EF and interpersonal symptoms (r = -.18), and social cognition and interpersonal symptoms (r = -.10).

Disorganized symptoms were not included in the mediation analyses as no significant association was found with mediators in the correlation analysis. First, the mediation

effect of EF on TSEs and cognitive-perceptual symptoms was examined. The results indicated indirect effects of TSEs on cognitive-perceptual symptoms through EF in the unadjusted model (ACME = .007, CI = .0033 -.01 , $p < 0.001$; total effect mediated = 12.1%), and the demographic and family history adjusted model (ACME = .002, CI = .001-.01 , $p < 0.05$; total effect mediated = 4.1%), but was not significant in the all covariates adjusted model (ACME = .0004, CI = -.0018 - 0, $p = 0.22$) (see Figure 4.1). Next, the mediation effect of EF on TSEs and interpersonal symptoms was also examined. No indirect effects of TSE on interpersonal symptoms through EF were found in the unadjusted model.

Third, the mediation effect of SC on TSEs and interpersonal symptoms was examined. No indirect effects of TSE on interpersonal symptoms through SC were found in the unadjusted model.

Discussion

The present study investigated the associations between exposure to cumulative traumatic stressful events (TSEs) and three dimensions of schizotypal symptoms, with exploratory mediation analyses examining executive function (EF) and social cognition (SC) that may underlie these associations. The prevalence of TSE was high (54%) in the current population, which aligns with previous reports (La Greca et al., 2008). The research reported 61.8 % trauma exposure observed in a nationally representative sample of US adolescents ages 13–17 years (K. A. McLaughlin et al., 2013). The types of TSEs in the two studies do not fully overlap with each other as McLaughlin et al. (2013) investigated more trauma types, such as kidnapping, and life-threatening illnesses.

Cumulative TSEs had a significant positive association with each dimension of schizotypal symptoms, and a significant negative association with EF and SC. More deficits in EF were associated with higher endorsement of cognitive-perceptual symptoms and interpersonal symptoms, while more deficits in SC were associated with higher endorsement of interpersonal symptoms in adolescents. No associations were identified between disorganized symptoms and EF or SC. There were significant mediation effects of TSEs on cognitive-perceptual symptoms through EF when adjusting for demographic factors; however, this mediation effect was no longer significant when adding symptomatic factors (e.g., psychosis spectrum symptoms, mood disorder, anxiety disorder, and behavior disorder). No mediation effect of EF or SC was found in associations between TSEs and interpersonal symptoms.

Although the TSEs measurement captured the three categories of trauma-- physical assault, sexual assault, and non-assaultive community-level trauma, such as natural disaster and witnessing traumatic events, cumulative TSEs in this community sample are mainly non-assaultive trauma, with only a few proportion of physical assault or sexual assault. Cumulative TSEs were found to have a significant positive association with each dimension of schizotypal symptoms, which is consistent with existing research (Berenbaum, Thompson, Milanak, Boden, & Bredemeier, 2008; Shevlin, Houston, Dorahy, & Adamson, 2008; Velikonja et al., 2019). However, the correlation was small when compared to research that studied the relationship between childhood maltreatment and schizotypal symptoms (Berenbaum et al., 2008). The assessment tools in the current study did not capture childhood maltreatment, which is also common in adolescents.

No correlation was found between disorganized symptoms and EF. Contrary to the existing literature (Zouraraki et al., 2016), Zouraraki et al. (2016) found that decreased disorganized symptoms were associated with poorer inhibitory control in an adult sample which consists of unaffected relatives of schizophrenia patients and community participants. Different components of EF mature at different rates (Davidson, Amso, Anderson, & Diamond, 2006), and inhibitory control continues to mature during adolescence (Luna, Garver, Urban, Lazar, & Sweeney, 2004; Luna, Marek, Larsen, Tervo-Clemmens, & Chahal, 2015). This contradiction between the current paper and the existing literature may be due to the sample characteristics as the current study was of younger age and had less symptom severity than many of the previous studies. Additionally, the current study used a comprehensive factor score to represent EF, which did not capture inhibitory control as a component of EF testing.

As hypothesized, EF is a partial mediator in the association between TSEs and cognitive-perceptual symptoms. Research supports that trauma exposure is associated with several altered neuropsychological function findings, which in turn might pose risks for the development of psychopathology (Agorastos, Pervanidou, Chrousos, & Baker, 2019; Teicher & Samson, 2016). The findings suggest that trauma-caused executive dysfunction plays a vital role in the development of cognitive-perceptual symptoms. Screening tools for PSS at Time 1 in the PNC study overlap with items examined for schizotypal symptoms at Time 2, especially cognitive-perceptual symptoms. Although PSS may disappear, previous research found that PSS was persistent in more than half of the adolescents in a two-year interval in a similar population (Calkins et al., 2017). The

overlap between PSS symptoms and cognitive-perceptual symptoms may explain the non-significant mediation effects, after controlling for PSS and other covariates.

Contrary to the hypothesis, no mediation effect was found in the association between TSEs and interpersonal symptoms through social cognition. This non-significant indirect effect is probably the result of the small association between TSEs, social cognition, and interpersonal symptoms. A recent systematic review suggested that social cognition may represent a mediator between early life adversities and later psychotic symptom severity (Rokita, Dauvermann, & Donohoe, 2018b). The early life adversities in this review paper mostly include childhood maltreatment, which were not measured in the current study. Correlation between childhood maltreatment and schizotypal symptoms was reported higher than the correlation between TSEs and schizotypal symptoms in the current study (Berenbaum et al., 2008). In addition, as schizotypal symptoms have their onset in adolescents, the progression of interpersonal symptoms could change this relationship.

Implications

These findings add to the understanding of the association between TSEs and dimensional schizotypal symptoms in the existing literature. It is possible that TSEs impacted different dimensions of schizotypal symptoms through different pathways.

A better understanding of executive dysfunction and social cognition deficits associated with schizotypal symptoms also has important practical implications for evidence-based assessment and intervention advancement. Approaches may include enhancing screening, prevention, and treatment with improved awareness for treatment mechanisms. Findings from the study highlight the need to assess and screen for

executive dysfunctions and SC deficits in a traumatized adolescent population with schizotypal symptoms. The most common screening tools include neuropsychological test batteries, such as the Penn Computerized Neurocognitive Battery, and other available validated rating measures, such as Behavior Rating Inventory of Executive Function (Gioia, Isquith, Guy, & Kenworthy, 2000). In terms of prevention and treatment approaches, there are no specific psychological interventions for adolescent populations who manifest cognitive-perceptual symptoms. Adolescents who have cognitive-perceptual symptoms often show executive dysfunction, including deficits in processing information and impairments in executive mental control (Debbané, Van der Linden, Balanzin, Billieux, & Eliez, 2012). Teaching compensatory strategies targeting improving EF to adolescents may help alleviate the development of cognitive-perceptual symptoms. Therefore, executive function interventions for trauma-exposed adolescents that address cognitive-perceptual symptoms may be particularly important and need to be taken into consideration in primary health services.

Strengths and Limitations

The present study contributes to the existing literature by exploring the association between TSEs and schizotypal symptoms by addressing the gaps in previous work. It provides four notable strengths: (1)a focus on the effect of exposure to cumulative trauma (largely community level trauma) rather than a single type of trauma on different dimension of schizotypal symptoms; (2) the study of proposed neuropsychological mechanisms of effects —namely, EF and SC — on TSEs and schizotypal symptoms, respectively; (3) the use of longitudinal design among a community-based US adolescent

population; and (4) an emphasis on generating generalizable findings by controlling demographic, family historical, and symptomatic factors as these factors influence an individual's immediate response and long term reactions to TSEs.

Despite these strengths, the current study has several limitations which should be considered when evaluating the implications of the results. The first limitation pertains to trauma measurement. The assessment tools did not capture childhood maltreatment, a common traumatic history in adolescents. The absence of information on this trauma type may explain the non-significant finding in the present study. Second, the present study did not capture the timing or chronicity of trauma endured by adolescents. Trauma events which occur at different developmental stages may have very different influences on the development of psychotic symptoms. Third, the current study used factor scores of EF/SC. Factor scores gave EF/SC components different weight in the composite depending on how correlated the components in the PNC sample were. The present results are not generalizable to samples which have a distinct different feature with the PNC sample.

Future direction

The current study used Time 1 and Time 2 from the PNC dataset. TSEs measured in the present study were on average two years ahead of the screening of schizotypal symptoms. However, the study did establish a temporary time lag to examine the long-term effect of trauma on the development of schizotypal symptoms. The null results of the proposed mediation model should be worthy to examine in future studies, as there are at least two possibilities: (1) a two-year interval could not reflect an even longer lingering

effect; (2) the dynamic development of EF and SC may change their correlation with schizotypal symptoms. Future studies should utilize Time 3 and Time 4 data to capture the long-term lingering effect of trauma, and the dynamic development of neuropsychological characteristics.

Moreover, additional research is needed to further explore the mediation hypothesis among in-patient adolescents following major traumatic events. The current study treated TSEs as distinct from biological factors; therefore, future research should take into account complex factors such as gene-environment correlation as genetic factors also contribute to the development of schizotypal symptoms (Ettinger, Meyhöfer, Steffens, Wagner, & Koutsouleris, 2014; Walter et al., 2016).

Conclusion

The findings of this study pointed to adolescence as a risky period for exposure to traumatic stressful events, and suggest that cognitive-perceptual symptoms are closely related to cumulative TSEs. Thus, health providers should raise awareness of screening cumulative trauma and its consequences, particularly in adolescents at risk for schizotypal symptoms. Paying close attention to the entire traumatic history could guide health providers toward more direct questions regarding adolescents' traumatic experiences. Moreover, the results suggest a partial mediation effect of EF in the connection between TSEs and cognitive-perceptual symptoms. Early intervention to teach compensatory strategies to mitigate the effects of EF impairments might be helpful for the improvement of the cognitive-perceptual symptoms in adolescents.

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Table 4.1 Demographic Characteristics of the Sample ($N = 426$)

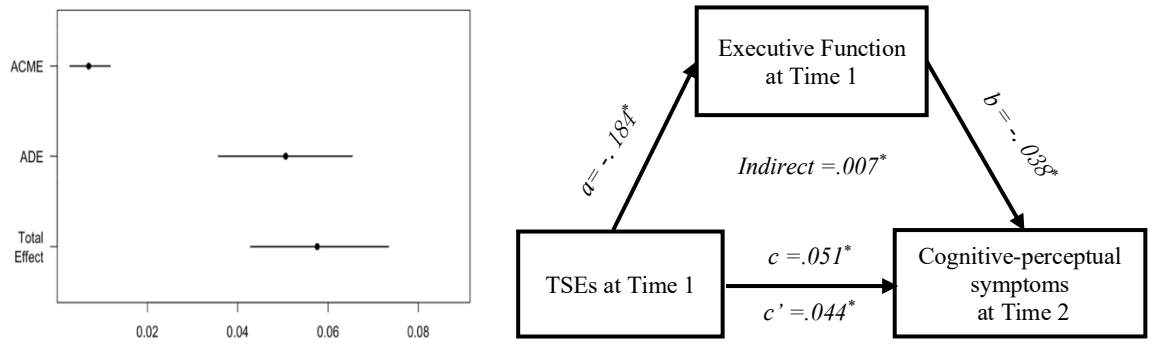
Demographic Characteristics	
Age at Time 1 (years)	
Mean (SD)	15.2 (3.01)
Age at Time 2 (years)	
Mean (SD)	17.2 (3.15)
Sex	
Male	206 (48 %)
Female	220 (52 %)
Race	
White	186 (44 %)
Black	198 (46 %)
Other	42 (10 %)
Father Education (years)	
Mean (SD)	13.8 (2.54)
Mother Education (years)	
Mean (SD)	14.4 (2.34)

Table 4.2 Descriptive Characteristics and Pearson Correlation Coefficients of Study Variables

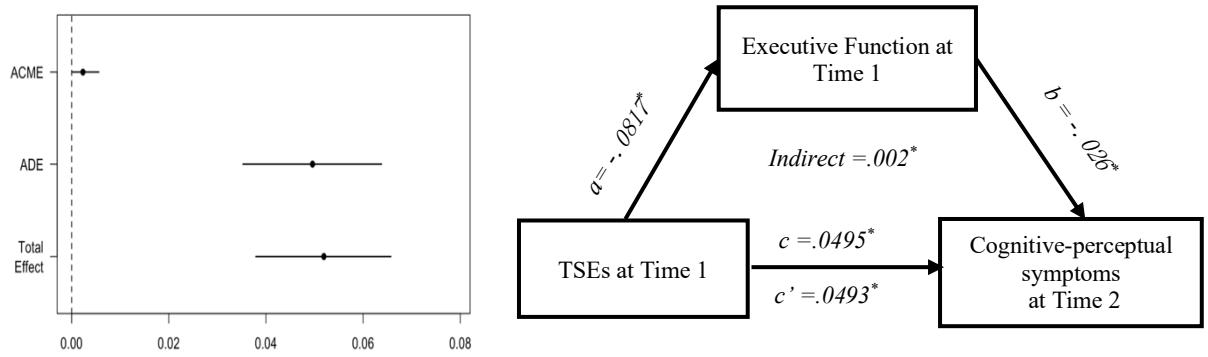
	1	2	3	4	5	6
1.TSE total	-					
2.Cognitive perceptual symptoms	0.334***	-				
3. Interpersonal symptoms	0.194***	0.569***	-			
4. Disorganized symptoms	0.148**	0.634***	0.528***	-		
5. Executive function	-0.229***	-0.244***	-0.176***	0.004	-	
6. Social Cognition	-0.151**	-0.071	-0.097*	-0.004	0.554***	-
Mean (SD)	0.99 (1.2)	0.30 (0.21)	0.32 (0.21)	0.36 (0.27)	0.069 (0.97)	0.066 (0.94)

Notes. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$

A. No covariates



B. Adjusting for demographic and family history factors



. Adjusting for demographic, family history and symptomatic factors

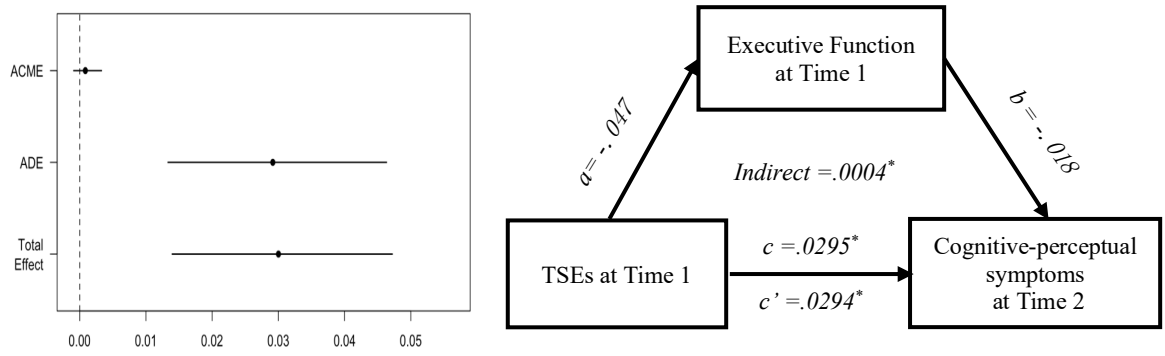


Figure 4.1 Conditional Indirect Effects of Traumatic Stressful Events through Executive Function on Cognitive-Perceptual Symptoms.
Notes. Estimates (points) and 95% confidence intervals for the average causal mediation effect (ACME), average direct effect (ADE), and total effect; ab = indirect effect, c' = the direct effect, c = the total effect, c = c' + ab.
* $p < 0.0$

CHAPTER FIVE GENERAL DISCUSSION

Main Findings

In this dissertation, early life factors that impact the development of schizotypal symptoms were first synthesized through a systematic review of twenty-four existing studies. The main findings of this systematic review (Chapter 2) demonstrated an association between a broad range of early life factors and schizotypal symptoms in adolescents. These early life factors focused on 1) factors within prenatal and postnatal periods, including parental psychopathology, pregnancy complication, and paternal age; 2) childhood and adolescence trauma such as physical abuse and psychosocial adversity; and 3) parental factors, including disturbances in early parental bonding/attachment. Childhood traumatic stressful events (TSEs) were the most studied factor among early life factors. However, TSEs are not well studied in the adolescent population due to the limited number of studies, and the variability of measurements for both early life factors and schizotypal symptoms. In addition, it is unclear whether there are the specific associations between particular traumatic events and the three dimensions of schizotypal symptoms as more than two-thirds of the included studies used total schizotypal scores rather than dimensional scores. Moreover, the possible mechanisms underlying the association between early life traumatic events and schizotypal symptoms remains unclear. The findings of this systematic review lay the basis for proposed future research directions on the association between early life factors and schizotypal symptoms in the adolescent population.

Based on the gaps in research identified through this systematic review, this dissertation study utilized the PNC dataset to first examine the association between TSEs (different types and cumulative TSEs) and schizotypal symptoms in a longitudinal community-based cohort study of US adolescents (Chapter 3). The mediation effects of executive function (EF) and social cognition (SC) were further explored in the association between cumulative TSEs and dimensional schizotypal symptoms (Chapter 4). The main findings were: 1) More than half of the adolescents experienced a childhood TSE. Non-assaultive trauma, mainly witness traumatic events, had the highest prevalence of 42% with assaultive trauma (including physical assault and sexual assault) at 12%. 2) Significant effects were found in the specific TSE types on three dimensions of schizotypal symptoms while controlling demographic and family history factors. However, after further controlling the symptomatic factors, no significant effects remained. A dose-response effect of cumulative TSEs on cognitive-perceptual symptoms was significant after controlling for all the relevant factors; 3) There was a significant mediation effect of TSEs on cognitive-perceptual symptoms through EF when adjusting the demographic factors and family history factors. However, no mediation effects were found to be significant when adding symptomatic factors. No mediation effect of EF or SC was found in the associations between TSEs and interpersonal symptoms, nor were mediation effects found in the associations between TSEs and disorganized symptoms.

The high prevalence of TSE in this dissertation aligns with the view that adolescents are more vulnerable to experiencing potentially traumatic events (McLaughlin, Brent, & Hermann, 2018). The finding of the relationship between cumulative TSEs and cognitive-

perceptual symptoms is consistent with the conceptual framework of traumatic stressful events on adolescent neuropsychological vulnerability to schizotypal symptoms. This study used different models to establish the complex association between TSEs and schizotypal symptoms. Specificities of TSEs on different dimensions of schizotypal symptoms were found after controlling demographic and family history covariates, but no specificities were found when further controlling symptomatic factors. This study took symptomatic factors, including PSS, depression and anxiety disorders as covariates when establishing the association between TSEs and schizotypal symptoms. A high prevalence of symptomatic factors is evident in adolescents with schizotypal symptoms or at high risk for psychosis (Calkins et al., 2017; Fusar-Poli, Nelson, Valmaggia, Yung, & McGuire, 2014). The current study had an enriched sample for adolescents with the presence of PSS (one of the symptomatic factors), which helped ensure the variance of schizotypal symptoms. These symptomatic factors serve as important risk factors for the subsequence schizotypal symptoms and needed to be ruled out to examine the real contribution of TSEs on schizotypal symptoms. However, these symptomatic factors have overlapping expressions with schizotypal symptoms and could play other roles besides increasing vulnerability, including prediction of transition to and ongoing experience of a psychotic disorder (Vorontsova, Garety, & Freeman, 2013). This study found that the symptomatic factors plus demographic and family history factors explained a large portion of the associations between cumulative TSEs and cognitive-perceptual symptoms, and fully explained between specific TSE type and dimensional schizotypal symptoms, and between cumulative TSEs and interpersonal/disorganized symptoms.

In general, the non-significant findings after further controlling symptomatic factors should be interpreted cautiously for two main reasons: 1) The non-significant findings were influenced by the low variance of TSE types and the relatively short follow-up period of two years in this adolescent population with the mean age of 17.2 years; 2) The non-significant findings of the effects of TSEs were also influenced by controlling PSS and child depression and anxiety disorder at Time 1 which may overlap with the expressions of schizotypal symptoms at Time 2. Therefore, when interpreting results, it is important to take the significance of the clinical practice of this research study into consideration. The findings of this study are further viewed from the trauma lens, the neurodevelopmental perspective, and the context of behavioral health services.

Trauma Lens

Viewing the findings from a trauma lens requires health providers to fully understand the features of trauma, not only types, but also severity, timing, frequency, chronicity, and perceptions, and then respond to the symptoms which occur after the trauma (Forkey, 2019). For example, a recent study found those exposed to child maltreatment during early childhood (ages 0–5) had depression symptoms that were up to twice as high as those exposed during later developmental stages (Dunn, Nishimi, Powers, & Bradley, 2017). Importantly, the features of trauma are interrelated and uniquely meaningful for mental health outcomes (Claessens et al., 2011). Within trauma research, how TSEs are defined and quantified is essential to the research on the association between TSEs and mental health outcomes.

This study used a longitudinal design to help understand the long-term impact of trauma types on the three dimensions of schizotypal symptoms. Using an eight-item measurement of TSEs, this study captured two trauma types (assaultive trauma including physical and sexual assault, and non-assaultive trauma, mainly reflecting witness trauma). The findings showed that witness trauma was the most frequent self-reported trauma type in the current sample. The reported prevalence of sexual assault (2.3%) in the community-based adolescent population was much lower than that reported (8%) in the national representative samples (Gewirtz-Meydan & Finkelhor, 2019; Saunders & Adams, 2014). Due to the low prevalence, our study did not have a large enough sample size to differentiate the impacts of sexual assault and physical assault on the dimensional schizotypal symptoms.

The measurement of TSEs in this study also captured the number of traumatic experiences. This study found the association between exposure to cumulative TSEs and more schizotypal symptoms, especially cognitive-perceptual symptoms. Adolescents who are exposed to more types of maltreatment are found to have a higher level of PTSD symptoms, anger, or dissociation (Barzilay et al., 2019). Other studies have found a positive relationship between cumulative trauma experiences and symptom complexity (Briere, Kaltman, & Green, 2008; Hodges et al., 2013).

However, the measurement did not include childhood abuse and neglect, which are also important trauma types. Estimates of trauma exposure rates and subsequent mental health outcomes have varied depending on the type of trauma measurement. A substantial number of population-based studies have suggested that childhood abuse and neglect

impacted the manifestation of psychopathological symptoms (Kessler et al., 2010). Longitudinal study found that individuals with higher levels of childhood trauma had higher levels of attenuated positive symptoms after a 2-year follow-up (Kraan et al., 2015).

Neurodevelopmental Perspective

The integration of a neurodevelopmental approach helps uncover the mechanisms by which TSEs during childhood put individuals at risk for mental health problems (Casey, Oliveri, & Insel, 2014). TSEs were found to impact neurocognitive development (De Bellis, Woolley, & Hooper, 2013; Zilberstein, 2014), which contributes to a variety of mental health problems(Clarkson Freeman, 2014; Lucenko, Sharkova, Huber, Jemelka, & Mancuso, 2015). These findings suggest that TSEs lead to neurocognitive alterations that embed latent vulnerability to a psychiatric disorder.

This study found that larger trauma exposures were associated with executive dysfunction and social cognition deficits in adolescents. This study also found negative correlations between EF and cognitive-perceptual symptoms/interpersonal symptoms, and social cognition and interpersonal symptoms. Only a partial mediation effect of EF was found between TSEs and cognitive-perceptual symptoms when adjusting for demographic and family history factors.

Neurodevelopmental research shows specific windows of neural development that exist for the optimal wiring of children's sensory systems. During brain development, how adolescents interact with environmental factors and respond to their life's traumatic experiences, ultimately, integrates them into fully developed human neurocognition (E. J.

McCrory, Gerin, & Viding, 2017), including EF (Kilford, Garrett, & Blakemore, 2016) and SC (Crone & Steinbeis, 2017). Although the EF tests and SC tests in the Penn Web-Based Computerized Neurocognitive Battery were already validated to measure EF and SC, the factor score of EF/SC used in the current study may not capture the full characteristics of EF/SC components. In addition, using lower factor scores as the proxies for impairment of function in a brain region may be limited. And the relatively short follow-up period may not capture the specific windows of EF and SC development. Thus, the limitations of the factor scores may lead to the null significant mediation effects of EF/SC between TSEs and interpersonal symptoms.

Trauma-informed Care in Behavioral Health Services

Individuals are shaped by their life experiences. From a behavioral health perspective, many individuals with schizophrenia spectrum disorders who seek treatment have histories of trauma. However, they are often unaware of how traumatic experiences can affect their lives; either they don't make connections between their trauma histories and their current mental health issues, or they avoid the topic altogether. The findings in this study show that many individuals who report schizotypal symptoms, especially cognitive-perceptual symptoms, can be interpreted in terms of cumulative TSEs exposure. These findings are consistent with clinical observations and a growing body of research which show genetic factors related to schizophrenia spectrum disorders cannot fully explain the development of schizotypal symptoms (Ettinger et al., 2014).

TSEs are preventable risk factors for the development of psychotic symptoms (McGrath et al., 2017). Trauma-informed care helps individuals understand and

acknowledge how trauma affects their past and current health status, and then creates protective environments for them. Research finds that trauma-informed care shows promising effects for the cognitive-perceptual symptoms of psychosis (Brand, McEnery, Rossell, Bendall, & Thomas, 2018). Health providers should integrate the trauma-informed approach into their treatment programs while working with adolescents with schizotypal symptoms. Health providers can ask questions that are directly related to an individual's traumatic experiences, prepare to address trauma-related cases proactively, or manage traumatic stressors effectively within the constraints of their treatment programs, the program's clinical orientation, or their health agency's directives.

Implications

This dissertation has implications for theory, practice, and policy.

The longitudinal nature of the PNC dataset employed in this study helped establish temporal order between cumulative trauma exposures and more cognitive-perceptual symptoms subsequently by controlling the relevant covariates. These findings contribute to the understanding of traumatic stressful events as the second hit on the development of schizotypal symptoms among the adolescent population. Furthermore, the findings validated the conceptual framework of "Traumatic stressful events on adolescent neuropsychological vulnerability to schizotypal symptoms".

Nurses, clinicians, and other health professionals can benefit from understanding the outcomes of this dissertation study. Psychiatric nurses and other mental health professionals need to be particularly sensitive to the comprehensive assessment of trauma in the treatment of adolescents. These findings strongly suggest the need for significant

changes in screening/clinical practice. Effective screening tools of history of traumatic events during childhood and adolescence can end up reducing the length of the course of treatment. Health care professionals working with adolescents may ask about the traumatic history of adolescents, for early identification of at-risk adolescents sooner and more successful use of timely, tailored preventive interventions. This study reinforces the need for trauma-informed care. More specifically, it highlights the need for an effective treatment in order to decrease schizotypal symptoms for adolescents who have experienced potentially traumatic events.

Policymakers should understand the impact of exposure to trauma on adolescents, and figure out the best approach that will improve outcomes for adolescents exposed to trauma. Due to higher prevalence of assaultive TSE in black adolescents in the literature (K. A. McLaughlin et al., 2013) and in this sample, there is also a need to implement policies that reduce the effects of trauma on families and children, as well as policies that promote social support at the societal, community, and family levels.

Strength and Limitation

The findings resulting from this dissertation addressed a significant gap in the current literature on the relationship between TSEs and schizotypal symptoms, as the results added to the extremely limited body of evidence on early life factors for schizotypal symptoms among the adolescent population. Second, nurses, clinicians, and other health professionals can benefit from understanding the outcomes of this research by providing a comprehensive assessment of trauma and designing relevant early trauma-informed

intervention programs that can have life-long implications for improving adolescents' mental health.

Although this dissertation has the strengths of a large, community-based adolescent population, its conceptual framework, and a longitudinal design, its design still has some limitations. First, it was a secondary analysis of the PNC data; the original data were not collected to achieve the present study aims. The TSEs in the PNC dataset had been measured differently than the measurements that would be applied in a research study specifically designed to investigate the association between TSEs and schizotypal symptoms. Some very important aspects of TSEs in adolescences, such as childhood abuse and neglect, were not measured during either the Time 1 or Time 2 interviews. In addition, the sample was not a random sample from the community-based population. Secondly, assessing exposure to TSEs and schizotypal symptoms relied largely on retrospective self-reporting methods, so the possibility that bias in memory might have affected responses cannot be ruled out. Furthermore, the sample may have a biased perception of traumatic experiences due to the presence of PSS, compared to the sample without PSS. Thirdly, although the incorporation of a large number of covariates into ANCOVA and mediation analysis makes the independent association between TSEs and the three dimensions of schizotypal symptoms more reliable, this study should be examined with larger datasets, especially in the mediation analysis. A relatively small sample size did not have enough power to address the statistically significant mediation effect of executive function and social cognition on the association between TSEs and dimensional schizotypal symptoms.

Future Directions

Given the limitations of the current study and the lack of significant results to the research questions, it is recommended that future research focus on modifying various conditions of this study to generate more meaningful results regarding the mental health treatments of adolescents. First, the hypothesis can be retested in a longer follow-up period by utilizing Time 3 PNC data (4 years interval). Second, longitudinal studies are needed to better understand how TSEs alter the neuropsychological function and therefore contribute to the development of schizotypal symptoms. Future research may be conducted with the consideration of limitations reviewed in this study, by using a better comprehensive measurement of traumatic stressful events. More precisely, future longitudinal studies would allow the valid identification of the influence of important variables including such as type of TSEs, age of exposure, and duration of TSEs.

The study using ANCOVA analyses showed different results when adjusting different covariate factors. The ANCOVA analyses could find the unique contribution of TSEs for schizotypal symptoms, but provide limited insight into the complex relationship between TSEs and demographic, family history, and symptomatic factors. Future studies that adopt different analytic approaches should also be considered as approaches such as network analysis which can offer a novel way to both quantify and visualize the complex interplay between many interacting variables (Borsboom, 2017).

Conclusion

The study of schizotypal symptoms in adolescence is a relatively recent field that needs to be the object of more exhaustive and systematic research. The present study

provided a step towards understanding the relationships between TSEs and dimensional schizotypal symptoms. This study found that TSEs are common in childhood but that no direct relationship existed between types of TSEs and dimensional schizotypal symptoms. Nonetheless, this study found a significant direct relationship between traumatic stressful life events in childhood and cognitive-perceptual symptoms in adolescence. The findings suggest that intervention programs addressing schizotypal symptoms may incorporate screening instruments for TSEs in order to identify high-risk adolescents in need of interventions relative to stress and coping. Results also showed that executive function may serve as a mediator between TSEs and cognitive-perceptual symptoms. Therefore, neuropsychological factors affecting adolescent mental health are relevant to emerging schizotypal symptoms and should be incorporated into interventions in order to reduce the burden of schizotypal symptoms in the adolescent population.

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