HHS Public Access

Author manuscript

Clin Psychol Rev. Author manuscript; available in PMC 2017 November 01.

Published in final edited form as:

Clin Psychol Rev. 2016 November ; 49: 92–105. doi:10.1016/j.cpr.2016.08.003.

Trauma and the psychosis spectrum: A review of symptom specificity and explanatory mechanisms

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Abstract

Traumatic life events have been robustly associated with various psychosis outcomes, including increased risk of psychotic disorders, the prodrome of psychosis, and dimensional measures of psychotic symptoms, such as attenuated positive psychotic symptoms. However, trauma exposure has been linked to various mental disorders; therefore, the specificity of trauma exposure to psychosis remains unclear. This review focuses on two understudied areas of the trauma and psychosis literature: 1) the specificity between trauma and psychosis in relation to other disorders that often result post-trauma, and 2) proposed mechanisms that uniquely link trauma to psychosis. We begin by discussing the underlying connection between trauma exposure and the entire psychosis spectrum with a focus on the influence of trauma type and specific psychotic symptoms. We then consider how the principles of multifinality and equifinality can be useful in elucidating the trauma-psychosis relationship versus the trauma-other disorder relationship. Next, we discuss several cognitive and neurobiological mechanisms that might uniquely account for the association between trauma and psychosis, as well as the role of gender. Lastly, we review important methodological issues that complicate the research on trauma and psychosis, ending with clinical implications for the field.

Keywords

Trauma; Adversity; Psychosis; Schizophrenia

1. Traumatic Life Events as a Risk Factor for Psychosis: The Underlying Relationship

Studies yield consistent findings that traumatic life events (TLEs) are one of the most robust environmental risk factors for the development of psychosis (Bendall, Alvarez-Jimenez, Nelson, & McGorry, 2013a; Varese et al., 2012a). Overall odds of developing a psychotic disorder or positive psychotic symptoms in adolescents and adults with TLE histories ranges between 2.78 and 11.50, depending on the study methodology or TLE type (Janssen et al., 2004; Varese et al., 2012a). Individuals with psychotic disorders are also significantly more likely to report TLE histories than controls or their siblings, indicating that differences in TLE exposure may yield discordance in psychotic diagnoses (van Dam et al., 2014a).

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Further, methodologically rigorous clinical and general population studies find medium to large effect sizes and dose-response relationships for TLEs and psychosis, such that risk for psychotic disorders or symptoms increases substantially for each additional adversity (Janssen et al., 2004; Matheson, Shepherd, Pinchbeck, Laurens, & Carr 2012; Thompson et al., 2009; Trauelsen et al., 2015).

There is also evidence that TLEs temporally precede the onset of psychosis, as longitudinal studies find TLEs predict psychotic symptoms (Arseneault et al., 2011; Mackie, Castellanos-Ryan, & Conrod, 2011) and that discontinuation of abuse predicts a significant reduction in psychotic experiences (Kelleher et al., 2013). Similarly, individuals experiencing psychosis with TLE histories compared to those with no TLE histories present with higher rates of psychotic symptoms, comorbid disorders, cognitive deficits, and treatment resistance, as well as earlier and more frequent hospitalizations (Hassan & De Luca, 2015; Schenkel, Spaulding, DiLillo, & Silverstein, 2005). The strength of the TLEs and psychosis association is underscored by findings that this relationship persists despite the addition of the following potential covariates: familial psychiatric history, psychiatric comorbidities, cannabis use, genetic risk, ethnicity, and education level, suggesting that TLEs are at least in part independent from these variables (Bendall et al., 2013a; Fisher et al., 2014a; Janssen et al., 2004; Kelleher et al., 2008).

A series of studies, including prospective longitudinal studies, have consistently substantiated the relationship between TLEs and the entire continuum of psychosis (Elklit & Shevlin, 2010; Shevlin, Dorahy, & Adamson, 2007), clinical high risk (CHR) for psychosis (Addington et al., 2013; Bechdolf et al., 2010; Thompson et al., 2009), and subclinical psychosis (Arseneault et al., 2011; Kelleher et al., 2013; Mackie et al., 2011). Despite findings linking TLEs to psychosis, TLEs also have been associated with other mental disorders (Green et al., 2010; McLaughlin et al., 2010), although these large comorbidity studies did not include assessment of psychotic or personality disorders. These studies also yield minimal diagnostic specificity for the onset or persistence of one disorder versus another given a TLE history. The disorders most strongly linked to TLEs (i.e., mood, anxiety, and substance use and borderline personality disorders) also are comorbid with psychotic disorders (Buckley, Miller, Lehrer, & Castle, 2009). Collectively, these findings underscore the diagnostic complexity connected to trauma sequelae, the importance of adjusting for co-occurring symptomatology when exploring the impact TLEs have on mental health, and the need for delineating why, given a TLE history, an individual may develop one disorder versus another. Therefore, it remains unclear how TLEs specifically increase risk for psychotic disorders and symptoms.

This review is intended to 1) differentiate the associations between TLEs and three psychosis outcomes from the associations between TLEs and other disorders (i.e., mood, trauma and stressor, substance use, and personality), and 2) identify the potential mechanisms specifically involved in the TLE-psychosis spectrum relation. In this article, we review the role of TLEs as a risk factor for psychosis, the specificity of the trauma – psychosis association in relation to other disorders also related to TLEs, and potential mechanisms that may uniquely link trauma to psychosis.

2. Methodology

Controversy exists about how to define psychological trauma both clinically and empirically (Weathers & Keane, 2007). Traditionally, studies have not distinguished "trauma" from "adversity" or "other negative life events." For example, the Adverse Childhood Experiences (ACE) study, one of the largest nationally representative studies to investigate the prevalence and short- and long-term social and health outcomes of traumatic and/or adverse experiences, considered several discrete types of events under the definition of ACEs (Centers for Disease Control and Prevention [CDC], 2014). These include emotional, physical, or sexual abuse; emotional or physical neglect; and household dysfunction, including: mother treated violently, household substance abuse, household mental illness, parental separation or divorce, or incarcerated household member (CDC, 2014). Further, the US National Comorbidity Survey Replication II, a large adult general population that assessed childhood adversities and the risk factors and consequences of mental health disorders, did not discriminate between overarching trauma-based or adversity-based events, merging such categories as loss events (e.g., parental divorce), parental maladjustment (e.g., criminality), maltreatment (e.g., rape), and "other childhood adversities" (e.g., serious physical illness; McLaughlin et al., 2010).

The categorization of different stressful life events has differed depending on the field of research. For instance, the depression and anxiety disorder literature has differentiated trauma, which tends to include more intrusive and/or interpersonal abuse experiences (e.g., physical abuse), from other negative life events, which tend to capture a broader category, such as parental maladjustment (Hovens et al., 2012). Distinctions have also been drawn between events that are non-intentional (e.g., motor vehicle accident) and those that are intended to inflict harm (e.g., assault), the latter which have been associated with increased prevalence of posttraumatic stress disorder (PTSD) and first episode psychosis (Raune, Kuipers, & Bebbington, 2009; Santiago et al., 2013). However, the psychosis literature often defines TLEs and more general adversities under the same category (Lataster, Myin-Germeys, Lieb, Wittchen, & Van Os, 2012; Varese et al., 2012a). Although the life event-psychosis connection appears relevant for both traumatic events and adversities, no study has determined whether TLEs or more general adversities, when grouped together, are differentially related to psychosis, despite the possibility that each category of events operate via different mechanisms in their influence on psychosis.

2.1 Definition of Terms

Given the lack of separation between life event categories in the psychosis literature, the current review broadly defines TLEs to include traumas, adversities, and negative life events. This review includes studies that measure TLEs in three overarching ways. The first is based on Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM 5) criteria, which require that an individual is exposed to (via direct exposure, witnessing in person, indirectly learning about someone close to the individual, or repeated or extreme indirect exposure to details of a TLE) "death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence" (APA, 2013). The second includes TLEs encountered that are predominantly defined as: experiences of physical, sexual, or emotional/

psychological abuse, neglect, or bullying (Gray, Litz, Hsu, & Lombardo, 2004; van Dam et al., 2012; Varese et al., 2012a). The third, less common category (often referred to as "adversities") includes: parental loss or separation; natural catastrophes; serious accidents; imprisonment; and being kidnapped or held hostage (Gray et al., 2004; Kessler, Davis, & Kendler, 1997). In response to the lack of consensus about what constitutes TLEs, we chose to adopt a comprehensive definition.

In the present review, findings pertaining to three psychosis outcomes will be discussed: 1) a diagnosis of a psychotic disorder (e.g., schizophrenia), 2) classification as clinical high risk (CHR) for psychosis (i.e., a prepsychotic stage describing individuals who are at an increased risk for developing psychosis; Fusar-Poli, Yung, McGorry, & van Os, 2014), and 3) the extended psychosis phenotype, which denotes subclinical or attenuated psychosis (i.e., less frequent, severe, convincing and/or distressing positive psychotic symptoms) examined in non-clinical, general population samples. Deviations from these outcomes (e.g., schizotypy) will be appropriately defined.

2.2 Search Strategy

Potential studies were identified through a search of peer-reviewed articles in English via PsychINFO and PubMed databases using the following search terms: '[childhood] trauma,' '[childhood] adversity,' AND 'psychotic symptoms,' 'clinical high risk,' 'psychosis,' or 'schizophrenia.' The first author identified relevant articles via title and abstract search, which then were reviewed for inclusion by the third author. Articles that assessed TLEs experienced only in adulthood (with the exception of war trauma) or that were in dissertation or conference format were excluded. Studies that used a self-report or clinician-administered assessment of trauma or adversity, psychotic disorders/symptoms, or CHR were included.

3. The Psychosis Spectrum and TLEs

3.1 Clinical High Risk for Psychosis

Within CHR populations, TLEs have been found to be significantly more prevalent than in non-psychiatric controls, and mean TLE rates appear consistent across CHR and clinically diagnosed psychotic samples, falling around 85% for endorsement of at least one TLE (Addington et al., 2013; Kraan, Velthorst, Smit, de Haan, & van der Gaag, 2015; Larsson et al., 2013). Further, conversion to psychosis rates were significantly higher for individuals with trauma histories compared to those at CHR for psychosis without such histories (Bechdolf et al., 2010), although one study found that only childhood sexual abuse increased risk of conversion (Thompson et al., 2014).

3.2 The Psychosis Phenotype

Growing evidence supports the existence of an extended psychosis phenotype, whereby more common, subclinical psychotic symptoms appear to be associated with many of the same risk factors for psychotic disorders, such as cannabis use, obstetric complications, and TLEs (Linscott & van Os, 2010). Individuals who experience these attenuated positive psychotic symptoms have been the focus of recent global efforts to prevent and treat such severe mental conditions as psychosis (van Os & Linscott, 2012). Attenuated positive

psychotic symptoms occur in 5–8% of non-clinical, healthy populations and have been linked to elevated risk for developing a psychotic disorder (Kaymaz et al., 2012; van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009; van Os & Linscott, 2012). Consistent support has emerged for TLEs being linked to this psychosis spectrum, such that TLEs are related to both diagnostic (i.e., schizophrenia, schizophreniform, schizoaffective, and delusional disorders) and dimensional outcomes of psychosis, such as schizotypy and attenuated positive symptoms (Gibson et al., 2014; Shevlin, Houston, Dorahy, & Adamson, 2008; Varese et al., 2012a; Velikonja, Fisher, Mason, & Johnson, 2014). These findings indicate that TLEs are implicated in the pathway to both broad and strict psychosis classifications.

4. Does TLE Type Matter?

The majority of evidence suggests that the relationship between TLEs and psychosis persists regardless of trauma type. Specifically, a meta-analysis demonstrated that no specific TLE predicted diagnostic or dimensional levels of psychosis in the general population more frequently than others (Varese et al., 2012a). Nevertheless, other studies have found individual differences in TLE types, which is important to consider given the potential for underpowered findings to be obscured by meta-analytic procedures. Further, the Varese et al. (2012a) meta-analysis did not include CHR samples, which also have produced significant differences among TLE types with regard to psychosis outcomes. Additionally, a recent review of findings in general population and psychotic disordered samples suggested links between specific TLEs and certain symptom dimensions, such as child sexual abuse with hallucinations and neglect with paranoia (Bentall et al., 2014). One consistent finding is that interpersonal TLEs characterized by intent to harm (e.g., physical or sexual abuse) are associated with a worse psychotic disorder trajectory (Arseneault et al., 2011; van Nierop et al., 2014a).

The bulk of studies that examine specific TLEs focus on childhood sexual abuse (CSA), childhood physical abuse (CPA), childhood emotional abuse (CEA), childhood neglect, childhood bullying, life-threatening events, and/or war exposure (Bonoldi et al., 2013; Matheson et al., 2012; Varese et al., 2012a). Table 1 presents the odds ratios for the four most commonly reported TLE types (i.e., CSA, CPA, CEA, and neglect) in relation to psychotic symptoms and disorders, and is intended to highlight the finding that the specific type of TLE experienced is not as salient as the endorsement of the TLE itself in predicting risk of various psychosis outcomes. Reported below is a summary of the findings for these four most commonly reported TLEs, as well as three TLE categories that may be distinct from early childhood abuse experiences and receive much less attention in the trauma and psychosis literature (i.e., life threatening events, bullying, and war exposure). Importantly, a recent study found that the odds of first-episode psychosis diagnosis for specific TLEs diminished after accounting for other TLEs, suggesting that each TLE experienced may have a shared impact on risk for psychosis (Trauelsen et al., 2015). These authors suggest that categorizing traumas into types obscured the overall trauma loading and may, in turn, account for the inconsistent findings for different TLEs increasing psychosis risk.

4.1 The Four Commonly Reported TLEs

Whereas evidence supports the link between general TLEs and psychosis, research is inconsistent as to whether specific TLE types are more strongly related to certain psychosis outcomes. For instance, while some studies find support for increased prevalence of CPA in individuals with psychotic disorders (Bonoldi et al., 2013; Larsson et al., 2013; Spence et al., 2006) or CHR for psychosis (Thompson et al., 2009) relative to CEA and CSA, CEA has been found to be more prevalent in individuals with psychotic disorders compared to CPA and CSA (Duhig et al., 2015). CPA was also the only TLE type to persist in predicting psychotic disorders compared to CSA, CEA, or neglect after accounting for several covariates, such as gender, age, ethnicity, social class, and depression (Shevlin et al., 2007; Fisher et al., 2010), as well as when accounting for other TLEs (Rubino, Nanni, Pozzi, & Siracusano, 2009). Despite the higher prevalence of CPA and CEA found for individuals experiencing psychosis, the link between CSA and schizotypal personality disorder and CSA and conversion to psychosis has been found to exceed that of other TLE types, such as CEA, CPA, and neglect (Afifi et al., 2011; Bechdolf et al., 2010; Thompson et al., 2014).

The association between neglect and psychosis at both the diagnostic and general population level is much more attenuated than CSA, CPA, and CEA (Daalman et al., 2012), and neglect may in fact have stronger connections to general psychopathology in psychotic samples (Heins et al., 2011; van Dam, Korver-Nieberg, Velthorst, Meijer, & de Haan, 2014b). These latter studies propose that one differentiating factor of neglect is that the child does not experience the stimulating, positive aspects that an otherwise normally developing brain encounters, which is more likely to lead to cognitive difficulties, rather than to dysregulated stress systems that are more frequently implicated in abuse. Nevertheless, a recent review suggests that neglect and being brought up in an institution may be linked to paranoid symptoms above and beyond other TLE types (Bentall et al., 2014). To our knowledge, there are no unique findings in the CHR literature regarding neglectful experiences during childhood.

4.2 Bullying

Studies find consistent associations between bullying and a variety of psychosis outcomes, although one meta-analysis indicated that associations were stronger for population-based samples endorsing attenuated levels of positive psychotic symptoms (van Dam et al., 2012). Evidence also suggests that bullying experiences may lead to specific functional difficulties, such as poor social functioning, compared to other types of trauma in CHR populations (Addington et al., 2013). The bullying-psychotic symptom relationship has also been found to endure regardless of other factors (e.g., family adversity, comorbid psychopathology, gender, age, or other negative life events; Schreier et al., 2009).

4.3 Non-Intentional Life Threatening Events

Support for the TLE-psychosis relationship is weaker, and somewhat inconsistent, when trauma is defined as experiencing a non-intentional life threatening environmental event, such as a serious injury or illness or experiencing a natural disaster. Nevertheless, several studies suggest links between life threatening events and psychosis outcomes. In a first-episode psychotic sample, the prevalence of life threatening events (e.g., a car accident

resulting in personal and vehicular injury) was highest compared to other TLEs, such as CSA or CPA (Neria, Bromet, Sievers, Lavelle, & Fochtmann, 2002). Additionally, a large population-based study demonstrated that serious illness, injury, or assault was linked to risk of psychotic disorders after adjusting for current depression and the interrelationship between other life events (Bebbington et al., 2004).

Despite these findings, several studies do not yield significant associations between life threatening events and psychotic symptoms or diagnoses. A first-episode sample study found decreased prevalence rates for non-interpersonal childhood TLEs (e.g., car accidents) compared to interpersonal childhood TLEs (Stain et al., 2014). Among a CHR sample, the "other trauma" category (primarily comprised of life-threatening events, such as accidents or natural disasters), did not yield significant results for conversion to psychosis (Bechdolf et al., 2010). An additional prospective study found that individuals exposed to a natural disaster were not at greater risk for experiencing psychotic symptoms 20 years post-trauma (Galletly, Van Hooff, & McFarlane, 2011). Thus, research on life threatening events in psychosis is limited and conflicting.

4.4 War Exposure

Research on the relationship between war exposure trauma and psychosis is far more limited than other TLEs. Elevations in psychotic diagnoses and symptoms have been found in various war-exposed populations that experienced their trauma in adulthood (e.g., Cambodian victims of the Pol Pot regime, prisoners of war; for a review, see Read, van Os, Morrison, & Ross, 2005). Further, PTSD may only partially account for the relation between war trauma and psychosis (Soosay et al., 2012). Nevertheless, conflict exposure may be considered discretely different than other commonly reported TLEs due to the diversity of TLEs conflict ridden environments produce. For instance, individuals in a post-conflict region of southeastern Asia frequently reported exposure to major disasters, witnessing murders, engaging in direct combat, or experiencing torture or assaults, each which are discretely different (Soosay et al., 2012). Thus, it can be difficult to parse apart the driving force behind potential risk for psychosis.

5. TLEs and Specific Psychotic Symptom Expression

5.1 Positive Symptoms

Several researchers have explored whether specific psychotic symptoms are more likely to emerge post-TLE exposure. In psychotic (Alemany, Goldberg, van Winkel, Gastó, & Fañanás, 2013; Duhig et al., 2015) and CHR (Kraan et al., 2015) samples, consistent relationships have been established between the positive symptom dimension of psychosis and TLEs. The preponderance of general population studies linking TLEs to psychosis classify psychotic symptoms based on the positive symptom dimension (Bentall, Wickham, Shevlin, & Varese, 2012; van Nierop et al., 2014a; Varese et al., 2012a). However, evidence is inconsistent as to whether TLEs impact the emergence of specific positive symptoms, as some large-scale studies find symptom specificity (Bentall et al., 2012) and others do not (Janssen et al., 2004; van Nierop et al., 2014a). For example, one study found that childhood

rape was associated with hallucinations, controlling for paranoia, whereas institutional care was associated with paranoia, controlling for hallucinations (Bentall et al., 2012).

Additional support for specificity between TLE type and symptom outcome include findings that CPA is more strongly linked to disorganization and suspiciousness among CHR individuals than CEA and CSA (Thompson et al., 2009), and that CEA is more strongly associated with the development of hallucinations relative to CPA and CSA (Daalman et al., 2012; McCarthy-Jones et al., 2014). CEA may also have a specific link to subthreshold forms of psychosis, such as schizotypy (Lobbestael, Arntz, & Bernstein, 2010; for a review, see Velikonja et al., 2014). Conversely, data from two large population-based samples did not support differential links between childhood trauma and hallucinations or delusions, instead proposing that TLEs are more frequently associated with their co-occurrence (van Nierop et al., 2014a).

5.2 Negative and Disorganized Symptoms

Few studies have examined TLEs in relation to negative symptoms of psychosis. Although correlations have been found between any TLE and/or specific abuse experiences and negative symptoms in those with psychotic disorders (Alemany et al., 2013; van Dam et al., 2014a), general population studies have not replicated these findings (Dominguez, Saka, Lieb, Wittchen, & van Os, 2010). However, recent studies reveal independent links between neglect and negative symptoms and abuse and positive symptoms in general population and psychotic disordered samples (Duhig et al., 2015; van Dam et al., 2014a).

Evidence for the link between TLEs and disorganized symptoms is even more sparse and equivocal. Dominguez and colleagues (2010) separated the effects of the negative/disorganized symptom cluster and found that disorganized symptoms were not associated with TLEs. Studies on the relationship between disorganized symptoms and specific TLEs are also limited and conflicting. For example, whereas one study did not find a significant association between thought disorder and CSA (Read, Agar, Argyle, & Aderhold, 2003), a study of female psychiatric inpatients found a significant association between psychotic thinking (e.g., paranoid and grandiose thinking) and CPA (Bryer, Nelson, Miller, & Krol, 1987). Given that most studies assess for the relationship between TLEs and positive symptoms, whether an association exists between TLEs and negative and disorganized symptoms remains unclear.

6. Multifinality

Researchers have emphasized that despite the worsening psychotic disorder trajectory found in the presence of psychological symptoms comorbid with psychosis, a “smoking gun” (i.e., plausible mechanism) linking these comorbidity patterns remains elusive (Buckley et al., 2009). Multifinality (i.e., that multiple outcomes are related to a single predictor) may offer a way to address the challenge of predicting which individual may develop one disorder versus another after being exposed to the same risk factor, in this case TLEs (Fusar-Poli et al., 2014).

6.1 TLEs and Diagnostic Ambiguity

An important diagnostic question regarding the relation between TLEs and psychosis is whether comorbid psychopathology accounts for this association, although most studies find the relation to persist after adjusting for psychological comorbidities (Varese et al., 2012a). Despite exposure to TLEs consistently linking to multiple psychological disorders, including psychotic, mood, substance use, personality, and anxiety- and stressor-related disorders, evidence is ambiguous as to whether there is a stronger association between TLEs and a particular diagnosis (Sideli, Mule, La Barbera, & Murray, 2012). Several researchers underscore the importance of considering comorbid affective, substance use, posttraumatic stress, and personality disorders when assessing TLEs in samples with psychosis or psychotic symptoms, as these disorders are the most common in psychosis comorbidity profiles and each independently link to TLEs (Buckley et al., 2009; van Nierop et al., 2014b). See Table 2 for a list of studies comparing the effect of TLEs on disorders comorbid with psychotic disorders. The following sections primarily compare *diagnostic* outcomes for individuals with a trauma history, and thus, the predominant focus is on psychotic disorders as an outcome. Few studies explore the role of TLEs in subclinical psychosis samples in comparing diagnostic sequelae. No CHR studies appear to have directly compared the TLE-other disorder versus TLE-CHR associations.

6.2 TLEs and PTSD vs. Psychotic Disorders

PTSD appears to be the only psychiatric outcome associated with TLEs at a more pronounced *and* consistent rate than psychotic disorders (Matheson et al., 2012), which is expected given that a diagnosis of PTSD is contingent upon TLE exposure. For example, a 41.1% mean prevalence rate of ever having PTSD as a result of intentional TLE exposure was reported in a recent study that compared PTSD rates across five different studies (Santiago et al., 2013). Additionally another study found that the rate of PTSD (4.0%) was larger than that of psychotic disorders (2.9%) in a sexually abused sample (Cutajar et al., 2010b). Despite the complex interrelation between posttraumatic symptoms, psychotic symptoms, and TLEs, there is minimal agreement as to whether psychosis is a risk factor for PTSD, whether PTSD is a risk factor for psychosis, or whether both disorders represent a continuum response to TLEs (Vauth & Nyberg, 2007). One theory is that exposure to childhood trauma may enhance risk for stress-related disorders (e.g., psychosis, PTSD, depression) via the neuropathology of the stress response system (i.e., alterations of the hypothalamic-pituitary-adrenal [HPA] axis; Matheson et al., 2012).

6.3 TLEs and Mood Disorders vs. Psychosis

Results conflict as to whether the TLE-psychosis link is more prominent than the TLE-mood disorder link. Nevertheless, depression has been cited as one of the two (the other being PTSD) most common psychiatric sequelae of childhood TLEs (Sideli et al., 2012). Studies have demonstrated a higher prevalence of mood compared to psychotic disorders in samples with TLE histories, such as Cutajar et al.'s (2010b) study, which found 6.4% and 2.9% of their sexually traumatized sample to have an affective versus psychotic disorder. Conversely, studies have found support for a stronger link between TLEs and psychotic disorders than with depressive or bipolar outcomes (Rubino et al., 2009; Spence et al., 2006). In Rubino

and colleagues' (2009) study, base rates of any TLE exposure varied greatly across general population (6.1%), major depressive disorder (14.4%), and schizophrenia (28.7%) samples. Also complicating the issue is that some studies yield similar prevalence rates of TLEs in psychotic and mood disorders (Alvarez et al., 2011; Friedman et al., 2002). TLEs also appear to have a stronger impact on the extended psychosis phenotype compared to mood disorders, as trauma was found to correlate with schizotypy in siblings of individuals with schizophrenia, but not bipolar individuals (Schürhoff et al., 2009), and as TLEs were associated with psychotic symptoms, but not bipolar or major depressive disorder diagnoses (Spauwen, Krabbendam, Lieb, Wittchen, & van Os, 2006). Despite contradictory results, epidemiological studies consistently find that controlling for depressive disorders or symptoms reduces, but does not eliminate, the significant relationship between childhood TLEs and psychotic symptoms (Sideli et al., 2012). An outstanding methodological concern in this literature is assessing and/or controlling for the presence of mood disorders with psychotic features. Only one of the aforementioned studies included this subgroup in their analyses, but individuals with these diagnoses were grouped with other psychotic disorders (Cutajar et al., 2010b). Therefore, it remains unclear if mood disorders with psychotic features represent a distinctly different group than those with discrete mood or psychotic disorders in the context of both the prevalence and clinical impact of TLE histories.

6.4 TLEs and Substance vs. Psychotic Disorders

Findings indicate that drug and alcohol use are particularly elevated for psychotic individuals with TLE histories, with comorbid substance use and psychotic disorders comorbidity rates ranging from 51% to 96% (Buckley et al., 2009). Further, in sorting out the differential impact of trauma exposure, TLEs have been found to be more common in the histories of women with comorbid psychosis and substance use than with comorbid severe depression and substance use or substance use alone (Aakre, Brown, Benson, Drapalski, & Gearon, 2014). This study also found that women with comorbid schizophrenia and substance use disorders were four times more likely to meet criteria for PTSD relative to women with severe and chronic depression and substance use. Hence, the overall influence of TLEs appears to be worse for comorbid substance use and psychosis compared to substance use alone with as high as 96% of women with comorbid substance use and schizophrenia spectrum disorders endorsing at least one TLE (Gearon, Kaltman, Brown, & Bellack, 2003). Independent of psychotic disorders, overall prevalence rates of alcohol and substance abuse or dependence have been found to be prevalent in roughly 14% and 9%, respectively, of maltreated samples (Scott, McLaughlin, Smith, & Ellis, 2012).

Cannabis use, which is strongly linked to symptoms and diagnoses of psychosis (Radhakrishnan, Wilkinson, & D'Souza, 2014), has received specific attention in the TLE and psychosis literature. Psychosis may be the result of a synergistic interaction between TLEs and cannabis, with psychosis being a more frequent outcome if cannabis use is part of the lifestyle of the traumatized individual (Harley et al., 2010; Konings et al., 2012). Odds of experiencing psychotic symptoms for youth with TLE histories that used cannabis range from 12.0 (Houston, Murphy, Adamson, Stringer, & Shevlin, 2008) to 20.0 (Harley et al., 2010). Nevertheless, results from the few studies directly comparing psychosis to substance use outcomes following TLEs are equivocal, as ORs are roughly similar (see Table 2).

6.5 TLEs and Personality vs. Psychotic Disorders

As noted in Table 2, the effect of TLEs appears significant across a range of personality disorders. One disorder that appears to be most directly associated with both TLEs and psychotic symptoms is borderline personality disorder, especially as psychotic symptoms not only are prominent in borderline pathology, but are often associated with trauma experiences (Barnow et al., 2010; Schroeder, Fisher, & Schäfer, 2013). The main effect of TLEs on borderline personality disorder appears particularly prominent, such that the association between sexual abuse and this disorder compared to the association for controls yielded an odds ratio of 6.07, the highest across all disorders assessed although the base rate of this disorder in the traumatized sample was 1.8% (Cutajar et al., 2010b). In a recent study comparing a sample of women with either schizophrenia or borderline personality disorder, TLEs of all types were more prevalent in the latter sample (Tschoeke, Steinert, Flammer, & Uhlmann, 2014). However, both samples in this study were selected based on the experience of auditory visual hallucinations in the past year, making it impossible to ascertain if the links between TLEs and borderline personality disorder persist controlling for psychotic experiences.

In conclusion, it does not appear that specificity exists for TLEs in relation to psychosis compared to other psychiatric conditions. Thus, a fundamental question remains: why do certain individuals develop psychosis versus other disorders, given a TLE history (van Nierop et al., 2014b)? It is imperative that future research investigates the longer-term outcomes of TLEs from a transdiagnostic perspective to reveal the unique mechanisms that influence transition to one disorder versus another. To isolate the variance of specific diagnostic dimensions and to rule out study findings being a function of comorbid conditions, it is critical that researchers engage in the uncommon practice of not only controlling for co-occurring symptoms when examining the relationship between TLEs and psychosis, but also controlling for psychotic symptoms when assessing the association between TLEs and other disorders (O'Hare, Shen, & Sherrer, 2013).

7. Equifinality

Equifinality is as important a concept as multifinality in developing and refining identification and treatment options for individuals expressing psychosis. The concept of equifinality suggests that various etiological mechanisms and developmental pathways lead to a single (diagnostic) end state, which fits with current etiological models of psychosis, such that psychosis represents the outcome of a complex interplay of predictors like neurodevelopmental or social risk factors, many of which may be non-overlapping (Debbané & Barrantes-Vidal, 2015; Howes & Murray, 2014). It is likely that TLEs lead to psychosis outcomes through multiple different pathways and that TLEs interact with other variables that are antecedent (e.g., obstetric complications) or consequent to TLEs (e.g., substance use) in increasing psychosis risk.

Several prospective studies of subclinical samples suggest specific pathways to psychosis stemming from TLEs. Fisher et al. (2013) found that one pathway involves exposure to domestic violence prior to age 6 leading to an anxiety disorder at age 10, which subsequently led to psychotic symptoms at age 12.9. Another pathway included exposure to

domestic violence prior to age 6 leading to poor self-esteem at 8.5 years of age, which then led to psychotic symptoms at age 12.9. Kramer and colleagues (2013) found that micro-level (i.e., momentary and hourly) increases in negative affect led to micro-level increases in paranoia, and subsequently, these momentary increases in paranoia were linked to follow-up psychotic symptoms, a pathway that was moderated at the paranoia level by a TLE history. These studies provide critical steps in illustrating unique pathways by which TLEs can impact psychosis outcomes. A remaining gap involves identifying the mechanisms that begin to explain the relationship between trauma and psychosis *once all comorbid symptomatology is accounted for* given the vast diagnostic heterogeneity that can occur post-trauma.

8. Proposed Mechanisms

Establishing mechanisms that lead to sensitivity and specificity is critical in light of the substantial heterogeneity and overlap in symptom expression of psychotic disorders and disorders comorbid with psychosis (Debbané & Barrantes-Vidal, 2015; van Nierop et al., 2014b). Several theoretical models have been proposed concerning the association between TLEs and psychosis yet empirical data supporting these models is scarce (Bentall & Fernyhough, 2008; van Winkel, van Nierop, Myin-Germeys, & van Os, 2013). Information processing biases, locus of control, stress sensitivity, negative schemas, and dissociation have been proposed as possible mechanisms involved in the relationship between TLEs and psychosis (Anglin, Polanco-Roman, & Lui, 2014; Bendall et al., 2013b; Fisher, Appiah-Kusi, & Grant, 2012; Fisher et al., 2013; Gibson et al., 2014). Nevertheless, there remains little data on these potential explanatory variables and most existing studies have examined these constructs in isolation, obscuring the complex interactions between these variables (Bebbington et al., 2011; Freeman & Fowler, 2012; Fisher et al., 2012; Fisher et al., 2013; Gracie et al., 2007; Perona-Garcelán et al., 2012).

8.1 Cognitive Mechanisms

8.1.1 Information Processing Biases—One model of psychosis posits that psychosis manifests as a result of aberrant attribution of salience to otherwise irrelevant stimuli (Kapur, 2003; Roiser, Howes, Chaddock, Joyce, & McGuire, 2013; van Winkel et al., 2013). Trauma fits within this model, as those exposed to TLEs often disproportionately allocate attention to threatening stimuli, which consequently could lead to incorrect inferences in line with paranoid ideation (Sherrer, 2011). These biases in information processing, measured behaviorally (e.g., Emotional Stroop task) or neurophysiologically (e.g., EEG), have been found in traumatized (Caparos & Blanchette, 2014; Wingenfeld et al., 2011), psychotic disordered (Bendall et al., 2013b; Besnier et al., 2010; Kinderman, Prince, Waller, & Peters, 2003; Wiffen et al., 2013), CHR (Rosier et al., 2013; Nieman et al., 2014), and subclinical psychosis samples (Fisher et al., 2014b; Marks, Steel, & Peters, 2012). These populations have been found to have longer reaction times for threatening words, suggesting a general attention bias towards threatening stimuli (Bendall et al., 2013b; Cisler et al., 2011; Wiffen et al., 2013). However, information processing biases have not been explored as a mediator of the TLE-psychosis association.

8.1.2 External Locus of Control—Bentall and Fernyhough (2008) hypothesized that experiences of victimization may trigger an external explanatory style, such that negative events are interpreted as caused by powers external to the self, which, in turn, facilitates threat anticipation and paranoid beliefs. Individuals with psychotic disorders have been found to have a bias toward interpreting private events and experiences with external attributions, such that they are more likely to believe that their behavior is controlled by outside forces (Bentall & Fernyhough, 2008; Frenkel, Kugelmass, Nathan, & Ingraham, 1995). In fact, Frenkel et al. (1995) found that an externalizing bias was one of the strongest longitudinal predictors of psychotic disorders. Further, among individuals diagnosed with schizophrenia, having an external attribution orientation is associated with poorer prognosis and more severe depressive, negative, and positive symptoms (Hutcheson, Fleming, & Martin, 2014). Both CHR (Thompson, Papas, Bartholomeusz, Nelson, & Yung, 2013) and subclinical levels of psychosis (Cooper et al., 2008; Levine, Jonas, & Serper, 2004; Thompson et al., 2011) have also been linked to significant elevations in measures of external locus of control. The only known study examining the mediating role of this construct in the TLE-psychosis relation was in a general population sample, which found that external locus of control levels prospectively mediated this relation, although only bullying and mothers' reports of harsh parenting and domestic violence in the home were investigated (Fisher et al., 2013). Cumulatively, these studies suggest that external locus of control may be a potential important mediator of the TLE-psychosis link.

8.1.3 Stress Sensitivity—Trauma-exposed (Glaser, van Os, Portegijs, & Myin-Germeys, 2006), psychotic (Lardinois, Lataster, Mengelers, van Os, & Myin-Germeyes, 2011; Myin-Germeys, van Os, Schwartz, Stone, & Delespaul, 2001), CHR (Aiello, Horowitz, Hepgul, Pariante, & Mondelli, 2012; Devylder et al., 2013), and subclinical psychotic samples (Collip et al., 2013a; Lataster et al., 2009) have been found to have heightened stress sensitivity, as measured by elevated physiological or subjective susceptibility to lab-induced or environmental stressors. Further, individuals in the CHR phase for psychosis endorse higher levels of subjective stress sensitivity for both life events and daily hassles (Trotman et al., 2014), and perceived stress has also been found to mediate the relation between TLEs and attenuated positive psychotic symptoms (Gibson et al., 2014). Nevertheless, stress sensitivity has been found to be a mediator for the relation between TLEs and a number of mental disorders (Heim & Binder, 2012). Therefore, it is important for future studies to decipher whether potential mediation findings hold after adjusting for other psychological symptoms.

8.1.4 Dissociation—Exposure to TLEs has been conceptualized as inducing dissociative tendencies due to reality discrimination deficits (between internally and externally generated events) that are thought to underlie hallucination-proneness (Anketell et al., 2010; Moskowitz & Corstens, 2008). Dissociation is strongly linked to a history of TLEs (Ogawa, Sroufe, Weinfield, Carlson, & Egeland, 1997), and robust associations have been established between dissociation and psychotic disorders with the belief that TLEs may lead to dissociation, which then facilitates the expression of psychosis (Braehler et al., 2013; Schäfer et al., 2012). The only study assessing dissociation in CHR did not find a significant association between dissociative symptoms and TLEs (Velthorst et al., 2013). In non-clinical

samples, higher dissociation was found to mediate the relationship between TLEs and positive psychotic experiences (Anglin et al., 2014; Perona-Garcelán et al., 2012; Varese, Barkus, & Bentall, 2012b). Given the strong link between dissociation and TLEs, it is unclear if dissociation remains an explanatory variable in the TLE-psychosis association when other disorders comorbid with psychosis that are also associated with dissociative tendencies (e.g., borderline personality disorder, PTSD) are accounted for in a comprehensive model (Pec, Bob, & Raboch, 2014; Stein et al., 2013).

8.1.5 Negative Schemas—Cognitive theories of psychosis purport that early adverse experiences can lead to the manifestation of negative schemas about the self involving vulnerability, humiliation and subordination, which are hypothesized to make psychotic symptom expression more likely in predisposed individuals (Garety, Kuipers, Fowler, Freeman, & Bebbington, 2001). Significant associations have been established between negative schemas (e.g., vulnerability to harm) and positive symptoms in those with schizophrenia spectrum disorders (Bortolon, Capdevielle, Boulenger, Gely-Nargeot, & Raffard, 2013; Fowler et al., 2011). Negative schemas have also been strongly associated with CHR for psychosis (Addington & Tran, 2009), to mediate the relationship between TLEs and subclinical paranoia (Fisher et al., 2012), and to predict to subclinical paranoia and hallucinations (Gracie et al., 2007). Nevertheless, no study has investigated whether negative schemas are a unique mediator of the TLE-psychosis relationship, which is an important question since other comorbid psychopathologies are also known to engage negative schemas (Calvete, Orue, & Hankin, 2013).

8.2 Gender Differences in the TLE-Psychosis Association

The few studies that have assessed for sex-specific risk in the TLE-psychosis relation have primarily yielded inconsistent findings (Bendall, Jackson, Hulbert, & McGorry, 2008). Although some studies suggest that gender moderates the relationship between TLEs and established psychosis (Fisher et al., 2009; Gayer-Anderson et al., 2015) and subclinical psychotic experiences (Gibson et al., 2014), others reveal no sex differences (Shevlin, Murphy, & Read, 2015). Of the studies that explore gender, a more significant TLE-psychosis pathway appears evident for females, whereby risk for psychosis following TLE exposure is more elevated in females versus males diagnosed with psychotic disorders (Bebbington et al., 2011; Cutajar et al., 2010a; Gayer-Anderson et al., 2015). One study found that females with psychotic disorders were significantly more likely to report sexual or physical abuse than their female control counterparts even after conservative adjustments (e.g., affective diagnoses), discrepancies that did not emerge for males (Fisher et al., 2009). Female CHR individuals with sexual abuse histories also were significantly more likely to endorse positive symptoms compared to males (Thompson et al., 2010). The importance of TLEs as a risk factor for psychosis in females is also emphasized by recent findings that there was no significant relationship between TLEs and attenuated positive psychotic symptoms for males in a general population sample of adults experiencing subclinical psychotic symptoms (Gibson et al., 2014).

Animal and human research suggests that females may be more sensitive to stress and trauma. For example, females demonstrate heightened physiological and neurochemical

stress reactivity (e.g., quicker release of and higher emission of glucocorticoids), as well as subjective stress sensitivity, compared to males (Goel, Workman, Lee, Innala, & Viau, 2014; Myin-Germeys, Krabbendam, Delespaul, & van Os, 2004). Increases in perceived stress also has been found to mediate the relationship between TLEs and attenuated positive psychotic symptoms for females only (Gibson et al., 2014). Additionally, in animal research, female rats have been found to produce significantly more corticotropic-releasing factor neurons and demonstrate increased activation of neurons in brain regions involved in threat perception compared to males (Babb, Masini, Day, & Campeau, 2013). Cumulatively, these findings suggest that the females may be predisposed to develop disorders that are closely linked to biological stress dysregulation, such as psychosis, Major Depressive Disorder, and/or PTSD, the latter two which are twice as prevalent in females (Shea, Walsh, MacMillan, & Steiner, 2005).

8.3 Neurobiological Mechanisms

8.3.1 Stress Neurobiology—One of the primary biological mechanisms implicated in the genesis of stress-based psychological disorders (e.g., psychosis, PTSD), as well as proposed to partially account for the trauma and psychosis pathway, is dysregulation of the stress response system, particularly the HPA axis and neurotransmitter systems (i.e., significantly elevated basal cortisol levels, hyper- or hypo-responsivity to stress), as well as hippocampal volume reductions (Ruby et al., 2014; Shea et al., 2004). Current theories suggest that childhood TLEs may activate a cascade of neurobiological changes, including increases in proinflammatory cytokines (Dennison, McKernan, Cryan, & Dinan, 2012), stress sensitization of the HPA axis via glucocorticoid- and striatal-related increases in dopamine (Pruessner, Champagne, Meaney, & Dagher, 2004; Wand et al., 2007), and reductions of the hippocampus, which has a critical role in regulating HPA axis activity (Mondelli et al., 2011). Despite stress cascade theories and findings, no studies have empirically tested if HPA axis hypo- or hyper-activity, as well as hippocampal reductions, moderate or mediate the relationship between TLEs and psychosis.

8.3.2 Gene-Environment Interactions—It is commonly accepted that TLEs are not the solitary catalyst for psychosis. Instead, it is likely that the interaction of TLE exposure and genetic and neurodevelopmental risk factors (both pre- and post-trauma) leads to maximum probability of psychosis development. For example, a general population study discovered that carriers of the Met allele for brain-derived neurotrophic factor (BDNF) had an increased the likelihood of experiencing positive psychotic symptoms in the context of early childhood adversity (Alemany et al., 2011). Other studies also support gene-environment interactions, whereby specific genetic alterations (e.g., single-nucleotide polymorphisms in FK506 binding protein 5, and variants of the serotonin transporter gene, 5-HTTLPR) moderate the effect of TLEs on the manifestation of psychosis (Aas et al., 2012; Collip et al., 2013b). In individuals with schizophrenia, carriers of a short allele of a serotonin transporter gene who experienced high levels of TLEs demonstrated more cognitive deficits, which are associated with stress sensitivity, than carriers of the long allele (Aas et al., 2012).

Within the trauma and stress literature, genetic polymorphisms linked to HPA axis functioning increased the likelihood of stress-based psychiatric disorders, including

depression (Bradley et al., 2008) and PTSD (Binder et al., 2008). Carriers of the Val allele of the catechol-O-methyltransferase (COMT) gene, which is linked to reduced dopamine neurotransmission in the prefrontal cortex and increased dopamine activity in the striatum (Chen et al., 2004), have been found to display marked increases in psychotic symptoms in response to stress (Stefanis et al., 2007; Simons et al., 2009). These studies on single candidate genes are critical to the gene by environment literature in the psychosis-stress relationship; however, they do not account for much variance, which is consistent with findings that single genes do not play a large etiological role in psychosis. Thus, more recent studies have explored the interactions between multiple genes, although primarily in the context of stress sensitivity (for a review, see Holtzman et al., 2013). Peerbooms and colleagues (2012) found that two genotypes (MTHFR C677T and COMT Val158Met) interacted in psychotic individuals compared to controls, such that those with both genotypes had the greatest reaction to daily stress, as measured by psychotic symptom severity. Although the gene by environment literature is still in early development, specifically in relation to the link between TLEs and psychosis, studies on the stress by psychosis interaction may be particularly informative.

8.3.3 Epigenetics—Epigenetics reference changes to the genome that alter gene expression, but not DNA sequence. For instance, certain hormones can impact DNA methylation, which can, in turn, modify protein production in regionally-specific parts of the body, including brain structures (for a review, see Holtzman et al., 2013). While studies exploring the influence of TLEs on psychosis via epigenetic processes hold great promise, no studies have yet been conducted in this realm in vivo in humans, likely due to concerns that peripheral epigenetic changes likely do not reflect epigenetic alterations in the brain. In underscoring the potential role epigenetics may play in early childhood experiences, specifically parental care, one postmortem study of a sample of individuals who completed suicide discovered that an epigenetic change (i.e., increased cytosine methylation of a glucocorticoid receptor promotor) was linked to childhood abuse (McGowan et al., 2009). Overall, the science of epigenetics has been long recognized as important to the pathogenesis of psychosis, but human in vivo studies are limited by methodological barriers.

9. Methodological Concerns

9.1 Reliability of Self-Report

The retrospective nature of TLE recall and the reporting of psychotic individuals have been questioned for their accuracy and validity (Susser & Widom, 2012). Two findings dispute one of the major concerns in TLE self-reporting, which is over-reporting. First, Varese and colleagues' (2012a) meta-analysis found that the odds of developing psychosis in TLE compared to no TLE groups was the same regardless of whether TLEs were reported pre- or post-psychosis onset. Second, odds for developing psychotic disorders in a community sample of individuals with documented versus undocumented TLEs were similar regardless of group (Cutajar et al., 2010a), and also similar to the odds ratios reported in the meta-analysis based primarily on retrospective TLE recall (Varese et al., 2012a). Such consistent ORs across studies makes over-reporting less likely for those who are psychotic or do not have documented abuse (Bendall et al., 2013a). False negatives may be a greater concern

than false positives, perhaps due to reluctance or forgetfulness (Hardt & Rutter, 2004). The evidence collectively suggests that the self-reporting of TLEs among psychotic individuals may be underrepresented, consistent across time, and in alignment with corroborating abuse reports (Fisher et al., 2011).

9.2 Study Design

Another methodological concern is that many of the available empirical studies assessing the TLE-psychosis relationship are cross sectional, which raises the issue of reverse causality (e.g., that psychotic experiences may lead to increased TLE exposure; Bendall et al., 2008). Directionality of effect issues also are underscored by alternative explanations that might account for the TLE-psychosis association, such as certain childhood factors that have been independently associated with risk for psychosis like premorbid cognitive difficulties and unusual behaviors (Bearden et al., 2000; Ellman, Yolken, Buka, Torrey, & Cannon, 2009; Niendam et al., 2003) potentially leading to increased risk of victimization during childhood (Sideli et al., 2012). Additionally, study designs that do not include control groups prevent researchers from drawing conclusions about the etiological relevance of TLEs in the pathway to psychosis, which highlights the importance of the many case-control studies that replicate the association between TLEs and the entire psychosis spectrum (Elklit & Shevlin, 2010; Heins et al., 2011; van Dam et al., 2014b).

9.3 TLE Measurement

Studies greatly vary in how they measure TLEs, both in terms of type of measurement (e.g., structured interview, self-report), as well as the type, timing, and severity of TLEs assessed (Bendall et al., 2008). These methodological differences impede conclusive statements and potentially explain minimal replications across studies. Varying methods for trauma assessment also yield different TLE disclosure rates, with self-reports tending toward higher rates of disclosure (Bendall et al., 2008). Nevertheless, reliable and valid self-report questionnaires have been developed and widely used over the years within psychosis research, such as the Childhood Trauma Questionnaire (Bernstein & Fink, 1998).

10. Conclusions

10.1 Clinical Implications

Given the immense societal cost of psychoses, it is imperative that individualized prevention and treatment efforts are developed or current methods refined. The early intervention and practical application prospects for understanding the TLE-psychosis relationship are great. First, in light of the importance of cognitive-based appraisals and schemas, tailoring treatment toward trauma-related cognitions that influence psychotic experiences may prove promising (Sherrer, 2011). Second, therapeutic efforts aimed at ameliorating stress sensitivity and emotional dysregulation are likely also useful interventions that could target comorbidities (e.g., depression, PTSD) and distress related to threat appraisals (Birchwood & Trower, 2006). Third, treatment that directly tackles traumas has been found to be efficacious in treating individuals with comorbid psychotic disorders and PTSD (Dvir, Denietolis, & Frazier, 2013). Overall, a variety of therapeutic avenues are available for clinicians who interface with individuals presenting with psychotic symptoms and who have

TLE histories. Equally important is the assessment of TLEs for individuals presenting with psychosis-related concerns, as TLE histories may play an important role in the phenomenology and treatment of psychosis. At the prevention level, community-based interventions aimed at reducing trauma exposure is likely to be critical in lowering the incidence of psychotic disorders (Kelleher et al., 2013). Given the strong link between TLEs and general psychopathology, community and policy efforts to prevent the incidence of traumatic life experiences, such as abuse, neglect, violence, and peer victimization, is imperative for public health.

10.2 Summary

Despite the consistent relationship between TLEs and psychosis, the temporal and dose-response patterns that exist for this association, and the many mechanisms proposed to account for it, exposure to trauma is not necessary or sufficient to cause psychosis. It is likely that TLEs interact with genetic vulnerability and/or other risk factors to produce psychosis outcomes. However, the experience of trauma is not psychosis-specific in terms of psychological sequelae; thus, specificity of TLEs to psychosis is critical to assess in future studies. Further, the genes implicated in the TLE-psychosis pathway are involved in other important domains (e.g., mood as indexed by the serotonin transporter gene), which is consistent with the transdiagnostic complexity that results in the aftermath of TLEs (van Winkel et al., 2013). Nevertheless, the lack of specificity does not undermine the robust association between TLEs and psychosis, and the value of better understanding the factors that explain this relationship. In conclusion, exposure to traumatic life experiences can significantly impact the pathogenesis of psychotic experiences as either a precipitating or exacerbating factor, and can lead to psychosis outcomes through myriad pathways that intersect with other genetic or environmental risk factors.

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Table 1

Association Between Type of Traumatic Life Events and Psychosis Outcomes

Author	Study Design	Psychosis Outcome (adjustments noted)	Type of TLE Assessed	Odds Ratio (95% Confidence Interval)
Bechdolf et al., 2010	Prospective, Clinical High Risk	Transition to Psychosis (adjusted for inclusion into multiple Ultra High Risk groups)	Physical Trauma, Total Cohort	0.87 (0.35–2.18)
			Emotional Trauma/Neglect, Total Cohort	0.80 (0.27–2.39)
			Sexual Trauma, Total Cohort	2.96 (1.16–7.57) *
Fisher et al., 2010	Epidemiological, case-control	First-episode Psychotic Disorder (adjusted for gender, age, ethnicity, study center, and highest parental social class)	Physical Abuse-Mother	2.91 (1.25–6.79) *
			Physical Abuse-Father	1.22 (0.66–2.25)
			Sexual Abuse	1.60 (0.87–2.95)
			Neglect-Mother	2.23 (1.03–4.83) *
			Neglect-Father	0.77 (0.39–1.51)
Trauelsen et al., 2015	Cross sectional, case-control	First Episode Psychotic Disorder Diagnosis (adjusted for gender, age, first degree psychiatric disorder, parental socio-economic status)	Sexual Abuse	8.51 (2.30–31.50) *
			Physical Abuse	3.53 (1.59–7.83) *
			Emotional Abuse	7.33 (3.54–15.21) *
			Emotional Neglect	16.93 (5.41–52.98) *
			Physical Neglect	6.23 (2.99–13.00) *
			Separation	7.45 (2.78–19.94) *
			Death of a Parent < age 18	1.20 (0.32–4.53)
Thompson et al., 2014 +	Prospective, Clinical High Risk	Transition to Psychosis (unadjusted, as adjustments for global functioning, gender, age at baseline, and education were consistent)	Emotional Abuse	1.01 (0.96–1.06)
			Physical Abuse	1.04 (0.99–1.09)
			Sexual Abuse	1.05 (1.01–1.09) *
			Emotional Neglect	1.01 (0.96–1.06)
			Physical Neglect	0.98 (0.90–1.07)
Afifi et al., 2011 **	Cross sectional, General population	Schizotypal Personality Disorder Diagnosis (adjusted for age, gender, education, income, race/ethnicity, marital status, any cluster B & C personality disorders, any lifetime mood, anxiety, or substance use disorder)	Physical Abuse	1.62 (1.28–2.03) *
			Emotional Abuse	1.76 (1.35–2.31) *
			Sexual Abuse	2.05 (1.59–2.65) *
			Physical Neglect	1.61 (1.26–2.05) *
			Emotional Neglect	1.35 (1.05–1.74) *
Whitfield et al., 2005 ***	Cross-sectional, cohort	Lifetime history of hallucinations (adjusted for age at survey, sex, race and educational attainment)	Emotional Abuse	2.30 (1.80–3.00)
			Physical Abuse	1.70 (1.40–2.10)
			Sexual Abuse	1.70 (1.40–2.10)
Galletly et al., 2011	Prospective, cohort	Positive Psychotic Symptoms (Psychosis Probe Positive)	Sexual Abuse	2.81 (1.06–7.46)
			Physical Abuse	5.48 (2.03–14.78) *
			Verbal Abuse	7.90 (3.02–20.66) *
			Physical Neglect	6.88 (1.87–25.38) *

Author	Study Design	Psychosis Outcome (adjustments noted)	Type of TLE Assessed	Odds Ratio (95% Confidence Interval)
			Emotional Neglect	4.19 (1.35–13.07) *
Kelleher et al., 2008	Cross sectional, General population	Positive Psychotic Symptoms (adjusted for gender and socio-economic status)	Sexual Abuse	4.16 (0.34–50.51)
			Physical Abuse	5.96 (1.27–27.97) *

* significant association;

** 99% CI reported,

*** significance values not reported;

+ hazard ratios reported instead of odds ratios

Table 2

Association Between Traumatic Life Events and Psychiatric Disorders Comorbid With Psychosis

Author	Study Design	Age; Type of TLE Assessed	Psychiatric Outcome	Adjusted Odds Ratio (95% Confidence Interval)
Cutajar et al., 2010b	Prospective, General population	≤16 year old; sexual abuse	Psychotic Disorders	2.13 (1.44–3.17) *
			Affective Disorders	2.07 (1.59–2.70) *
			Posttraumatic Stress Disorder	5.56 (3.44–8.99) *
			Other Anxiety Disorders	2.67 (1.97–3.61) *
			Alcohol Abuse	5.88 (3.26–10.63) *
			Drug Abuse	5.94 (3.68–9.58) *
			Borderline Personality Disorder	6.07 (2.87–12.85) *
Spauwen et al., 2006	Prospective, General population	14–24 years old; any trauma (physical threat, rape, sexual abuse, natural catastrophe, serious accident, imprisoned or kidnapped, terrible event to other)	Broadly Defined Positive Psychotic Symptoms	1.07 (0.82–1.40) *
			Narrowly Defined Positive Psychotic Symptoms	1.89 (1.16–3.08) *
			Bipolar Disorder	0.40 (0.10–1.57)
			Major Depression	1.16 (0.79–1.71)
Schurhoff et al., 2009	Cross sectional, case control	≥18; any trauma (physical, emotional, and sexual abuse, physical and emotional neglect)	Schizophrenia First Degree Relatives	3.60 (1.09–11.80) *
			Bipolar First Degree Relatives	1.64 (0.57–4.72)
Matheson et al., 2012	meta-analysis (cohort, case-control, and cross-sectional studies)	<18 years old; physical abuse, sexual abuse, neglect	Schizophrenia vs. Non-Psychiatric Controls	3.60 (2.08–6.23) *
			Schizophrenia vs. Affective Psychosis	1.23 (0.77–1.97)
			Schizophrenia vs. Anxiety Disorders	2.54 (1.29–5.01) *
			Schizophrenia vs. Depressive Disorder	1.37 (0.53–3.49)
			Schizophrenia vs. Dissociative Disorders & PTSD (sexual abuse only)	0.03 (0.01–0.15)
			Schizophrenia vs. Other Psychoses	0.69 (0.28–1.68)
			Schizophrenia vs. Personality Disorders (sexual abuse only)	0.65 (0.09–4.71)
Rubino et al., 2009	Cross sectional, case-control	>18 years old; any abuse (emotional, psychological, physical, and sexual abuse)	Schizophrenia vs. Non-Psychiatric Controls	6.57 (3.48–12.39) *
			Schizophrenia vs. Depressive Disorder	3.24 (1.93–5.45) *
Harley et al., 2010	Cross sectional, general population	12–15 years old; any trauma (sexual abuse, physical abuse, exposure to domestic violence)	Cannabis Use	4.86 (1.63–14.51) *+
			Positive Psychotic Symptoms	6.16 (1.65–23.1) *
Konings et al., 2012	Prospective, General population	18–64 (NEMESIS sample only); any abuse (emotional, physical, psychological, and	Positive Psychotic Symptoms	1.96 (1.73–2.20) *
			Positive Psychotic Symptoms Controlling for Cannabis Use	1.93 (1.71–2.18) *

Author	Study Design	Age; Type of TLE Assessed	Psychiatric Outcome	Adjusted Odds Ratio (95% Confidence Interval)
		sexual abuse)	Cannabis Use	1.57 (1.33–1.86) *
van Nierop et al., 2014b	Cross sectional, general population	18–65 (NEMESIS-2 sample only); any abuse (emotional neglect, physical abuse, psychological abuse, sexual abuse, and peer victimization)	≥1 Depression Symptom	1.21 (1.18–1.23) *
			≥1 Anxiety Symptom	1.18 (1.16–1.21) *
			≥1 Manic Symptom	1.19 (1.17–1.22) *
			≥1 Psychotic Symptom	1.23 (1.20–1.26) *

* significant association;

+ only unadjusted odds ratio reported