RESEARCH ARTICLE

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

Samantha L. Redman[1*], Cheryl M. Corcoran, David Kimhy, Dolores Malaspina[2]

Author Affiliations:

Icahn School of Medicine at Mount Sinai, New York, New York, USA

***Corresponding Author:** Samantha Redman, Icahn School of Medicine at Mount Sinai, Department of Psychiatry, 53 E 96th Street, New York, NY 10128, phone: 212-659-8756, E-mail: slr2184@tc.columbia.edu

[1] First Author

[2] Senior Author

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-Germeys, 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.,

2009). 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 withdraw/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-Poli 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 (Wood et al., 2003; Smith, Park, & Cornblatt, 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-Geile, 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.

References

Abuse, S. (2014). Mental Health Services Administration, Trauma-informed care in behavioral health services. *Treatment improvement protocol (TIP) series*, *57*.

Addington, J., & Tran, L. (2009). Using the brief core schema scales with individuals at clinical high risk of psychosis. Behavioural and Cognitive Psychotherapy, 37(02), 227–231.

Aiello, G., Horowitz, M., Hepgul, N., Pariante, C. M., & Mondelli, V. (2012). Stress abnormalities in individuals at risk for psychosis: a review of studies in subjects with familial risk or with "at risk" mental state. *Psychoneuroendocrinology*, *37*(10), 1600-1613.

Alemany, S., Arias, B., Aguilera, M., Villa, H., Moya, J., Ibáñez, M. I., ... & Fañanás, L. (2011). Childhood abuse, the BDNF-Val66Met polymorphism and adult psychotic-like experiences. *The British Journal of Psychiatry*, *199*(1), 38-42.

Amminger, G. P., Edwards, J., Brewer, W. J., Harrigan, S., & McGorry, P. D. (2002). Duration of untreated psychosis and cognitive deterioration in first-episode schizophrenia. *Schizophrenia research*, *54*(3), 223-230.

American Psychiatric Association (APA). (2000). Diagnostic and statistical manual of mental disorders: DSM-IV-TR. Washington, DC: American Psychiatric Association.

American Psychiatric Association (APA). (2013). Diagnostic and statistical manual of mental disorders: DSM-5 (5th ed.). Arlington, VA: American Psychiatric Publishing, Inc.

Appiah-Kusi, E., Fisher, H. L., Petros, N., Wilson, R., Mondelli, V., Garety, P. A., ... & Bhattacharyya, S. (2017). Do cognitive schema mediate the association between

childhood trauma and being at ultra-high risk for psychosis?. *Journal of psychiatric research*, *88*, 89-96.

Arseneault, L., Bowes, L., & Shakoor, S. (2010). Bullying victimization in youths and mental health problems:'Much ado about nothing'?. *Psychological medicine*, *40*(5), 717-729.

Arseneault, L., Cannon, M., Fisher, H. L., Polanczyk, G., Moffitt, T. E., & Caspi, A. (2011). Childhood trauma and children's emerging psychotic symptoms: a genetically sensitive longitudinal cohort study. *American Journal of Psychiatry*, *168*(1), 65-72.

Ashcroft, K., Kingdon, D. G., & Chadwick, P. (2012). Persecutory delusions and childhood emotional abuse in people with a diagnosis of schizophrenia. *Psychosis*, *4*(2), 168-171.

Axelson, D., Birmaher, B., Zelazny, J., Kaufman, J., & Gill, M. K. (2009). The Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version (K-SADS-PL) 2009 Working Draft. *Advanced Centre for Intervention and Services Research, Western Psychiatric Institute and Clinics*.

Baquet ZC, Gorski JA, Jones KR (2004) Early striatal dendrite deficits followed by neuron loss with advanced age in the absence of anterograde cortical brain-derived neurotrophic factor. *J Neurosci* **24**: 4250-4258

Bechdolf A, Thompson A, Nelson B, Cotton S, Simmons MB, Amminger GP, et al. Experience of trauma and conversion to psychosis in an ultra- high-risk (prodromal) group. *Acta Psychiatr Scand* (2010) 121(5):377–84. doi:10.1111/j.1600-0447.2010.01542.x

Bendall, S., Jackson, H. J., Hulbert, C. A., & McGorry, P. D. (2007). Childhood trauma and psychotic disorders: a systematic, critical review of the evidence. *Schizophrenia bulletin*, *34*(3), 568-579.

Bentall, R. P., & Fernyhough, C. (2008). Social predictors of psychotic experiences: Specificity and psychological mechanisms. Schizophrenia Bulletin, 34(6), 1012–1020.

Bernstein, D. P., & Fink, L. (1998). *Childhood trauma questionnaire: A retrospective self-report: Manual*. Psychological Corporation.

Bimonte-Nelson, H. A., Hunter, C. L., Nelson, M. E., & Granholm, A. C. E. (2003). Frontal cortex BDNF levels correlate with working memory in an animal model of Down syndrome. *Behavioural brain research*, *139*(1), 47-57.

Bois C, Whalley H, McIntosh A, Lawrie S. (2015), Structural magnetic resonance imaging markers of susceptibility and transition to schizophrenia: a review of familial and clinical high risk population studies. *J Psychopharmacol* 29(2):144–54. doi:10.1177/0269881114541015

Bonoldi, I., Simeone, E., Rocchetti, M., Codjoe, L., Rossi, G., Gambi, F., ... & Fusar-Poli, P. (2013). Prevalence of self-reported childhood abuse in psychosis: a meta-analysis of retrospective studies. *Psychiatry research*, *210*(1), 8-15.

Bremner, J. D., Vermetten, E., & Mazure, C. M. (2000). Development and preliminary psychometric properties of an instrument for the measurement of childhood trauma: the Early Trauma Inventory. *Depression and anxiety*, *12*(1), 1-12.

Brewer, W. J., Wood, S. J., Phillips, L. J., Francey, S. M., Pantelis, C., Yung, A. R., ... & McGorry, P. D. (2006). Generalized and specific cognitive performance in clinical high-risk cohorts: a review highlighting potential vulnerability markers for psychosis. *Schizophrenia bulletin*, *32*(3),

538-555.

Brown, A. S., & Susser, E. S. (2002). In utero infection and adult schizophrenia. *Developmental Disabilities Research Reviews*, *8*(1), 51-57.

Bueller, J. A., Aftab, M., Sen, S., Gomez-Hassan, D., Burmeister, M., & Zubieta, J. K. (2006). BDNF Val66Met allele is associated with reduced hippocampal volume in healthy subjects. *Biological psychiatry*, *59*(9), 812-815.

Buka, S. L., Tsuang, M. T., Torrey, E. F., Klebanoff, M. A., Bernstein, D., & Yolken, R. H. (2001). Maternal infections and subsequent psychosis among offspring. *Archives of general psychiatry*, *58*(11), 1032-1037.

Cannon, M., Jones, P. B., & Murray, R. M. (2002). Obstetric complications and schizophrenia: historical and meta-analytic review. *American Journal of Psychiatry*, *159*(7), 1080-1092.

Cannon, T. D., Rosso, I. M., Hollister, J. M., Bearden, C. E., Sanchez, L. E., & Hadley, T. (2000). A prospective cohort study of genetic and perinatal influences in the etiology of schizophrenia. *Schizophrenia Bulletin*, *26*(2), 351-366.

Carlson, E. B., & Dalenberg, C. J. (2000). A conceptual framework for the impact of traumatic experiences. *Trauma, Violence, & Abuse*, *1*(1), 4-28.

Carlson, E.B., Smith, S.R., Palmieri, P.A., Dalenberg, C.J., Ruzek, J.I., Kimerling, R., Burling, T.A., & Spain, D.A. (2011). Development and validation of a brief self-report measure of trauma exposure: The Trauma History Screen (PDF). *Psychological Assessment, 23*, 463-477. doi: 10.1037/a0022294

Carrión, R. E., McLaughlin, D., Goldberg, T. E., Auther, A. M., Olsen, R. H., Olvet, D. M., ... & Cornblatt, B. A. (2013). Prediction of functional outcome in individuals at clinical high risk for psychosis. *JAMA psychiatry*, *70*(11), 1133-1142.

Chen, Z. Y., Jing, D., Bath, K. G., Ieraci, A., Khan, T., Siao, C. J., ... & Hempstead, B. L. (2006). Genetic variant BDNF (Val66Met) polymorphism alters anxiety-related behavior. *Science*, *314*(5796), 140-143.

Chaumette B, Kebir O, Mam-Lam-Fook C, Morvan Y, Bourgin J, Godsil BP, et al. (2016). Salivary cortisol in early psychosis: new findings and meta-analysis. *Psychoneuroendocrinology* 63:262–70. doi:10.1016/j. psyneuen.2015.10.007

Choi, D. C., Maguschak, K. A., Ye, K., Jang, S. W., Myers, K. M., & Ressler, K. J. (2010). Prelimbic cortical BDNF is required for memory of learned fear but not extinction or innate fear. *Proceedings of the National Academy of Sciences*, *107*(6), 2675-2680.

Corcoran, C. M., Keilp, J. G., Kayser, J., Klim, C., Butler, P. D., Bruder, G. E., ... & Javitt, D. C. (2015). Emotion recognition deficits as predictors of transition in individuals at clinical high risk for schizophrenia: a neurodevelopmental perspective. *Psychological medicine*, *45*(14), 2959-2973.

Corcoran, C. M., Smith, C., McLaughlin, D., Auther, A., Malaspina, D., & Cornblatt, B. (2012). HPA axis function and symptoms in adolescents at clinical high risk for schizophrenia. *Schizophrenia research*, *135*(1), 170-174.

Corcoran, C., Walker, E., Huot, R., Mittal, V., Tessner, K., Kestler, L., & Malaspina, D. (2003). The stress cascade and schizophrenia: etiology and onset. Schizophrenia bulletin, 29(4), 671-692.

Dean, K., & Murray, R. M. (2005). Environmental risk factors for psychosis. *Dialogues in clinical neuroscience*, *7*(1), 69.

DeVylder, J. E., Ben-David, S., Kimhy, D., & Corcoran, C. M. (2013). Attributional style among youth at clinical risk for psychosis. *Early intervention in psychiatry*, *7*(1), 84-88.

Devylder, J. E., Ben-David, S., Schobel, S. A., Kimhy, D., Malaspina, D., & Corcoran, C. M. (2013). Temporal association of stress sensitivity and symptoms in individuals at clinical high risk for psychosis. *Psychological medicine*, *43*(2), 259-268.

Diekhof, E. K., Geier, K., Falkai, P., & Gruber, O. (2011). Fear is only as deep as the mind allows: a coordinate-based meta-analysis of neuroimaging studies on the regulation of negative affect. *Neuroimage*, *58*(1), 275-285.

Egan, M. F., Kojima, M., Callicott, J. H., Goldberg, T. E., Kolachana, B. S., Bertolino, A., ... & Lu, B. (2003). The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell*, *112*(2), 257-269.

Falukozi, E., & Addington, J. (2012). Impact of trauma on attenuated psychotic symptoms. *Psychosis*, *4*(3), 203-212.

Frenkel, E., Kugelmass, S., Nathan, M., & Ingraham, L. J. (1995). Locus of control and men- tal health in adolescence and adulthood. Schizophrenia Bulletin, 21(2), 219–226.

Fuller, R., Nopoulos, P., Arndt, S., O'Leary, D., Ho, B. C., & Andreasen, N. C. (2002). Longitudinal assessment of premorbid cognitive functioning in patients with schizophrenia through examination of standardized scholastic test performance. *American Journal of Psychiatry*, *159*(7), 1183-1189.

Funai, E. F., Paltiel, O. B., Malaspina, D., Friedlander, Y., Deutsch, L., & Harlap, S. (2005). Risk factors for pre-eclampsia in nulliparous and parous women: the Jerusalem Perinatal Study. *Paediatric and perinatal epidemiology*, *19*(1), 59-68.

Fusar-Poli, P., Bechdolf, A., Taylor, M. J., Bonoldi, I., Carpenter, W. T., Yung, A. R., & McGuire, P. (2012). At risk for schizophrenic or affective psychoses? A meta-analysis of DSM/ICD diagnostic outcomes in individuals at high clinical risk. *Schizophrenia bulletin*, *39*(4), 923-932.

Fusar-Poli, P., Cappucciati, M., Rutigliano, G., Schultze-Lutter, F., Bonoldi, I., Borgwardt, S., ... & McGlashan, T. H. (2015). At risk or not at risk? A meta-analysis of the prognostic accuracy of psychometric interviews for psychosis prediction. *World Psychiatry*, *14*(3), 322-332.

Fusar-Poli, P., Tantardini, M., De Simone, S., Ramella-Cravaro, V., Oliver, D., Kingdon, J., ... & Galderisi, S. (2017). Deconstructing vulnerability for psychosis: Meta-analysis of environmental risk factors for psychosis in subjects at ultra high-risk. *European Psychiatry*, *40*, 65-75.

Garety, P. A., Kuipers, E., Fowler, D., Freeman, D., & Bebbington, P. E. (2001). A cognitive model of the positive symptoms of psychosis. Psychological Medicine, 31(02), 189–195.

Gibson, L. E., Anglin, D. M., Klugman, J. T., Reeves, L. E., Fineberg, A. M., Maxwell, S. D., ... & Ellman, L. M. (2014). Stress sensitivity mediates the relationship between traumatic life events and attenuated positive psychotic symptoms differentially by gender in a college population sample. *Journal of psychiatric research*, *53*, 111-118.

Gracie, A., Freeman, D., Green, S., Garety, P. A., Kuipers, E., Hardy, A., ... Fowler, D. (2007). The association between traumatic experience, paranoia and hallucinations: A test of the predictions of psychological

models. Acta Psychiatrica Scandinavica, 116(4), 280–289.

Gratacòs, M., González, J. R., Mercader, J. M., de Cid, R., Urretavizcaya, M., & Estivill, X. (2007). Brain-derived neurotrophic factor Val66Met and psychiatric disorders: meta-analysis of case-control studies confirm association to substance-related disorders, eating disorders, and schizophrenia. *Biological psychiatry*, *61*(7), 911-922.

Gray, M. J., Litz, B. T., Hsu, J. L., & Lombardo, T. W. (2004). Psychometric properties of the life events checklist. Assessment, 11(4), 330–341.

Green, M. J., Matheson, S. L., Shepherd, A., Weickert, C. S., & Carr, V. J. (2011). Brain-derived neurotrophic factor levels in schizophrenia: a systematic review with meta-analysis. *Molecular psychiatry*, *16*(9), 960.

Guillin, O., Diaz, J., Carroll, P., & Griffon, N. (2001). BDNF controls dopamine D3 receptor expression and triggers behavioural sensitization. *Nature*, *411*(6833), 86.

Häfner, H., Nowotny, B., Löffler, W., an der Heiden, W., & Maurer, K. (1995). When and how does schizophrenia produce social deficits?. *European archives of psychiatry and clinical neuroscience*, *246*(1), 17-28.

Hamner, M. B., Frueh, B. C., Ulmer, H. G., & Arana, G. W. (1999). Psychotic features and illness severity in combat veterans with chronic posttraumatic stress disorder. *Biological Psychiatry*, *45*(7), 846-852.

Hariri, A. R., Goldberg, T. E., Mattay, V. S., Kolachana, B. S., Callicott, J. H., Egan, M. F., & Weinberger, D. R. (2003). Brain-derived neurotrophic factor val66met polymorphism affects human memory-related hippocampal activity and predicts memory performance. *Journal of Neuroscience*, *23*(17), 6690-6694.

Harrison, C.L., Fowler, D. (2004). Negative symptoms, trauma, and autobiographical memory: an investigation of individuals recovering from psychosis. J Nerv Ment Dis. 192:745– 753.

Heins, M., Simons, C., Lataster, T., Pfeifer, S., Versmissen, D., Lardinois, M., ... Myin-Germeys, I. (2011). Childhood trauma and psychosis: A case–control and case- sibling comparison across different levels of genetic liability, psychopathology, and type of trauma. American Journal of Psychiatry, 168(12), 1286–1294.

Holtzman, C. W., Trotman, H. D., Goulding, S. M., Ryan, A. T., Macdonald, A. N., Shapiro, D. I., ... & Walker, E. F. (2013). Stress and neurodevelopmental processes in the emergence of psychosis. *Neuroscience*, *249*, 172-191.

Howes, O.D., Bose, S.K., Turkheimer, F., Valli, I., Egerton, A., Valmaggia, L.R, et al. (2011). Dopamine synthesis capacity before onset of psychosis: a prospective [18F]-DOPA PET imaging study. *Am J Psychiatry* 168(12):1311–7. doi:10.1176/appi.ajp.2011.11010160

Howes, O.D., McCutcheon, R., Owen, M.J., Murray, R.M. (2017). The role of genes, stress, and dopamine in the development of schizophrenia. *Biol Psychiatry* 81(1):9–20. doi:10.1016/j.biopsych.2016.07.014

Hutton, S.B., Puri, B.K., Duncan, L.J., Robbins, T.W., Barnes, T.R., Joyce, E.M. (1998). Executive function in first-episode schizophrenia, Psychol Med. vol. 28 (pg. 463-473)

Hyman, C., & Hofer, M. (1991). BDNF is a neurotrophic factor for dopaminergic neurons of the substantia nigra. *Nature*, *350*(6315), 230.

Janssen, I., Krabbendam, L., Bak, M., Hanssen, M., Vollebergh, W., de Graaf, R. and van Os, J. (2004), Childhood abuse as a

risk factor for psychotic experiences. Acta Psychiatrica Scandinavica, 109: 38–45. doi:10.1046/j.0001-690X.2003.00217.x

Jones, P. B., Rantakallio, P., Hartikainen, A. L., Isohanni, M., & Sipila, P. (1998). Schizophrenia as a long-term outcome of pregnancy, delivery, and perinatal complications: a 28-year follow-up of the 1966 north Finland general population birth cohort. *American Journal of Psychiatry*, *155*(3), 355-364.

Kapur, S. (2003). Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *American journal of Psychiatry*, *160*(1), 13-23.

Kessler, R. C., Davis, C. G., & Kendler, K. S. (1997). Childhood adversity and adult psychiat- ric disorder in the US National Comorbidity Survey. Psychological Medicine, 27(05), 1101–1119.

Kimhy, D., Vakhrusheva, J., Bartels, M. N., Armstrong, H. F., Ballon, J. S., Khan, S., ... & Castrén, E. (2015). The impact of aerobic exercise on brain-derived neurotrophic factor and neurocognition in individuals with schizophrenia: a single-blind, randomized clinical trial. *Schizophrenia bulletin*, *41*(4), 859-868.

Kimhy, D., Vakhrusheva, J., Jobson-Ahmed, L., Tarrier, N., Malaspina, D., & Gross, J. J. (2012). Emotion awareness and regulation in individuals with schizophrenia: implications for social functioning. *Psychiatry research*, *200*(2), 193-201.

Kline, E., Millman, Z.B., Denenny, D., Wilson, C., Thompson, E., Demro, C et al. (2016). Trauma and psychosis symptoms in a sample of help-seeking youth. *Schizophrenia Research.* 175(1–3):174–9. doi:10.1016/j.schres.2016.04.006

Kraan, T., Velthorst, E., Smit, F., de Haan, L., & van der Gaag, M. (2015). Trauma and recent life events in individuals at ultra high risk for psychosis: review and meta-analysis. *Schizophrenia research*, *161*(2), 143-149.

Lieberman, J. A., Perkins, D., Belger, A., Chakos, M., Jarskog, F., Boteva, K., & Gilmore, J. (2001). The early stages of schizophrenia: speculations on pathogenesis, pathophysiology, and therapeutic approaches. *Biological psychiatry*, *50*(11), 884-897.

MacDonald, A. W., Pogue-Geile, M. F., Johnson, M. K., & Carter, C. S. (2003). A specific deficit in context processing in the unaffected siblings of patients with schizophrenia. *Archives of General Psychiatry*, *60*(1), 57-65.

Marshall, M., Lewis, S., Lockwood, A., Drake, R., Jones, P., & Croudace, T. (2005). Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review. *Archives of general psychiatry*, *62*(9), 975-983.

Matheson, S. L., Shepherd, A. M., Pinchbeck, R. M., Laurens, K. R., & Carr, V. J. (2013). Childhood adversity in schizophrenia: a systematic meta-analysis. *Psychological medicine*, *43*(2), 225-238.

Mayo, D., Corey, S., Kelly, L. H., Yohannes, S., Youngquist, A. L., Stuart, B. K., ... & Loewy, R. L. (2017). The role of trauma and stressful life events among individuals at clinical high risk for psychosis: a review. *Frontiers in psychiatry*, *8*.

McGorry, P. D., Yung, A. R., & Phillips, L. J. (2003). The “close-in” or ultra high-risk model: a safe and effective strategy for research and clinical intervention in prepsychotic mental disorder. *Schizophrenia bulletin*, *29*(4), 771-790.

McNally, R. J. (2009). Can we fix PTSD in DSM-V?. *Depression and anxiety*, *26*(7), 597-600.

Miller, B. J., Culpepper, N., Rapaport, M. H., & Buckley, P. (2013). Prenatal inflammation and neurodevelopment in schizophrenia: a review of human studies. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *42*, 92-100.

Millman, Z. B., Pitts, S. C., Thompson, E., Kline, E. R., Demro, C., Weintraub, M. J., ... & Schiffman, J. (2017). Perceived social stress and symptom severity among help-seeking adolescents with versus without clinical high-risk for psychosis. *Schizophrenia Research*.

Mittal, V. A., Gupta, T., Orr, J. M., Pelletier-Baldelli, A., Dean, D. J., Lunsford-Avery, J. R., . . . Millman, Z. B. (2013). Physical activity level and medial temporal health in youth at ultra high-risk for psychosis. *Journal of Abnormal Psychology, 122*(4), 1101-1110.

Myhrman, A., Rantakallio, P., Isohanni, M., Jones, P., & Partanen, U. (1996). Unwantedness of a pregnancy and schizophrenia in the child. *The British Journal of Psychiatry*, *169*(5), 637-640.

Myin-Germeys, I., van Os, J., Schwartz, J. E., Stone, A. A., & Delespaul, P. A. (2001). Emotional reactivity to daily life stress in psychosis. *Archives of general psychiatry*, *58*(12), 1137-1144.

Myles-Worsley, M., & Park, S. (2002). Spatial working memory deficits in schizophrenia patients and their first degree relatives from Palau, Micronesia. *American Journal of Medical Genetics Part A*, *114*(6), 609-615.

Nieman, D. H., Ruhrmann, S., Dragt, S., Soen, F., van Tricht, M. J., Koelman, J. H., ... de Haan, L. (2014). Psychosis prediction: Stratification of risk estimation with information- processing and premorbid functioning variables. Schizophrenia Bulletin, 40(6), 1482–1490.

Numata, S., Ueno, S. I., Iga, J. I., Yamauchi, K., Hongwei, S., Ohta, K., ... & Kameoka, N. (2006). Brain-derived neurotrophic factor (BDNF) Val66Met polymorphism in schizophrenia is associated with age at onset and symptoms. *Neuroscience letters*, *401*(1), 1-5.

Oswald, L.M., Wand, G.S., Kuwabara, H., Wong, D.F., Zhu. S., Brasic, J.R. (2014). History of childhood adversity is positively associated with ventral striatal dopamine responses to amphetamine. *Psychopharmacology.* 231(12):2417–33. doi:10.1007/s00213-013-3407-z

Park, S., Holzman, P. S., & Goldman-Rakic, P. S. (1995). Spatial working memory deficits in the relatives of schizophrenic patients. *Archives of General Psychiatry*, *52*(10), 821-828.

Patterson P., Skeate A., Birchwood M, et al. (2002). TADS-EPOS 1.2. Birmingham: University of Birmingham.

Peerbooms, O., Rutten, B. P. F., Collip, D., Lardinois, M., Lataster, T., Thewissen, V., ... & Myin-Germeys, I. (2012). Evidence that interactive effects of COMT and MTHFR moderate psychotic response to environmental stress. *Acta psychiatrica Scandinavica*, *125*(3), 247-256.

Perkins, D. O., Gu, H., Boteva, K., & Lieberman, J. A. (2005). Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. *American Journal of Psychiatry*, *162*(10), 1785-1804.

Pezawas, L., Verchinski, B. A., Mattay, V. S., Callicott, J. H., Kolachana, B. S., Straub, R. E., ... & Weinberger, D. R. (2004). The brain-derived neurotrophic factor val66met

polymorphism and variation in human cortical morphology. *Journal of Neuroscience*, *24*(45), 10099-10102.

Ray, M. T., Weickert, C. S., Wyatt, E., & Webster, M. J. (2011). Decreased BDNF, trkB-TK+ and GAD67 mRNA expression in the hippocampus of individuals with schizophrenia and mood disorders. *Journal of psychiatry & neuroscience: JPN*, *36*(3), 195.

Read, J., Os, J. V., Morrison, A. P., & Ross, C. A. (2005). Childhood trauma, psychosis and schizophrenia: a literature review with theoretical and clinical implications. *Acta Psychiatrica Scandinavica*, *112*(5), 330-350.

Reininghaus, U., Kempton, M. J., Valmaggia, L., Craig, T. K., Garety, P., Onyejiaka, A., ... & Dazzan, P. (2016). Stress sensitivity, aberrant salience, and threat anticipation in early psychosis: an experience sampling study. *Schizophrenia bulletin*, *42*(3), 712-722.

Reichenberg, A., & Harvey, P. D. (2007). Neuropsychological impairments in schizophrenia: Integration of performance-based and brain imaging findings. *Psychological bulletin*, *133*(5), 833.

Reichenberg, A., Weiser, M., Rabinowitz, J., Caspi, A., Schmeidler, J., Mark, M., ... & Davidson, M. (2002). A population-based cohort study of premorbid intellectual, language, and behavioral functioning in patients with schizophrenia, schizoaffective disorder, and nonpsychotic bipolar disorder. *American Journal of Psychiatry*, *159*(12), 2027-2035.

Roiser, J. P., Howes, O. D., Chaddock, C. A., Joyce, E. M., & McGuire, P. (2012). Neural and behavioral correlates of aberrant salience in individuals at risk for psychosis. *Schizophrenia bulletin*, *39*(6), 1328-1336.

Ross, C., Anderson, G., Clark, P. (1994). Childhood abuse and positive symptoms of schizophrenia. *Hospital & Community Psychiatry*. 45:489–491.

Ruby, E., Polito, S., McMahon, K., Gorovitz, M., Corcoran, C., & Malaspina, D. (2014). Pathways associating childhood trauma to the neurobiology of schizophrenia. *Frontiers in psychological and behavioral science*, *3*(1), 1.

Ruby, E., Rothman, K., Corcoran, C., Goetz, R. R., & Malaspina, D. (2015). Influence of early trauma on features of schizophrenia. *Early intervention in psychiatry*.

Russo, D.A., Stochl, J., Painter, M., Dobler, V., Jackson, E., Jones, P.B., et al. (2014). Trauma history characteristics associated with mental states at clinical high risk for psychosis. *Psychiatry Research.* 220(1–2):237–44. doi:10.1016/j.psychres. 2014.08.028

Sahin, S., Yuksel, C., Guler, J., Karadayi, G., Akturan, E., Gode, E., et al. (2013). The history of childhood trauma among individuals with ultra high risk for psychosis is as common as among patients with first-episode schizophrenia. *Early Interv Psychiatry* 7(4):414–20. doi:10.1111/eip.12022

Seidman, L. J., Giuliano, A. J., Meyer, E. C., Addington, J., Cadenhead, K. S., Cannon, T. D., ... & Woods, S. W. (2010). Neuropsychology of the prodrome to psychosis in the NAPLS consortium: relationship to family history and conversion to psychosis. *Archives of general psychiatry*, *67*(6), 578-588.

Shalev, A. Y., & Ursano, R. J. (2003). Mapping the multidimensional picture of acute responses to traumatic stress. *Reconstructing early intervention after trauma*, *118*, 129.

Sherrer, M. V. (2011). The role of cognitive appraisal in adaptation to traumatic stress in adults with serious mental illness: A critical review. *Trauma, Violence, & Abuse*, *12*(3), 151-167.

Smith, C. W., Park, S., & Cornblatt, B. (2006). Spatial working memory deficits in adolescents at clinical high risk for schizophrenia. *Schizophrenia research*, *81*(2), 211-215.

Spauwen, J., Krabbendam, L., Lieb, R., Wittchen, H. U., & van Os, J. (2006). Impact of psychological trauma on the development of psychotic symptoms: relationship with psychosis proneness. *The British Journal of Psychiatry*, *188*(6), 527-533.

Stampfer, H.G. (1990). Negative symptoms': a cumulative trauma stress disorder? Aust N Z J Psychiatry. 24:516–528.

Steen, Y., Gimpel-Drees, J., Lataster, T., Viechtbauer, W., Simons, C. J. P., Lardinois, M., ... & Myin-Germeys, I. (2017). Clinical high risk for psychosis: the association between momentary stress, affective and psychotic symptoms. *Acta Psychiatrica Scandinavica*, *136*(1), 63-73.

Stowkowy, J., Addington, J. (2013). Predictors of a clinical high risk status among individuals with a family history of psychosis. *Schizophrenia Research.* 147(2–3):281–6. doi:10.1016/j.schres.2013.03.030

Stowkowy, J., Liu, L., Cadenhead, K.S., Cannon, T.D., Cornblatt, B.A., McGlashan, T.H., et al (2016). Early traumatic experiences, perceived discrimination and conver- sion to psychosis in those at clinical high risk for psychosis. *Soc Psychiatry Psychiatr Epidemiol* 51(4):497–503. doi:10.1007/s00127-016-1182-y

Sugranyes, G., Thompson, J. L., & Corcoran, C. M. (2012). HPA-axis function, symptoms, and medication exposure in youths at clinical high risk for psychosis. *Journal of psychiatric research*, *46*(11), 1389-1393.

Taliaz, D., Stall, N., Dar, D. E., & Zangen, A. (2009). Knockdown of brain-derived neurotrophic factor in specific brain sites precipitates behaviors associated with depression and reduces neurogenesis. *Molecular psychiatry*, *15*(1), 80.

Thompson, J. L., Kelly, M., Kimhy, D., Harkavy-Friedman, J. M., Khan, S., Messinger, J. W., ... & Corcoran, C. (2009). Childhood trauma and prodromal symptoms among individuals at clinical high risk for psychosis. *Schizophrenia research*, *108*(1), 176-181.

Thompson, A., Marwaha, S., Nelson, B., Wood, S.J., McGorry, P.D., Yung, A.R, et al. (2016). Do affective or dissociative symptoms mediate the association between childhood sexual trauma and transition to psychosis in an ultra-high risk cohort? *Psychiatry Research.* 236:182–5. doi:10.1016/j.psychres.2016.01.017

Thompson, A., Nelson, B., McNab, C., Simmons, M., Leicester, S., McGorry, P.D., et al. (2010). Psychotic symptoms with sexual content in the "ultra high risk" for psychosis population: frequency and association with sexual trauma. *Psychiatry Research.*177(1–2):84–91. doi:10.1016/j.psychres.2010.02.011

Thompson, A., Sullivan, S., Lewis, G., Zammit, S., Heron, J., Horwood, J., ... Harrison, G. (2011). Association between locus of control in childhood and psychotic symptoms in early adolescence: Results from a large birth cohort. Cognitive Neuropsychiatry, 16(5), 385–402.

Thompson, E., Kline, E., Ellman, L. M., Mittal, V., Reeves, G. M., & Schiffman, J. (2015). Emotional and behavioral

symptomatology reported by help-seeking youth at clinical high-risk for psychosis. *Schizophrenia research*, *162*(1), 79-85.

Thompson, P. M., Vidal, C., Giedd, J. N., Gochman, P., Blumenthal, J., Nicolson, R., ... & Rapoport, J. L. (2001). Mapping adolescent brain change reveals dynamic wave of accelerated gray matter loss in very early-onset schizophrenia. *Proceedings of the National Academy of Sciences*, *98*(20), 11650-11655.

Tikka, M., Luutonen, S., Ilonen, T., Tuominen, L., Kotimäki, M., Hankala, J., & Salokangas, R. K. (2013). Childhood trauma and premorbid adjustment among individuals at clinical high risk for psychosis and normal control subjects. *Early intervention in psychiatry*, *7*(1), 51-57.

Trauelsen, A. M., Bendall, S., Jansen, J. E., Nielsen, H. G. L., Pedersen, M. B., Trier, C. H., ... Simonsen, E. (2015). Childhood adversity specificity and dose–response effect in non-affective first-episode psychosis. Schizophrenia Research, 165(1), 52–59.

Trotman, H. D., Holtzman, C. W., Walker, E. F., Addington, J. M., Bearden, C. E., Cadenhead, K. S., ... & Tsuang, M. T. (2014). Stress exposure and sensitivity in the clinical high-risk syndrome: initial findings from the North American Prodrome Longitudinal Study (NAPLS). *Schizophrenia research*, *160*(1), 104-109.

Üçok, A., Kaya, H., Ugurpala, C., Cikrikcili, U., Ergul, C., Yokusoglu, C, et al. (2015). History of childhood physical trauma is related to cognitive decline in individuals with ultra-high risk for psychosis. *Schizophrenia Research.* 169(1–3):199–203. doi:10.1016/j.schres.2015.08.038

U.S. Department of Health and Human Services, Administration for Children and Families, Administration on Children Youth and Families, Children's Bureau. *Child Maltreatment 2014*. (2016). Available from http://www.acf.
hhs.gov/programs/cb/research-data-technology/statistics-research/child-maltreatment

van Dam, D. S., Van Der Ven, E., Velthorst, E., Selten, J. P., Morgan, C., & De Haan, L. (2012). Childhood bullying and the association with psychosis in non-clinical and clinical samples: A review and meta-analysis. Psychological Medicine, 42(12), 2463–2474.

van Dam, D. S., van Nierop, M., Viechtbauer, W., Velthorst, E., van Winkel, R., Bruggeman, R., ... Wiersma, D. (2014a). Childhood abuse and neglect in relation to the presence and persistence of psychotic and depressive symptomatology. Psychological Medicine, 45(7), 1363–1377.

van Dam, D. S., Korver-Nieberg, N., Velthorst, E., Meijer, C. J., & de Haan, L. (2014b). Child- hood maltreatment, adult attachment and psychotic symptomatology: A study in pa- tients, siblings and controls. Social Psychiatry and Psychiatric Epidemiology, 49(11), 1759–1767.

Van Der Velde, J., Opmeer, E. M., Liemburg, E. J., Bruggeman, R., Nieboer, R., Wunderink, L., & Aleman, A. (2015). Lower prefrontal activation during emotion regulation in subjects at ultrahigh risk for psychosis: an fMRI-study. *npj Schizophrenia*, *1*, 15026.

Van Os, J., & Selten, J. P. (1998). Prenatal exposure to maternal stress and subsequent schizophrenia. The May 1940 invasion of The Netherlands. *The british journal of psychiatry*, *172*(4), 324-326.

van Winkel, R., Stefanis, N. C., & Myin-Germeys, I. (2008). Psychosocial stress and psychosis. A review of the neurobiological mechanisms and the evidence for gene-stress interaction. *Schizophrenia bulletin*, *34*(6), 1095-1105

van Winkel, R., van Nierop, M., Myin-Germeys, I., & van Os, J. (2013). Childhood trauma as a cause of psychosis: linking genes, psychology, and biology. *The Canadian Journal of Psychiatry*, *58*(1), 44-51.

Varese, F., Smeets, F., Drukker, M., Lieverse, R., Lataster, T., Viechtbauer, W., ... Bentall, R. P. (2012a). Childhood adversities increase the risk of psychosis: A meta-analysis of patient-control, prospective-and cross-sectional cohort studies. Schizophrenia Bulletin, 38(4), 661–671.

Varese, F., Smeets, F., Drukker, M., Lieverse, R., Lataster, T., Viechtbauer, W., ... & Bentall, R. P. (2012). Childhood adversities increase the risk of psychosis: a meta-analysis of patient-control, prospective-and cross-sectional cohort studies. *Schizophrenia bulletin*, *38*(4), 661-671.

Veras, A. B., Peixoto, C., Messinger, J. W., Getz, M., Goetz, R., Buckley, P., ... & Kranz, T. M. (2017). Early trauma and clinical features of schizophrenia cases influenced by the BDNF met allele. *Schizophrenia Research*.

Verdoux, H., Geddes, J. R., Takei, N., Lawrie, S. M., Bovet, P., Eagles, J. M., ... & Stober, G. (1997). Obstetric complications and age at onset in schizophrenia: an international collaborative meta-analysis of individual patient data. *American Journal of Psychiatry*, *154*(9), 1220-1227.

Walker E.F., Brennan, P.A., Esterberg, M., Brasfield, J., Pearce, B., Compton, M.T. (2010). Longitudinal changes in cortisol secretion and conversion to psychosis in at-risk youth. J Abnormal Psychol. 119:401–408.

Walker EF, Trotman HD, Pearce BD, Addington J, Cadenhead KS, Cornblatt BA, et al. (2013). Cortisol levels and risk for psychosis: initial findings from the North American prodrome longitudinal study. *Biol Psychiatry* 74(6):410–7. doi:10.1016/j.biopsych.2013.02.016

Weickert CS, Hyde TM, Lipska BK, Herman MM, Weinberger DR, & Kleinman JE (2003) Reduced brain-derived neurotrophic factor in prefrontal cortex of patients with schizophrenia. *Mol Psychiatry* **8**: 592-610.

Wood, S. J., Pantelis, C., Proffitt, T., Phillips, L. J., Stuart, G. W., Buchanan, J. A., ... & McGorry, P. D. (2003). Spatial working memory ability is a marker of risk-for-psychosis. *Psychological medicine*, *33*(7), 1239-1247.

Woodberry, K. A., Seidman, L. J., Giuliano, A. J., Verdi, M. B., Cook, W. L., & McFarlane, W. R. (2010). Neuropsychological profiles in individuals at clinical high risk for psychosis: relationship to psychosis and intelligence. *Schizophrenia research*, *123*(2), 188-198.

Yung, A. R., & McGorry, P. D. (1996). The initial prodrome in psychosis: descriptive and qualitative aspects. *Australian and New Zealand Journal of Psychiatry*, *30*(5), 587-599.

Zuccato, C., Ciammola, A., Rigamonti, D., Leavitt, B. R., Goffredo, D., Conti, L., ... & Timmusk, T. (2001). Loss of huntingtin-mediated BDNF gene transcription in Huntington's disease. *Science*, *293*(5529), 493-498.

