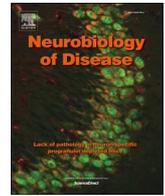




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## Review

## Child maltreatment and psychosis

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## A B S T R A C T

This paper reviews the literature on the association between experiences of child abuse and neglect and the development of psychoses. It then explores the premise that psychotic patients with a history of maltreatment may comprise a clinically and biological distinct subgroup. The review demonstrates that there is a growing consensus in the field that experiences of child maltreatment contribute to the onset of psychotic symptoms and psychotic disorders. There is also strong support for the premise that patients with psychotic disorders and histories of child maltreatment have distinct clinical characteristics and unique treatment needs, and emerging preliminary data to suggest psychotic patients with a history of maltreatment may comprise a distinct neurobiological subgroup. The mechanisms by which experiences of child maltreatment confers risk for psychotic disorders remains unknown, and the review highlights the value of incorporating translational research perspectives to advance knowledge in this area.

## 1. Introduction

Child maltreatment is a non-specific, but potent risk factor for a broad array of psychiatric (Kendler et al., 2000; Kaufman, 1991; Nanni et al., 2012; Morgan & Gayer-Anderson, 2016; Green et al., 2010; Scott et al., 2010; Kessler et al., 2010; McGrath et al., 2017), substance abuse (Green et al., 2010; Scott et al., 2010; Molnar et al., 2001; Afifi et al., 2012), and physical health problems (Felitti et al., 1998; Anda et al., 2008; Romans et al., 2002; Brown et al., 2010). This paper reviews the literature on the association between experiences of child abuse and neglect and the development of psychoses. It then explores the premise that psychotic patients with a history of maltreatment may comprise a clinically and biological distinct subgroup.

Since the publication of the first paper reporting elevated rates of child sexual abuse in adult patients with schizophrenia in 1984 (Friedman & Harrison, 1984), there have been nine systematic reviews of the literature examining the association between child maltreatment and psychosis (Morgan & Gayer-Anderson, 2016; Varese et al., 2012; Read et al., 2005; Morgan & Fisher, 2007; Bendall et al., 2008; Carr et al., 2013; Matheson et al., 2013; Ackner et al., 2013; Bonoldi et al., 2013). In a review of 20 studies focusing on patients with schizophrenia ( $N = 896$ ), the weighted average rate of child sexual abuse was estimated at 42% in female patients, and 28% in male patients. Irrespective of sex, it was estimated that approximately 35% of the patients with schizophrenia had a history of physical abuse, and 50% experienced either sexual or physical abuse, or both forms of maltreatment (Morgan & Fisher, 2007).

In 2013 Teicher and Samson reviewed the literature on

maltreatment as a risk factor for depressive, anxiety, and substance use disorders, and examined clinical and neurobiological differences between patients with and without a history of maltreatment who met criteria for each of these diagnoses. Based on their review, they concluded patients with these disorders with a history of maltreatment constituted a distinct subtype within each of these diagnostic categories (Teicher & Samson, 2013). Psychotic disorders were excluded from their review given the high heritability associated with these diagnoses, but given the high prevalence of maltreatment in patients with psychotic disorders, a review of the clinical and neurobiological correlates of psychotic disorders in patients with and without histories of child maltreatment appears warranted.

## 2. Child maltreatment as a risk factor for psychosis

Child maltreatment includes experiences of neglect and emotional, physical, and sexual abuse. The definitions for these different types of maltreatment categories are delineated in Table 1 (Holbrook et al., 2015). While other childhood adversities have been examined in the literature in association with the development of psychosis (e.g., poverty, parental divorce, death of a parent, parent psychopathology, peer bullying), maltreatment is the focus of this review due to the larger research base focusing on child maltreatment, and the well-documented and replicated strength of the associations between experiences of child maltreatment and the development of multiple forms of psychopathology (Kendler et al., 2000; Kaufman, 1991; Nanni et al., 2012; Morgan & Gayer-Anderson, 2016; Green et al., 2010; Scott et al., 2010; Kessler et al., 2010; McGrath et al., 2017).

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**Table 1**  
Definitions of child maltreatment categories.

<i>Neglect.</i> Child lacked appropriate care: not provided enough to eat or drink, hygiene not attended to, lacked shelter, not provided routine or urgent medical care, left alone when too young to care for himself/herself, or left with inappropriate caregiver (e.g., sex offender, intoxicated individual).
<i>Emotional abuse.</i> A parent or other adult in the household told child that s/he is no good, yelled at child in a scary way, or threatened to harm, abandon, leave, or send child away.
<i>Physical abuse.</i> A parent or other adult in the household physically assaulted the child (e.g., hit, push, choke, shake, throw, bite, burn) causing bruises or physical injury. This may have occurred in the context of disciplining the child, or independent of discipline.
<i>Sexual abuse.</i> A parent, other adult, or peer five years or older than the child, made child see (e.g., watch pornography, watch other masturbate) or do something sexual (e.g., fondle, oral, anal, or vaginal intercourse).

Initial studies examining child maltreatment as a risk factor for psychosis were conducted in relatively small convenience samples (Friedman & Harrison, 1984; Morgan & Fisher, 2007). This association has now been examined in clinical and population-based samples, utilizing both cross-sectional and longitudinal prospective designs (Morgan & Gayer-Anderson, 2016). The most comprehensive meta-analysis published to date of studies examining the association between experiences of maltreatment and the presence of psychotic symptoms or psychotic diagnoses included 36 studies: 18 case-control studies ( $N = 2048$  psychotic patients and 1856 non-psychiatric controls), 10 prospective and quasi-prospective investigations ( $N = 41,803$ ), and 8 population-based cross-sectional studies ( $N = 35,546$ ). Significant associations between psychosis and maltreatment were detected across all research designs, with maltreatment exerting an overall effect or odds ratio of 2.78 (95% CI 5 2.34–3.31) in predicting the presence of psychotic symptoms or psychotic diagnoses (Varese et al., 2012). Considering the specific forms of maltreatment, the odds ratios were 2.90 (95% CI: 1.71–4.92) for neglect; 3.40 (95% CI: 2.06–5.62) for emotional abuse; 2.95 (95% CI, 2.25–3.88) for physical abuse; and 2.38 (95% CI, 1.98–2.87) for sexual abuse (Varese et al., 2012).

Risk for psychosis is also increased in individuals who have experienced more types of maltreatment, and those with the most severe maltreatment experiences. Ten studies included in the meta-analysis tested the impact of experiencing multiple types of maltreatment experiences, and nine of the ten studies supported a dose-response effect, with greater risk for psychosis associated with experiencing more types of maltreatment or other adverse childhood experiences (Varese et al., 2012). In terms of maltreatment severity, one of the studies included in the meta-analysis focused exclusively on experiences of sexual abuse and reported odds ratios for developing psychotic symptoms separately for different levels of child sexual abuse. Consistent with expectations, the highest risk for the development of psychosis was associated with experiences of non-consensual sexual intercourse with an odds ratio of 10.15 (95% CI: 4.8–21.3) (Bebbington et al., 2011).

To rule out the possibility that the association between experiences of child abuse and psychosis were due to familial loading factors that influence exposure to negative environments or increase sensitivity to the effects of abuse, Fisher and colleagues used a large epidemiological case-control sample to explore the interplay between child physical abuse and familial loading for psychiatric illness on the onset of psychosis (Fisher et al., 2014). In a cohort of 172 first presentation psychosis cases and 246 geographically matched controls from the Aetiology and Ethnicity of Schizophrenia and Other Psychoses (AESOP) study: parental psychosis was more common among psychosis cases than unaffected controls (adjusted OR = 5.96, 95% CI: 2.09–17.01,  $P = .001$ ); and parental psychosis was also associated with physical abuse from mothers in both cases (OR = 3.64, 95% CI: 1.06–12.51,  $P = .040$ ) and controls (OR = 10.93, 95% CI: 1.03–115.90,  $P = .047$ ). Nevertheless, adjusting for parental psychosis did not measurably impact the abuse-psychosis association (adjusted OR = 3.31, 95% CI:

1.22–8.95,  $P = .018$ ), and no interaction was found between familial liability and maternal physical abuse in determining psychosis caseness, suggesting that the reported associations between child abuse and psychotic disorders are not due to underlying familial loading for psychiatric illness.

Several investigators have also conducted gene by environment (GxE) analyses to determine if reported associations between child abuse and psychosis are due to, or exacerbated by, genetic risk factors. In a recent study examining a polygenic risk score associated with schizophrenia (Trotta et al., 2016), both childhood adversity and elevated scores on the polygenic risk factor were associated with the presence of a psychotic disorder, but there was no evidence of a GxE interaction, such that the effect of the polygenic risk score was not increased in the presence of a history of childhood adversity. In candidate gene studies (Aas et al., 2013; Aas et al., 2014; Collip et al., 2013; Green et al., 2014), GxE interactions were also not significant in predicting psychotic symptoms or psychotic disorder caseness, but rather only the presence of endophenotypes associated with psychosis (e.g., elevated cortisol, cognitive disturbances, hippocampal volume reduction).

### 3. Maltreatment-related clinical correlates of psychotic disorders

Child abuse histories among patients with psychotic disorders is associated with an earlier age of onset (Alvarez et al., 2011), more hospital admissions (Alvarez et al., 2011; Schenkel et al., 2005), more persistent course of psychosis (Trotta et al., 2015), greater functional impairment (Trotta et al., 2016; Alameda et al., 2015), higher rates of treatment non-response (Misiak & Frydecka, 2016; Hassan & De Luca, 2015), and higher rates of treatment drop out (Schalinski et al., 2015). A history of child abuse is also associated with more severe psychotic symptoms (Alvarez et al., 2011; Schenkel et al., 2005; Schalinski et al., 2015; Alameda et al., 2016; Scott et al., 2007; Grivel et al., 2017), higher rates of suicidality (Schenkel et al., 2005; Grivel et al., 2017) and suicide attempts (Alvarez et al., 2011; Grivel et al., 2017; Schafer & Fisher, 2011), elevated symptoms of depression and anxiety (Schenkel et al., 2005; Alameda et al., 2016; Schafer & Fisher, 2011), greater likelihood of bouts of violent behavior (Spidel et al., 2010), higher rates of comorbid Posttraumatic Stress Disorder (PTSD) diagnoses (Schafer & Fisher, 2011; Swan et al., 2017), as well as higher rates of comorbid alcohol and/or substance use disorders (Schalinski et al., 2015; Schafer & Fisher, 2011; Tomassi et al., 2017). No studies were identified which documented higher rates in any of these outcomes in patients with psychotic disorders without a history of child abuse (See Table 2 for a summary of the clinical characteristics of patients with psychotic

**Table 2**

Clinical characteristics of patients with psychotic disorders with histories of child abuse when compared to patients with psychotic disorders without histories of child abuse.

Earlier age of onset for psychotic disorders (Alvarez et al., 2011)
History of more psychiatric hospitalizations (Alvarez et al., 2011; Schenkel et al., 2005)
Greater functional impairment (Trotta et al., 2016; Alameda et al., 2015)
Higher rates of treatment non-response and treatment drop out (Schalinski et al., 2015; Hassanain et al., 2005; Misiak et al., 2017)
More severe psychotic symptoms and more persistent course of illness (Trotta et al., 2016)
Higher rates of comorbid mood and anxiety disorders and alcohol and substance use disorders (Schenkel et al., 2005; Alameda et al., 2015; Schalinski et al., 2015; Schafer & Fisher, 2011; Tomassi et al., 2017)
Higher rates of suicidality and suicide attempts (Alvarez et al., 2011; Schenkel et al., 2005; Grivel et al., 2017; Schafer & Fisher, 2011)

Across all studies, worse clinical outcomes were reported in patients with psychotic disorders with histories of child abuse; no studies documented higher rates in any of the above measures in patients with psychotic disorders without a history of child abuse.

disorders that have a history of child abuse).

There is an emerging literature that trauma-focused psychological treatments such as prolonged exposure therapy, cognitive behavior therapy (CBT), eye movement desensitization and reprocessing, and written emotional disclosure can be used effectively in patients with psychotic disorders (Swan et al., 2017). In a recent review of 15 studies conducted with patients with PTSD and psychotic disorders, the trauma-focused interventions were effective in reducing PTSD symptoms (Swan et al., 2017). The conclusion of that review is corroborated by a recent meta-analysis which demonstrated small, yet significant effects of trauma-focused interventions in not only reducing PTSD symptoms, but also positive symptoms and delusions, with non-significant changes reported in depression and anxiety symptoms, and changes in positive symptoms not maintained at follow-up (Brand et al., 2018). The Impact of Events Scale, one of the most widely used instruments in PTSD research, has been found to be reliable when used with psychotic patients (Schafer et al., 2011), facilitating ongoing work in this area and the conduct of combined psychotherapy plus medication trials to enhance outcomes associated with trauma-focused interventions. Mansueto and Faravelli delineated some valuable clinical implications of these research findings which include: systematically assessing psychotic patients for exposure to childhood and adult adversities to help identify high-risk subjects; incorporating strategies to reduce stress (e.g., self-relaxation, distraction techniques, CBT) into the treatment of psychotic patients; and utilizing interventions aimed at promoting protective factors (e.g. social supports) to enhance resilience (Mansueto & Faravelli, 2017).

#### 4. Maltreatment-related neurobiological correlates of psychotic disorders

This section reviews structural, diffusion tensor, and functional neuroimaging studies with patients with psychotic disorders that examined the impact of child adversity on imaging findings. Findings from structural brain imaging studies with patients with psychotic disorders and child maltreatment histories are generally consistent with the findings in the field of trauma research, with only one psychotic symptom specific structural neuroimaging correlate of child maltreatment reported in the literature. A history of child maltreatment has been associated with numerous structural brain imaging changes, including reduced volume in the following areas: hippocampus (Dannlowski et al., 2012; Paquola et al., 2016; Woon et al., 2010), amygdala (Paquola et al., 2016), anterior cingulate cortex (ACC) (Dannlowski et al., 2012), cerebellum (De Bellis & Kuchibhatla, 2006), dorsolateral prefrontal cortex (PFC) (Paquola et al., 2016), inferior frontal gyrus (Lim et al., 2014), and total gray matter (Paquola et al., 2016; Edmiston et al., 2011), with the majority of these structural brain imaging findings supported by meta-analyses. Many of these alterations have been reported in both patients with PTSD and healthy controls with histories of maltreatment (Dannlowski et al., 2012). Child abuse has also been associated with reduced cortical thickness in multiple brain regions implicated in stress-related psychiatric disorders (Busso et al., 2017; Gold et al., 2016; Kelly et al., 2016). As depicted in Table 3, consistent with the child maltreatment research findings, dimensional measures of child maltreatment have been found to predict reductions in global cortical thickness (Habets et al., 2011) and reductions in the following brain regions in patients with psychotic disorders: amygdala (Aas et al., 2012; Hoy et al., 2012), hippocampus (Hoy et al., 2012), ACC (Kumari et al., 2014), cerebellum (Kumari et al., 2013), dorsolateral PFC (Cancel et al., 2015), inferior frontal gyrus (Sheffield et al., 2013; Poletti et al., 2016), and total brain gray matter (Cancel et al., 2015). Reduced thalamic volumes were also reported in association with child maltreatment and adverse childhood experiences in patients with psychotic disorders (Kumari et al., 2013; Poletti et al., 2016), with reductions in thalamic volumes not previously reported in prior structural MRI studies with maltreated cohorts (Paquola et al., 2016). As altered

thalamic connectivity with multiple brain regions has been found to predict conversion to full-blown psychotic illness among high risk adolescents and young adults who meet criteria for prodromal syndromes (Anticevic et al., 2015), further follow-up of these findings in patients with psychotic disorders with and without histories of childhood trauma appears warranted.

Table 4 summarizes the diffusion tensor imaging (DTI) and functional neuroimaging studies that have been conducted in patients with psychotic disorders that examined the impact of early adversity on neuroimaging findings. There has only been one such DTI study conducted in patients with schizophrenia, and a history of greater childhood adversity was associated with reduced fractional anisotropy in multiple white matter tracts (Poletti et al., 2015). Each of the tracts impacted by early adversity identified in the cohort of patients with schizophrenia were also previously associated with a history of child maltreatment in healthy controls and/or patients with non-psychotic psychiatric disorders, with child maltreatment in prior studies associated with reduced fractional anisotropy in the corona radiata (Daniels et al., 2013; Hanson et al., 2013; Huang et al., 2012), thalamic radiations (Daniels et al., 2013), corpus callosum (Huang et al., 2012; Jackowski et al., 2008; Rinne-Albers et al., 2016; Lu et al., 2013), cingulum bundle (Daniels et al., 2013; Hanson et al., 2013; Banihashemi et al., 2017), superior longitudinal fasciculus (Daniels et al., 2013; Hanson et al., 2013), inferior fronto-occipital fasciculus (Huang et al., 2012), and uncinate fasciculus (Hanson et al., 2015).

In terms of the functional MRI studies that have been conducted with patients with psychotic disorders that examined the effects of early adversity, one study examined neural correlates of working memory (Quide et al., 2017), and two studies examined the impact of early adversity on neural correlates of emotion processing (Benedetti et al., 2011; Cancel et al., 2017). The results of the imaging study examining working memory are consistent with the findings in the field of child trauma (Philip et al., 2016), with childhood trauma in patients with psychosis associated with diminished performance on the N-back working memory task, and increased activation in the inferior parietal lobe during task performance (Quide et al., 2017). The studies that have examined the neural correlates of emotion processing are not consistent with the child trauma literature, but these two studies included smaller cohorts. In the first study, a history of higher childhood adversity was associated with reduced activation in the amygdala when processing emotional stimuli (Benedetti et al., 2011). While there is one study in the literature that reported reduced amygdala activation in processing emotional stimuli in healthy controls with histories of adverse childhood experiences (Taylor et al., 2006), the opposite finding is most frequently reported, with a recent meta-analysis of 20 studies which included 1733 participants reporting child maltreatment was associated with increased bilateral amygdala activation to emotional face stimuli (Taylor et al., 2006). The second study that examined the impact of early adversity on neural correlates of emotion processing reported reduced functional connectivity between the amygdala and the left posterior cingulate, left precuneus, and right calcarine sulcus in the schizophrenic patient group with histories of sexual abuse (Cancel et al., 2017). To the best of our knowledge, similar patterns of functional connectivity have not been reported in association with child maltreatment in non-psychotic cohorts, with altered amygdala connectivity with frontal cortex brain regions most consistently reported in the child maltreatment literature (Fonzo et al., 2013; Jedd et al., 2015; Cisler et al., 2013).

While the breadth and depth of the research is limited, the findings from neuroimaging studies with patients with psychotic disorders and early trauma histories suggest that patients with psychotic disorders and histories of child maltreatment may comprise a distinct subgroup of patients with unique neurobiological correlates. The findings reported in patients with psychotic disorders and histories of child maltreatment, however, are generally consistent with the findings reported in the field of trauma research. Many of the findings reported in patients with

**Table 3**  
Structural neuroimaging studies with patients with psychotic disorders that examined the impact of child abuse on outcomes.

Structural neuroimaging studies			
Reference	Child trauma assessment	Sample characteristics	Main findings
Hoy et al., 2012 (Hoy et al., 2012)	CTQ total score	21 First Episode Psychosis (10 SCZ, 3 BP, 2 MDD, 6 Other)	Childhood trauma was negatively correlated with total hippocampal and amygdala volume
Aas et al., 2012 (Aas et al., 2012)	Physical or Sexual abuse, or Experiences of Separation or Loss	45 First Episode Psychosis (average duration > 1 year)	A history of two or more childhood traumas was associated with reduced total, R and L amygdala volume
Kumari et al., 2013 (Kumari et al., 2013)	Physical Abuse	14 ASD-violent 13 SCZ-violent 15 SCZ-non-violent 15 HC-non-violent	Physical abuse ratings were associated with reduced whole brain, cerebellar, and thalamus volume across diagnostic groups.
Kumari et al., 2014 (Kumari et al., 2014)	Physical and Sexual Abuse	14 ASD-violent 13 SCZ-violent 15 SCZ-non-violent 15 HC-non-violent	Ratings of physical and sexual abuse were associated with reduced total, R, and L ACC volumes across diagnostic groups, with comparable correlations observed in violent and non-violent patients with schizophrenia
Sheffield et al., 2013 (Sheffield et al., 2013)	CTQ total and child sexual abuse scores	60 Patients with Psychotic Disorders (26 SCZ, 17 SCZ-A, 17BP) 26 HC	CTQ total and sexual abuse ratings correlated negatively with total brain gray matter volume. Patients with psychotic disorders and a history of sexual abuse had reduced L. and R. ACC and L. inferior frontal gyrus than patients with psychotic disorders without a history of sexual abuse.
Cancel et al., 2015 (Cancel et al., 2015)	CTQ total and child neglect scores	21 SCZ 30 HC	CTQ emotional neglect scores were negatively correlated with total brain gray matter volume and R. dorsal lateral PFC volume. Effects of emotional neglect greater among patients than HC.
Poletti et al., 2016 (Poletti et al., 2016)	Median split on measure of ACE	206 BP-D 96 SCZ 136 HC	In high ACE subjects: HC > BP-D > SCZ Inferior frontal gyrus; HC = BP-D > SCZ thalamus When analyses were restricted to the low ACE subjects, no group differences emerged.
Habets et al., 2011 (Habets et al., 2011)	CTQ total score	88 SCZ 98 siblings of SCZ patients 87 HC	Group x CTQ interaction observed, such that higher CTQ scores were associated with reduced cortical thickness in the patients with SCZ. The effects were global and not significantly associated with any of the 68 regions assessed in the study. Higher CTQ scores were not associated with reduced cortical thickness in the healthy controls or the healthy sibling group.

Findings from structural brain imaging studies with patients with psychotic disorders and child maltreatment histories are generally consistent with findings in the field of trauma research, with the exception of reduction in thalamus volumes, which to the best of our knowledge, has not been reported in samples of patients with maltreatment histories with non-psychotic disorders.

Abbreviations. CTQ = Child Trauma Questionnaire; ACE = Adverse Childhood Experiences; SCZ = Schizophrenia; BP = Bipolar; MDD = Major Depressive Disorder; ASD = Antisocial Personality Disorder; HC = Healthy Control; SCZ-A = Schizoaffective Disorder; BP-D = Bipolar, Depressed; R = Right; L = Left.

**Table 4**  
DTI and fMRI studies with patients with psychotic disorders that examined the impact of child abuse on outcomes.

Diffusion tensor imaging studies			
Reference	Child trauma assessment	Sample characteristics	Main findings
Poletti et al., 2015 (Poletti et al., 2015)	Median split on measure of ACE	83 SCZ	Higher ratings on the ACE measure were associated with reduced fractional anisotropy in the following white matter tracts: corona radiata, thalamic radiations, corpus callosum, cingulum bundle, superior longitudinal fasciculus, inferior fronto-occipital fasciculus, uncinata fasciculus.
Functional neuroimaging studies			
Reference	Child trauma assessment	Sample characteristics	Main findings
Quidé et al., 2017 (Quidé et al., 2017)	CTQ, with trauma exposed = moderate to extreme levels of trauma on one or more CTQ subscales	50 SCZ 42 BP-P 47 HC	A history of childhood trauma was associated with diminished task performance and increased activation in the inferior parietal lobe in patients and controls while performing an N-back working memory task.
Benedetti et al., 2011 (Benedetti et al., 2011)	Median split on measure of ACE	20 SCZ 20 HC	SCZ and HC with higher ACE scores had reduced activation in the amygdala when processing emotional stimuli in a matching task (e.g., faces vs. shapes).
Cancel et al., 2017 (Cancel et al., 2017)	CTQ sexual abuse and physical neglect scores	21 SCZ 25 HC	Within SCZ group, when determining the emotional content of negative vs. positive valenced stimuli sexual abuse was associated with reduced functional connectivity between the amygdala and the L posterior cingulate, L precuneus, and R calcarine sulcus; and physical neglect was associated with reduced functional connectivity between the amygdala and the L precuneus.

Abbreviations. CTQ = Child Trauma Questionnaire; ACE = Adverse Childhood Experiences; SCZ = Schizophrenia; BP-P = Bipolar with lifetime history of psychosis; HC = Healthy Control; R = Right; L = Left.

psychotic disorders and histories of child maltreatment have also been reported in healthy controls and non-psychotic patients with a history of abuse, suggesting that some of these brain imaging findings may represent transdiagnostic vulnerability markers for psychopathology, rather than susceptibility markers for psychotic illness.

## 5. Translational research studies and future directions

The mechanisms by which child maltreatment confers risk for psychotic disorders remains largely unknown. Translational research approaches using animal models can provide an invaluable tool to examine the effects of genetic and environmental risk factors; with the breadth of GxE animal models utilized in schizophrenia research recently detailed elsewhere (Ayhan et al., 2016). Extant models target a number of known genetic markers (e.g., DISC1, Nurr1, Tap1, Reelin, PACAP, Gad67, Nrg1, COMT), and multiple environmental risk factors (e.g., infection, cannabis, methamphetamine, and toxin exposure, stress). The majority of stress paradigms used in these models, however, examine stress in adolescence and adulthood. Given the high rate of early adversity in patients with schizophrenia, more research focusing on early life stress appears warranted (see Kaffman and Krystal for a detailed discussion of alternate animal models to study the neurodevelopmental origins of psychiatric illness and stress-related disorders) (Kaffman & Krystal, 2012).

Using unbiased transcriptomics and other molecular tools, the transient down-regulation of the Orthodenticle homeobox 2 (*Otx2*) gene in the ventral tegmental area (VTA), a key reward circuit brain region, was putatively associated with the development of depressive-like behaviors in a mouse model of early life stress (Pena et al., 2017). The transient down-regulation of *Otx2* following early life stress was also associated with the persistent down regulation of several target genes, including *Wnt1*, with *Wnt1* signaling pathways implicated in schizophrenia (Singh, 2013). We recently tested the translational applicability of these mouse model findings by examining peripheral markers of methylation of *OTX2* in relation to measures of depression and resting state functional connectivity data collected as part of a larger study examining risk and resilience in maltreated children (Kaufman et al., 2018a). After controlling for demographic factors, cell heterogeneity, and three principal components, maltreatment history and methylation in *OTX2* significantly predicted depression in the children (Kaufman et al., 2018a). *OTX2* methylation was also found to be associated with increased functional connectivity between the right vmPFC and bilateral regions of the medial frontal cortex and the cingulate, including the subcallosal gyrus, frontal pole, and paracingulate gyrus (Kaufman et al., 2018a) – key structures implicated in depression symptoms observed in association with multiple diagnostic categories (Riva-Posse et al., 2017; Akil et al., 2018; Mayberg et al., 1997; Ducharme et al., 2014; Dichter et al., 2010). As genes associated with schizophrenia have recently been shown to have *OTX2*-binding sites (Sakai et al., 2017), we also examined *OTX2* methylation in relation to measures of psychotic symptoms, and after controlling for demographic factors, cell heterogeneity, and three principal components, maltreatment history and methylation in *OTX2* also significantly predicted psychotic symptoms in the children (Kaufman et al., 2018b). These preliminary data suggest the potential applicability of this model in delineating the mechanisms by which early life stress confers risk for a broad range of stress-related psychopathologies, including the onset of psychotic symptoms and psychotic disorders.

## 6. Conclusions

There is a growing consensus in the field that experiences of child maltreatment contribute to the onset of psychotic symptoms and psychotic disorders (Morgan & Gayer-Anderson, 2016). Clinically, there is also strong support that patients with psychotic disorders with histories of child maltreatment have distinct clinical characteristics and

treatment needs that distinguish them from patients with psychotic disorders without histories of child abuse. To date, there is only preliminary data to suggest psychotic patients with a history of maltreatment may comprise a distinct neurobiological subgroup; further work is needed in this area. Translational research studies will help to delineate the mechanisms by which experiences of early life stress confer risk for psychotic symptoms and psychotic disorders, and may help to identify novel treatments for this vulnerable population.

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