Effects of early trauma on psychosis development in clinical high-risk individuals and stability of trauma assessment across studies: a review

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Abstract:
Early trauma (ET), though broadly and inconsistently defined, has been repeatedly linked to numerous psychological disturbances, including various developmental stages of psychotic disorders. The prodromal phase of psychosis highlights a unique and relevant population that provides insight into the critical periods of psychosis development. As such, a relatively recent research focus on individuals at clinical high risk (CHR) for psychosis reveals robust associations of early life trauma exposures with prodromal symptoms and function in these cohorts. While prevalence rates of ET in CHR cohorts remain consistently high, methodological measures of traumatic experiences vary across studies, presenting potential problems for reliability and validity of results. This review aims to 1) highlight the existing evidence identifying associations of ET, of multiple forms, with both symptom severity and transition rates to psychosis in CHR individuals, 2) present data on the variability among trauma assessments and its implications for conclusions about its relationship with clinical variables, 3) describe cognitive deficits common in CHR cohorts, including perceptual and neurocognitive impairments, and their neural correlates, that may modify the relationship of ET to symptoms, and 4) propose future directions for standardization of trauma assessment in CHR cohorts to better understand its clinical and cognitive correlates.

Key Words: Early Trauma, Clinical High Risk, Psychosis, Trauma Assessment

Introduction
Trauma, while relatively broad by interpretation, has been empirically defined as a highly stressful event that involves the threat of injury or threat to the integrity of one’s self or other that overwhelms one’s ability to cope, frequently manifesting as fear, helplessness, or disorganized or agitated behavior (American Psychiatric Association, 2000). While more concrete uses of the word tend to reflect incidents of
physical threat, violation, or injury, as in the cases of sexual abuse, violence, or life-threatening situations, the psychological experience of trauma is, by definition, subjective. Thus, the individualized experience and implications of trauma vary by many factors, including a wide range of biological and environmental features. Along the spectrum of traumatic life experiences, early trauma (ET) in childhood and adolescence has been consistently linked to psychosis in adulthood (Read, van Os, Morrison, & Ross, 2005; Spauwen, Krabbendam, Lieb, Wittchen, & van Os, 2006). Recent literature has considered childhood trauma exposure as a potential precipitator in the pathogenesis of psychosis (Falukozi & Addington, 2012; Arseneault et al., 2011; Tikka et al., 2013) and as a factor that shapes the clinical features of the illness (Ruby et al., 2014; Veras et al., 2017; Bechdolf et al., 2010; Thompson et al., 2010; Thompson et al., 2011).

The “clinical high risk” (CHR) model for psychosis risk underscores a series of genetic and environmental risks factors that are associated with an increased vulnerability for developing psychosis (McGorry, Yung, & Phillips, 2003). Alternatively referred to as the ultra-high-risk (UHR) state for psychosis, inclusion criteria for this population is defined by three non-exclusive, internationally validated conditions: (1) attenuated psychotic symptoms (APS), (2) brief and limited intermittent psychotic symptoms (BLIPS), and (3) genetic risk and deterioration syndrome (GRD) (Fusar-Poli et al., 2015). The initial concept of the prodromal state was defined clinically as a period of distress and disturbance that precedes the first psychotic episode, often experienced in early teen and young adult years (Yung & McGorry, 1996). While the majority (approximately 65%) of those labeled as CHR do not transition to psychosis (Mayo et al., 2017), a range of clinical patterns and phenomena observed in CHR populations, including attenuated psychotic symptoms, mood disturbances, and behavioral changes, offer a wealth of information for identifying potential risk factors that may enhance early intervention and possible prevention efforts. The CHR paradigm has gained considerable attention in recent years due to accumulating evidence that demonstrates its clinical importance, and this paradigm provides researchers with a unique window into a critical developmental period in psychotic disorders.

Investigators have long debated the respective roles of genetic and environmental factors in the etiology of psychosis, though the current consensus emphasizes a synergistic relationship between the two. Aside from biological vulnerability, several socio-environmental factors have been found to increase risk for psychosis (Van Winkel, Stefanis, & Myin-Germeyns, 2008). Among them, ET is most consistently linked to negative physical and mental health outcomes later in life (Ashcroft, Kingdon & Chadwick, 2012). While ET has been studied extensively in relation to psychotic symptoms, the specificity of this relationship, especially in CHR populations, remains unclear.

This review focuses on the extant literature on the associations of early exposure to trauma with symptoms in CHR cohorts. We begin by reporting on the existing evidence that identifies ET, of multiple varieties, as a consistent component of the CHR profile, and its potential relationship to transition rates to psychosis. We then describe the methodologies of these studies in respect to different trauma assessments, outlining the strengths and weaknesses of different assessments, and the ramifications for drawing clear conclusions about the relationship of trauma to symptoms. Next, we discuss distinguishable patterns of trauma type among CHR cohorts and examine the neurobiological, perceptual, and
neurocognitive impairments in CHR individuals that may confound or modify these associations. Finally, we discuss future research directions in respect to standardization of trauma assessment across CHR cohorts, and its implication for understanding mental health outcomes of CHR individuals.

1. Effects of Trauma on Symptom Specificity

Up to 90% of individuals at CHR for psychosis report a lifetime history of traumatic events and victimization in childhood (Mayo et al., 2017). When compared to non-psychiatric controls, CHR individuals endorse much higher rates of traumatic events, with a mean prevalence rate of approximately 85% across CHR samples (Addington et al., 2013; Kraan, Velthorst, Smit, Haan, & van der Gaag, 2015). CHR individuals with trauma histories exhibit significantly higher transition rates to psychosis than those with no reported trauma exposure (Bechdolf et al., 2010). A meta-analysis of studies on trauma in CHR cohorts reveals that childhood adversity/ET has an estimated 33% attributable risk for psychosis, even after controlling for potential confounds such as genetic vulnerability, comorbidities, drug use, ethnicity, urbanicity, and IQ (Varese et al., 2012). These data indicate a clear relationship between traumatic events in childhood and risk for psychosis. We build on these findings by looking at associations of different types of trauma with specific symptom profiles in CHR individuals.

1.1. Positive Symptoms

The prevalence of ET is high in CHR individuals, and associated with the severity of their positive symptoms (Thompson et al., 2009). Likewise, Kraan et al. (2015) reported a significant correlation between positive symptoms and ET in their CHR cohort and Kline et al. (2016) linked ET broadly to positive symptoms in CHR and early-psychosis groups. Earlier studies explored the association between specific positive symptoms and various types of trauma exposure, finding significant correlations of childhood trauma with both hallucinations and delusions (Read, van Os, Morrison, & Ross, 2005). Victims of early sexual and physical abuse exhibit significantly more positive symptoms, including voices commenting, ideas of reference, thought insertion, paranoid ideation, mind-reading, and visual hallucinations, as compared to individuals with no abuse history (Ross, Anderson, & Clark, 1994). Increased ET has been significantly correlated with delusional thinking, including grandiose thoughts of status and power, feelings of being watched or followed, and unusual negative thoughts regarding the self (Falukozi & Addington, 2012). Positive symptoms are strongly linked to increased dopaminergic transmission, while early trauma and stress can elicit elevated glucocorticoid levels (Ruby et al., 2014). Given the interaction between glucocorticoid and dopaminergic pathways, the mechanisms underlying this association may be that early experiences of trauma increase glucocorticoid levels, subsequently leading to hyperactivity of dopaminergic systems, and ultimately the development of positive symptoms in adolescence and young adulthood.

1.2. Negative Symptoms

The literature is inconclusive in respect to the association of ET and negative symptoms in CHR individuals. An early study showed no association of ET, defined broadly, with negative symptoms in a small CHR cohort (Thompson et al., 2009). A later study in the same extended cohort however, showed that impaired stress tolerance characterized CHR individuals,
and was associated, over time, with both positive and negative symptom severity, as well as depression, anxiety, and poor functioning (Devylder et al., 2013). It has been hypothesized that early trauma may lead to increased sensitization to stress, and subsequently, to both positive and negative symptoms in vulnerable individuals (Ruby et al., 2014). Negative symptoms may paradoxically reduce exposure to concurrent stressful events by leading to social withdrawal, as CHR youths endorse fewer recent life events than healthy peers, which may be similar to the avoidance characteristic of post-traumatic stress disorder (PTSD) (Kraan et al., 2015). Of interest, PTSD involves high rates of psychosis, with reported prevalence as high as 75% for psychotic symptoms of hallucinations and delusions (Hamner, Frueh, Ulmer, & Arana, 1999). Given the overlap between PTSD and psychosis, some researchers hypothesize that psychotic episodes, often accompanied by stressful experiences of confusion, fear, and potential hospitalization, may serve as traumatic experiences in and of themselves (Harrison & Fowler, 2004; Stampfer, 1990). Recall of such events in individuals with psychosis may worsen negative symptoms, evoking anxiety and depression and fostering avoidance behaviors.

2. Variability in Trauma Assessment

Despite different measures being used to assess trauma across studies, there is a clear signal that early trauma is prevalent among CHR individuals, in whom it is related to positive symptom severity. Details of that association are less clear, given the discrepancies in definition and measurement of trauma across studies. Some studies circumscribe their definition of trauma to interpersonal events classified by intent to harm (i.e. physical or sexual abuse), while others also include childhood emotional abuse, neglect, bullying, catastrophic events, and/or exposure to war (Bonoldi et al., 2013; Matheson, Shepard, Pinchbeck, Laurens, & Carr, 2013; Varese et al., 2012a). The variability in definition of trauma in these assessments reflects an ongoing debate among investigators. Some argue that the definition of trauma should be restricted only to catastrophic events, and that including other non-life-threatening experiences will create an excessive and overgeneralized classification of trauma, leading to overestimate of prevalence (McNally, 2009). However, others contend that the defining features of a traumatic event are negative valence, lack of controllability, and suddenness (Carlson & Dalenberg, 2000) and that perceived threat of injury or death is not a necessary condition for being traumatized (Shalev & Ursano, 2003). The field of research on the effects of early trauma on the onset and prevalence of psychotic-like and associated symptoms would benefit from a standardized approach and assessment of trauma.

2.1. Definitions of Trauma

While definitions of trauma vary, a recent review by Gibson and colleagues (2016) highlights a few central systems of classification used by trauma researchers: (1) exposure, via several pathways, to an event of actual death, threats of death or injury, or actual or threatened sexual violence as defined by criteria in the Diagnostic and Statistical Manual of Mental Disorders-5th edition (DSM-5) (American Psychological Association, 2013); (2) experiences of physical, sexual, and/or emotional/psychological abuse, neglect, or bullying (Gray, Litz, Hsu, & Lombardo, 2004; van Dam et al., 2012; Varese et al., 2012a); and (3) experiences of parental loss or separation, natural disasters, serious accidents, imprisonment, being kidnapped or held hostage, more generally denoted as adversities (Gray et al., 2004; Kessler, Davis, & Kendler, 1997). Depending on
which features are included in trauma assessments, estimated prevalence will vary, as may findings of association with symptom severity, making it particularly difficult to compare studies or aggregate data from multiple studies, when different trauma assessments are used. This has been demonstrated in a recent study by Trauelsen et al. (2015) that showed a decrease in correlation of specific traumatic events with symptoms in first-episode psychosis after controlling for other types of traumatic events, suggesting potential confounding; the authors argue that it may be useful to find a measure of overall trauma burden.

2.2. Measures of Trauma

One challenge in the categorization of trauma is the level of subjectivity involved in assessing traumatic experiences. Whether an event is judged to be of a catastrophically traumatic nature or as non-threatening, but adverse, there may be wide variability in how the same event is experienced by individuals in respect to its traumatic nature. Self-report is among the most commonly used methods of collecting data on ET. Recently, Mayo and colleagues (2017) reviewed 24 studies, comprising 14 distinct samples that studied ET and its clinical correlates in CHR individuals. Among more recent studies of ET in CHR, conducted by six research groups, eight used the self-report measure of the Childhood Trauma Questionnaire (CTQ), a 28-item screen for five types of trauma including emotional, physical, and sexual abuse, and emotional and physical neglect (Bernstein & Fink, 1998). Other trauma assessments used in CHR studies include the Trauma History Screen (THS), a 14-item self-report measure designed for PTSD (Carlson et al., 2011), the Trauma and Distress Scale (TADS), a European self-rating scale of childhood and early adult traumatic experiences (Patterson et al., 2002), the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime (KSAD-PL), a semi-structured diagnostic interview (Axelson, Birmaher, Zelazny, Kaufman, & Gill, 2009), and the Childhood Trauma and Abuse scale, an adapted measure of self-report used for perceived discrimination by the North American Prodromal Longitudinal Study (NAPLS) group (Addington et al., 2013). Among these assessments, definitions of trauma vary, with some using specific classifications and others categorizing trauma more broadly. Differing methodologies (e.g. structured interview vs. self-report) also contribute to variations in results, with self-report methods yielding higher rates of endorsement (Bendall, Jackson, Hulbery, & McGorry, 2007). In addition to variance in measures, it should be kept in mind that other potential sources of bias and variability arise due to the retrospective nature of the recall of trauma that occurred years previously, with potential recall bias and forgetting, especially among at-risk individuals with cognitive deficits, and social desirability bias.

3. Impacts of Trauma Type

3.1. Sexual Abuse History

Specific exposure to sexual abuse has been strongly correlated with greater positive symptom severity in CHR cohorts, with these positive symptoms reflecting greater incidence of sexual content (Thompson et al., 2010). Remarkably, in a large CHR cohort (n=416), sexual abuse in childhood was a significant predictor of psychosis transition (Thompson et al., 2014). Across studies, the range of prevalence of sexual abuse history is 22-31% in CHR individuals, somewhat higher than the lifetime prevalence of 15-25% in the general population (Kraan et al., 2015; Falukozi & Addington, 2012; Bechdolf et al., 2010; Russo et al., 2014; Thompson et al., 2016; Thompson et al., 2010; Thompson et al.,...
The increased prevalence of sexual abuse history in CHR individuals, and its predictive power for psychosis onset, may reflect the development of altered awareness and distorted interpretations of the external world, increasing risk for paranoia, perceptual abnormalities, and social withdrawal/avoidance, based on early experiences of mistrust and violation.

3.2. Physical Abuse History

Like sexual abuse, physical abuse is more prevalent in CHR individuals than in the general population, including demographically-matched, healthy controls (Sahin et al., 2010; Stowkowy et al., 2013; Stowkowy et al., 2016). An early study reported that physical abuse was endorsed by 83% of CHR individuals queried, and was specifically associated with severity of disorganization and suspiciousness among CHR samples (Thompson et al., 2009). Later studies found an association of reported childhood abuse with cognitive deficits in CHR individuals, which may mediate the association of early physical abuse with later psychotic symptoms, as such deficits are common in CHR cohorts (Ucok et al., 2015; Yung et al., 2015). Early experiences of physical abuse may increase the use of threat appraisals in cognitive development, predisposing individuals to the misinterpretation of external stimuli, and the expression of psychotic symptoms. Additional mechanisms potentially involved in the association between early physical trauma and psychosis risk may include frequent, and/or increased hyperarousal of the body’s acute stress response to threatening situations, which may indirectly influence the heightened stress sensitivity to both life events and daily activities observed in CHR samples (Trotman et al., 2014).

3.3. Emotional Abuse, Neglect & Bullying

Beyond sexual and physical abuse, emotional abuse, neglect, and maltreatment can also have significant negative effects on mental health. There are high rates of reported emotional abuse (41.5-75%) and neglect (59-100%) in CHR youths as compared to healthy controls (33%) (Thompson et al., 2009; Tikka et al., 2013). Further, emotional abuse and neglect among CHR samples has been associated with greater Schneiderian first-rank symptoms and higher Schneiderian total scores (Sahin et al., 2013). A recent large CHR study of the NAPLS-2 cohort (n=764) showed that CHR individuals report high perceived levels of trauma, discrimination, and bullying, with discrimination serving as a significant predictor of transition to psychosis (Stowkowy et al., 2016). These higher rates of reported emotional trauma and bullying have been associated in the large NAPLS CHR consortium with depression, anxiety, and poor self-esteem (Addington et al., 2013), associations that exists more broadly beyond CHR, specifically for bullying, and including associations also with aggression and suicidality in addition to poor self-esteem, depression, and positive symptoms (Arseneault, Bowes, & Shakoor, 2010). Specific to CHR youth, up to 60% of the NAPLS cohort endorsed a lifetime history of physical or psychological bullying, compared to 36% in healthy controls (Addington et al., 2013). This experience of bullying, likely contributes to the poor social function that has been shown to be so common among CHR youths (Carrion et al., 2013), and merits further research. The link between of emotional neglect and mistreatment with prodromal symptoms and social impairment may be explained by a failure of a child’s environment to provide stimulating, positive support to the developing brain, leading to disruptions in cognitive functioning (Heins et al., 2011;
van Dam, Korver-Nieberg, Velthorst, Meijer, & de Haan, 2014b). However, the causal direction of the association is not entirely clear, as individuals with an increased risk for developing psychosis may have been more susceptible to bullying and maltreatment in general.

### 3.4. Pre-and Perinatal Trauma

Prenatal/perinatal trauma, specifically obstetric complications, are known risk factors for schizophrenia and related psychotic disorders, such that it is not surprising that there is a significantly increased prevalence of obstetric complications among CHR individuals compared to controls (Fusar-Polli et al., 2017). Hypoxia-associated obstetric complications have also been associated with an earlier risk of onset in schizophrenia (Rosso et al., 2000). After controlling for prenatal infection and fetal growth retardation, fetal hypoxia remains significantly more prevalent in early-onset schizophrenia, as compared with non-psychiatric controls, unaffected siblings, and later-onset schizophrenia cases. A dose-dependent association has also been found, with a linear relationship between the number of hypoxia-causing obstetric complications and earlier age of schizophrenia onset (Cannon et al., 2000). In a large schizophrenia cohort (n=854), individuals with illness onset prior to age 22 were 2.7 times more likely to have a history of abnormal presentation at birth, and 10 times more likely to have a history of Cesarean birth complications, as compared to individuals with later illness onset (Verdoux et al., 1997). The consistent correlation between fetal hypoxia/birth complications and psychosis onset, particularly early onset, suggests a mechanism of neurotoxicity affecting brain development, in the context of both genetic vulnerability and early environmental stress, in the pathogenesis of psychosis (Dean & Murray, 2005).

Beyond perinatal and delivery complications, a meta-analysis of population-based studies shows strong and significant associations between schizophrenia and complications in pregnancy, including bleeding, preeclampsia, diabetes, and abnormal fetal growth/development (low weight, congenital deformities, small head circumference) (Cannon, Jones, & Murray, 2002). Maternal gestational infections, including influenza, herpes simplex, and rubella have been clearly identified as risk factors for psychosis in offspring (Brown & Susser, 2002; Bulka et al., 2001), as have maternal depression during pregnancy (Jones, Rantakallio, Hartikainen, Isohanni, & Sipila, 1998), unwanted pregnancy (Myhrman, Rantakallio, Isohanni, Jones, & Partanen, 1996), and exposure to war and disasters (van Os & Selten, 1998; Funai, Paltiel, Malaspina, Friedlander, Deutsch, & Harlap, 2005). While the causal mechanisms remain unclear, one theory suggests that a reactivation of the initial infection causes an inflammatory response in the developing fetal brain that may facilitate the neuropathological effects related to an increased risk for psychosis (Miller, Culpepper, Rapaport, & Buckley, 2013). Other forms of prenatal maternal stress exposure may increase psychosis risk by increasing stress responsivity via modifications of the Hypothalamic-Pituitary-Adrenal (HPA) axis in utero (Corcoran et al., 2003).

### 4. Clinical Implications of Studying Trauma in CHR

Aside from the methodological issues with defining and measuring trauma, the subjective and retrospective nature of trauma assessment, in general, may prove difficult for this group of individuals. Several
neurobiological impairments, genetic predispositions, and perceptual and neurocognitive deficits that often present in prodromal patients may pose significant conflict in accurately evaluating trauma in this population.

4.1. Stress sensitivity

Increased stress sensitivity has been identified as a potential causal factor in the expression of several psychiatric conditions, including psychosis. Individuals with a genetic vulnerability for psychosis also have dysregulation in their HPA axis and associated neurotransmitter systems (Ruby et al., 2014; Walker et al., 2011). Hyperactivity of the HPA axis is a replicated finding in CHR studies, as evidenced by increased abnormalities in cortisol secretion, and significantly higher mean diurnal salivary cortisol levels compared to healthy individuals (Sugranyes et al., 2012; Chaumette et al., 2016; Walker et al., 2013). Increased cortisol levels are positively correlated with symptom severity in CHR persons (Walker et al., 2013), specifically suspiciousness, as well as impaired stress tolerance and anxiety (Corcoran et al., 2012). Neuroimaging studies show functional abnormalities in striatal dopamine synthesis and release in CHR samples, with some predictive power for psychosis onset (Bois, Whalley, McIntosh, & Lawrie, 2015; Howes, McCutcheon, Owen, & Murray, 2017; Howes et al., 2011). Reductions of hippocampal volume, a brain structure with a critical role in regulating the HPA axis, is also a replicated finding in psychosis and CHR cohorts (Mondelli et al., 2011; Ruby et al., 2015, see Aiello et al., 2012 for review).

Enhanced stress response to daily events and activities has also been found in first-degree relatives of CHR individuals and psychosis patients, compared with healthy controls (Myin-Germeys, van Os, Schwartz, Stone, & Delespaul, 2001; Aiello et al., 2012). Thus, HPA hyperactivity may be a familial risk factor for psychosis. Ruby et al. (2014) posit that individuals with predisposition to stress sensitivity may experience greater distress in response to both traumatic events and other childhood stressors relative to others with similar exposures. Thus, early life events may be experienced as more traumatic, and interact with epigenetic pathways to modify gene expression and worsen stress sensitivity. As such, the activation of these pathways in the stress cascade, prior to symptom onset, may worsen the effects of ET in CHR individuals.

4.2. Genetic Influences

Socio-environmental and genetic factors are known interdependent factors in the pathogenesis of psychosis (Van Winkel, Stefanis, & Myin-Germeys, 2008). For example, in a study of the general population, Alemany et al. (2011) found increased psychotic experiences in the context of early trauma exposure in carriers of the MET allele for brain-derived neurotrophic factors (BDNF). BDNF serves a vital role in several neurobiological regulatory systems including hippocampal neurogenesis, and dopaminergic and GABAergic synthesis and functioning (Ray, Weickert, Wyatt, & Webster, 2011; Hyman & Hofer, 1991; Guillin, Diaz, Carroll, & Griffon, 2001; Ruby et al., 2014). A functional gene variant, Val66Met, resulting in the downregulation of BDNF, is linked to reduced hippocampal volume in human and animal models (Chen et al., 2006; Egan et al., 2003), a common finding in CHR and psychosis cohorts (Ruby et al., 2014). Studies on this BDNF polymorphism in healthy populations show that met-BDNF allele carriers have worse episodic memory performance and reduced hippocampal engagement during functional magnetic resonance imaging (fMRI), as well as bilateral reductions in hippocampal gray matter, independent of age and gender.
(Pezawas et al., 2004; Bueller et al., 2006; Egan et al., 2003; Hariri et al., 2003). Additionally, cultured hippocampal neurons transfected with met-BDNF fail to concentrate BDNF in secretory granules and dendritic processes, and show decreased depolarization-induced secretion (Egan et al., 2003, Chen et al., 2006). Together with animal data linking BDNF to the modulation of essential neural processes in the hippocampus (Taliaz, Stall, Dar, & Zangen, 2009; Choi et al., 2010), these findings suggest that the genotypic expression of BDNF polymorphisms, specifically the presence of the met-BDNF allele, elicits changes in synaptic and cellular plasticity via activity and context-dependent mechanisms that compromise both the development and function of the hippocampus (Pezawas et al., 2004). With its strong association to hippocampal functions of learning and memory, several genetic studies have investigated possible correlations between BDNF polymorphisms and psychosis risk, showing significantly increased risk of schizophrenia among met-BDNF allele carriers compared to case-controls (Gratacos et al., 2007; Green, Matheson, Shepherd, Weickert, & Carr, 2011). Implicated in several neurodevelopmental and neurodegenerative disorders (Huntington’s disease, Down’s syndrome, Alzheimer’s disease, schizophrenia) (Zuccato et al., 2001; Bimonte-Nelson, Hunter, Nelson, & Granholm, 2003; Weickert et al., 2003, Banquet, Gorski, & Jones, 2004), the altered expression of BDNF may be a genetically driven factor in the reduction of development and plasticity of the hippocampus, interfering with the normal developmental maturation of many essential cognitive and behavioral functions.

A genetic link between ET and psychological symptoms has been shown in a group of met-BDNF carriers with schizophrenia, highlighting the importance of gene-environment interactions (Veras et al., 2017), including a higher sensitivity to trauma among met allele carriers, likely explained by pathological stress-induced changes in neural systems related to impaired BDNF functioning. Other studies have also shown clinical effects of gene-environment interactions, including psychosis (Peerbooms et al., 2012; for review see Holtzman et al., 2013). Individuals with a genetic predisposition for psychosis may experience greater amounts of stress and/or enhanced stress perception based on gene-environment interactions. Given the high prevalence of met-BDNF alleles in schizophrenia, CHR individuals may also be at increased risk of carrying BDNF polymorphisms, potentially predisposing them to related impairments in hippocampal-dependent memory functions.

4.3. Altered Perceptions

Several models of psychosis propose an association between altered cognitive and perceptual mechanisms and the manifestation of symptoms. While trauma exposure may contribute to the genesis and/or exacerbation of psychosis, preceding perceptual biases or disturbances may influence how trauma is experienced and recalled in at-risk populations. Individuals at CHR for psychosis endorse higher levels of subjective stress to both life events and daily stressors relative to healthy controls (Trotman et al., 2014). Perceived stress level is indicated as a mediator between ET and attenuated positive psychotic symptoms (Gibson et al., 2014). Further evidence from a large systematic review of 170 independent data sets presents high perceived levels of stress as prevalent in CHR cohorts (Fusar-Poli et al., 2017). Additionally, Millman et al. (2017) showed a positive correlation between greater perceptions of social stress with symptom severity in CHR individuals. Stronger associations between activity-related stress
and psychotic symptoms are found in CHR patients, relative to those with threshold psychosis (Steen et al., 2017), suggesting that stress sensitivity may drive positive symptom expression early in the course of illness, but that symptoms may become more endogenous and independent of the environment later in illness course.

4.3.1. Information Processing

Aberrant attribution of salience to irrelevant stimuli has been hypothesized as core to psychotic symptoms (Kapur, 2003; Roiser, Howes, Chaddock, Joyce & McGuire, 2012; van Winkel et al., 2013). Disproportional allocation of attention to threatening stimuli has been linked to inappropriate inferences and paranoid ideation (Sherrer, 2011). Behavioral and neurophysiological measures of such information processing biases have been shown in CHR individuals, as they have longer reaction times to threatening words on the Emotional Stroop Task (Bendall et al., 2008; Roiser et al., 2013; Nieman et al., 2014). Increased sensitivity to minor stressors and enhanced threat anticipation characterize early course in psychosis, as compared with healthy individuals (Reininghaus et al., 2016), with an increased association of aberrant salience with psychotic experiences in CHR cohorts. There may be an initial attention bias towards threatening stimuli, which may aggravate psychological and physiological experiences of trauma.

4.3.2. Externalizing Bias

A common feature found in both psychosis patients and CHR individuals is the interpretation of private events and experiences as having external implications, with an increased prevalence of believing that behavior may be controlled by forces outside themselves (Bentall & Fernyhough, 2008; Frenkel, Kugelmass, Nathan, & Ingraham, 1995). Commonly referred to as an externalizing bias, such orientations towards an external locus of control have been shown to be a predictor of psychosis (Frenkel et al., 1995). A large longitudinal study (n=6,455) showed that children who reported externalizing biases were at significantly increased risk of developing psychotic symptoms by age 13 (Thompson et al., 2011). One study found that CHR individuals have increased concerns about locus of control, as compared with non-CHR patient controls (Thompson et al., 2015), but a separate study found that CHR individuals and healthy individuals had a similar external-personalizing attributional style (Devylder et al., 2013).

4.3.3. Negative Schemas

Many models of psychosis posit a relationship between negative schemata about the self and vulnerability for psychosis (Garety, Kuipers, Fowler, Freeman, & Bebbington, 2001). Negative schemas have shown to be a strong mediator in the relationship between ET and subclinical paranoia and the prediction of paranoia and hallucinations in CHR populations (Addington & Tran, 2009; Gracie et al., 2007). A recent study by Appiah-Kusi et al. (2017) has shown that relative to healthy controls, CHR individuals present with more negative schemas, and less positive schemas, about themselves and others, in addition to increased reports of various types of childhood trauma exposures. The direction of such negative schemas remains unclear and the possibility exists that these individuals start out with altered cognitive scripts, which may in turn amplify early experiences of trauma.

4.3.4. Emotion Processing

Regulating and recognizing emotions, in oneself and in others, is an important and adaptive skill necessary to thrive in our social world. Unfortunately, patients with
psychotic disorders often struggle to attain this skill and typically demonstrate profound and detrimental disturbances in emotion processing. Comprehensive evaluations of emotion awareness, regulation, and social functioning in schizophrenia patients, shows a significantly reduced ability to describe and identify their own emotions relative to healthy controls (Kimhy et al. 2012). This same study established further deficits in emotion regulation among persons in the schizophrenia group, who presented with decreased use of effective emotion regulation techniques (less reappraisal) and increased use of ineffective emotion regulation strategies like suppression. Similar findings have been replicated in CHR cohorts, indicating significant difficulties in verbalizing, identifying, and analysis of their own emotions relative to controls and healthy siblings (Van der Velde et al., 2015). Dysfunctional emotion regulation in CHR cohorts includes reduced reports of actively using effective emotion regulation strategies, specifically reappraisal, in daily life relative to controls. Neuroimaging data of the same CHR subjects suggests mechanisms that underlie emotional processing deficits, specifically decreased activation of the left ventrolateral prefrontal cortex, a brain region involved in reappraisal (Diekhof, Geier, Falkai, & Gruber, 2011), during fMRI reappraisal tasks (Van der Velde et al., 2015). Kimhy and colleagues (2016) corroborate such findings, illustrating extensive emotion awareness and regulation deficits, of comparable severity, in both CHR and schizophrenia groups relative to healthy controls. Further investigations of impaired emotional processing in CHR populations suggest a potentially predictive value of these deficits. One such study showed significantly poorer performance in facial emotion recognition among those CHR individuals who later transitioned to schizophrenia, relative to both non-converters and healthy controls (Corcoran et al., 2015).

Current research reports a strong link between dysfunctional emotion awareness and poor social functioning in CHR individuals, showing such deficits, particularly an inability to describe feelings, predicted 23.2% of variance in social functioning (Kimhy et al., 2016). Taken together, these findings add to the consistent characterization of limited emotional processing among at-risk, and psychotic individuals, as well as underscore the important role these emotional capacities serve in one’s abilities to socialize. As such, current evidence offers robust indications for emotion processing issues in CHR cohorts that may ultimately affect their interpretation of early experiences, as well as predispose them as victims of social trauma like bullying, victimization, and emotional abuse.

4.4. Neurocognitive Impairments

Premorbid intellectual and neurocognitive impairments, including learning, memory, and executive functioning deficits, are common in psychotic disorders (Fuller et al., 2002; Reichenberg et al., 2002; Hutton et al., 1998). Specific impairments in the visual reproduction and memory indexes of the Wechsler Memory Scale-Revised (WMS-R) are found in CHR patients who transition to psychosis, relative to non-converters and healthy controls (Brewer et al., 2006). Spatial working memory and assessment of short term memory are also significantly worse in CHR groups compared to controls (Brewer et al., 2006). Spatial working memory and assessment of short term memory are also significantly worse in CHR groups compared to controls (Wood et al., 2003; Smith, Park, & Comblatt, 2006). Working memory deficits are also observed in non-psychiatric relatives of patients with schizophrenia (Park, Holtzman, & Goldman-Rakic, 1995; Myles-Worsley & Park, 2002; MacDonald, Pogue-Geitle, Johnson, & Carter, 2003), suggesting these cognitive deficits have a genetic component. Correspondingly, in the large
NAPLS cohort, CHR individuals with a family history of psychosis have worse cognitive functioning (Woodberry et al., 2010), which itself predicted transition to psychosis. Recent research shows an association between aerobic fitness level and improved neuropsychological functioning, and positive effects of aerobic exercise on cognitive functioning in psychosis and at-risk samples (Kimhy et al., 2015; Mittal et al., 2013). Relative to a treatment as usual (TAU) intervention group, and their own baseline, schizophrenia patients assigned to an aerobic exercise treatment group increased their overall aerobic fitness, improved dramatically on neurocognitive assessments, and showed elevated BDNF serum levels (Kimhy et al., 2015). Similar studies in CHR cohorts demonstrate significant correlations between high levels of inactivity and decreased occupational functioning in at-risk individuals relative to healthy controls (Mittal et al., 2013). Such data reflects a probable relationship between physical activity and neuropsychological functioning in psychosis, implicating a sedentary lifestyle in the potential development and/or exacerbation of neurocognitive deficits observed in these populations. These findings, in addition to neuroimaging data documenting aberrations in frontal and medial temporal lobes in relation to executive functioning, episodic and working memory in schizophrenia patients, further support the interaction between environmental exposures and genetic liability in psychosis development (Reichenberg & Harvey, 2007).

Conclusion

The accumulation of comprehensive and consistent research on the initial prodromal phase of psychosis underscores the importance of both early identification and intervention in CHR populations. Longer duration of untreated psychosis (DUP) is related to worse general outcomes, including greater total and positive symptom severity, decreased overall functioning, decreased quality of life, and poorer response to antipsychotic medications (Marshall et al., 2005; Perkins, Gu, Boteva, & Lieberman, 2005). Moreover, longer DUP may have neurotoxic effects on the brain, resulting in gray matter volume reduction with symptom progression and increased cognitive deterioration (Lieberman et al., 2001; Amminger, Edwards, Brewer, Harrigan, & McGorry, 2002). Neuroimaging studies show increased brain abnormalities in early onset schizophrenia cases, as progressive patterns of gray matter loss in several brain regions correlate with both psychotic symptom severity and increased neuromotor, perceptual, and frontal executive deficits observed in disease advancement (Thompson et al., 2001). Additionally, retrospective accounts of schizophrenia cases prior to first hospitalization show increased rates of premorbid functional deficiencies resulting in various social, economic, professional, academic, and interpersonal losses (Hafner, Nowotny, Loffler, van der Heiden, & Maurer, 1995).

Given the critical developmental time period in which psychosis typically presents, patients with longer DUP are at higher risk of experiencing detrimental, and possibly irreversible, outcomes that may negatively affect quality of life and inhibit opportunities in the future. With so much at stake, evaluating risk factors to enhance detection methods of at-risk populations, should continue to be prioritized in future research.

As reviewed, documentation of ET may be a useful tool in understanding potential mechanisms of psychosis development and remains a research topic of interest in CHR cohorts. While there is a clear association of ET and symptom severity in CHR cohorts, nonetheless the field would benefit from standardization of trauma assessments employed. A comprehensive meta-analysis examining the association between
childhood adversity/trauma and psychosis risk, including a large assortment of case-controlled, prospective and quasi-prospective, population-based and cross-sectional studies, reports that all types of early trauma, regardless of the precise nature of exposure, are related to an increased risk of psychosis (Varese et al., 2012a). However, standardization of measures used would allow for a better understanding of the role of trauma types and their effects on specific symptoms, and a better estimate of prevalence. The use of self-administered, subjective report measures and semi-structured clinical interviews, in conjunction, is recommended as the most effective method of assessing trauma. While the initial self-administrated trauma inventories will promote a sense of safety and honest disclosure by reducing shame, guilt, and fear of judgment, a follow-up clinical interview by trained screeners ensures the subject adequately understands the content and process of the assessment to enhance clarification and accuracy of results (Abuse, 2014). We would advocate the use of The Early Trauma Inventory (ETI), which was employed in the early study by Thompson et al., (2009). It is a well-validated and reliable trauma assessment with demonstrated inter-rater reliability, test-retest reliability, internal consistency and validity (Bremner, Vermetten, & Mazure, 2000). With adapted versions for clinical interviews and self-administered measures, the ETI consists of 56 items reflecting physical, emotion, and sexual abuse, as well as general traumatic experiences, and shows good convergent validity relative to other trauma instruments. Given the heterogeneity of symptoms, early life experiences, and various biological vulnerabilities among CHR populations, such an extensive, yet easily standardized measure of trauma, is a unique, yet essential tool in the study of such complex relationships.

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