CHILDHOOD AND LATER LIFE STRESSORS AND PSYCHOSIS

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Abstract

The etiology of psychosis consists of a complex integration of several risk factors including genetic vulnerability, adverse life events and trauma, and substance use. This review discusses the current theories of the genesis of psychosis, with an emphasis on the importance of Adverse Childhood Experiences (ACEs) and later life events. ACEs in particular have a profound impact on an individual's health later in life; and specifically, those who have experienced ACEs are at an increased risk for psychosis. In addition, stressful life events later in life may be relevant for onset and relapse of psychotic episodes. Associations between types of life adversity and specific symptomatology of a psychotic episode have also been suggested. A multi-factorial approach is suggested for linking genetic and environmental contributors to the onset of psychosis. This approach may have an advantage over a purely bio-medical model by focusing less on disability and more on underlying contributors that may be responsive to intervention.

Key words: adolescence, childhood, child abuse/psychology, gene-environment interaction, life change events, pituitary-adrenal system, psychotic disorders/etiology, psychotic disorders/genetics, risk factors, young adult

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Introduction

Psychosis describes a complicated and highly variable set of experiences in which perceptions, behaviors and cognitions are distorted, resulting in delusions, hallucinations, thought disorder, or a mixture thereof. Psychotic experiences appear to lie on a continuum between relatively mild anomalous perceptions and idiosyncratic beliefs that are frequently present in the general population without evolving into a psychotic event (Horwood et al. 2008, Sommer et al. 2010, Bell et al. 2011), to more significant hallucinations, delusions, or thought disorder that extend beyond a day, a month, or six months, meeting criteria for a brief psychotic disorder, a schizophreniform disorder, or schizophrenia (American Psychiatric Association 2013). The transition between the relatively benign experiences and a psychotic episode often first occurs in late adolescence and it may persist across the lifespan, but the heterogeneity of clinical course, phenomenology, and response to pharmacotherapy have complicated efforts to ascertain the etiology of this transition (Basu 2007).

The present review will discuss current theories of the genesis of psychosis, with an emphasis on the importance of early childhood events and stressful life events in the etiology and onset of a psychotic episode. A number of theories of causality have emerged over the years but no consensus has been reached. Contemporary models tend to emphasize the value of considering a synergistic effect of genetic predisposition, environmental factors, such as adverse life events, urban upbringing, cannabis use and minority status, and gene-environment interactions, that may alter the expression of certain genes that may contribute to the genesis of a psychotic episode (Jaffee et al. 2007, Lataster et al. 2012, van Nierop et al. 2013). Genetic vulnerability clearly plays a large part in many cases of psychosis (McGuffin et al. 1984), and there is growing evidence to implicate variations in gene expression, or epigenetics, that may exert significant influence as well (Read et al. 2009, van Nierop et al. 2013). Some of the variability in gene expression may relate to the higher incidence of prior adverse life experiences that may precede a psychotic episode (Corcoran et al. 2003, Murray et al. 2008, Sommer et al. 2010, Lataster et al. 2012, van Nierop et al. 2013, Ames et al. 2014), including prenatal complications and maternal

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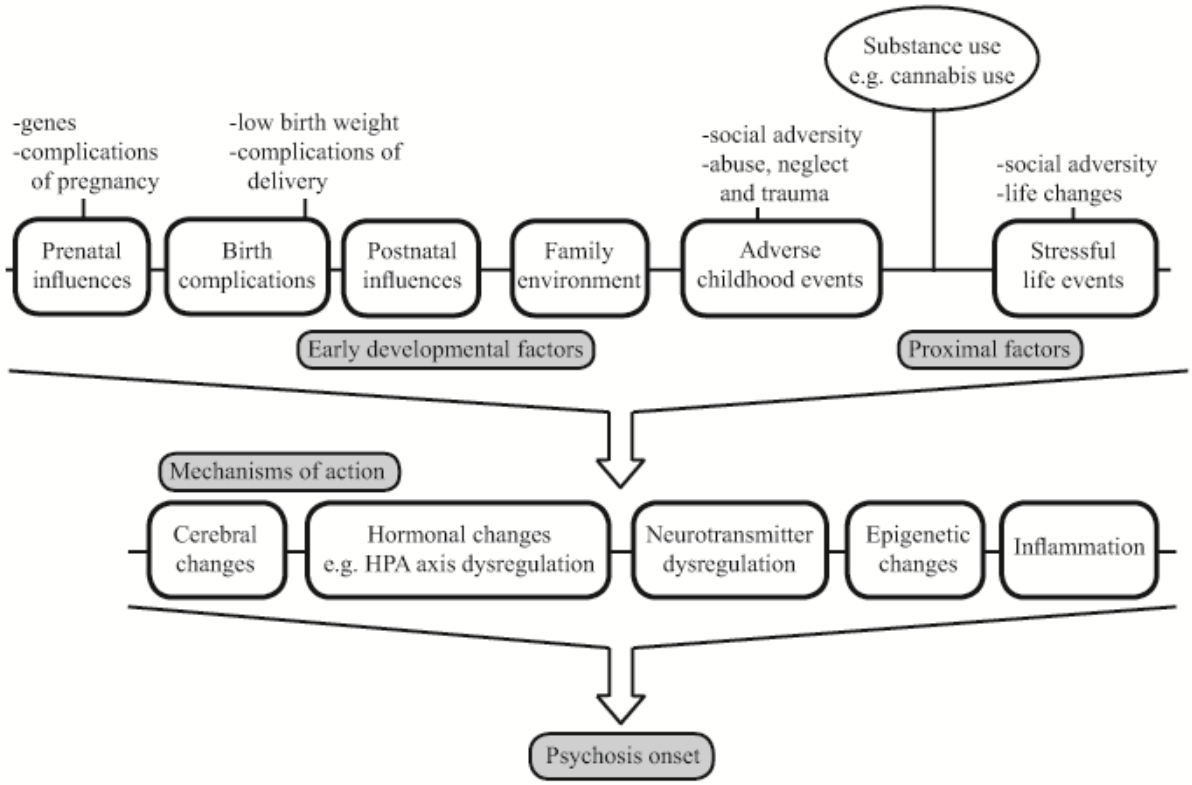
stressors (Cannon et al. 2002, Murray et al. 2008, King et al. 2010), adverse childhood experiences (Felitti et al. 1998, Varese et al. 2012), and recurrent stressful experiences throughout the lifespan and/or adversity later in life, all of which may contribute to negative health outcomes (Holmes and Rahe 1967, Salleh 2008). This review will emphasize a multi-factorial approach for linking genetic and environmental contributors to the onset of psychosis (**figure 1**). It is hoped that this approach will have an advantage over a purely bio-medical model by focusing less on disability and more on underlying contributors that may be susceptible to change (Laing 1969, Broome et al. 2005).

Figure 1. *The complex etiology of psychosis*



Biological Theories of Psychosis

As mentioned, early research regarding the genesis of psychosis focused on biological bases, with little attention to psychosocial and environmental causes (Read et al. 2009). Below is a brief summary of these biological bases of psychosis in the areas of genetics and neurobiological dysfunction including dopamine and other neurotransmitter dysregulation, brain morphology and inflammation.

Genetic Contributions to Psychosis

There is clear evidence to support a genetic contribution to the risk of psychosis (McGuffin et al. 1984). Adoption and twin studies have been utilized to show heritability estimates of psychosis. In the latter, identical (monozygotic) and fraternal (dizygotic) twins are observed and concordance rates of psychosis are measured. This measure leads to an estimation of the amount of phenotypic variance that may be explained by genetic and other factors. Heritability estimates from several studies have suggested a range from 50% to 80% (Gottesman et al. 1967, Cardno et al. 1999). An earlier study by Cardno et al. suggested that the heritability of schizophrenia was between 82 and 85%, and a later study also by the same team suggested that heritability of Schneiderian first-rank symptoms was 71% (Cardno et al. 1999, Cardno et al. 2002). Another study suggested that heritability of a psychotic episode was as high as 90%, and the heritability of having disorganized symptomatology was 84% (Rijsdijk et al. 2011). However, several studies have suggested that these heritability estimates are over-estimated. Indeed a recent study suggests that heritability estimates for schizophrenia are 31% within the nuclear family and 44% for extended family (Light et al. 2014). This may be due to inherent biases in how samples are obtained for heritability studies. In any case, some variance is unaccounted for in the phenotypic expression of psychosis and psychotic experiences which may be explained by environmental influences and factors acting in concert or in addition to the genetic predisposition (Murray et al. 2008, van Os et al. 2010).

As it is quite clear that genetics is important in the etiology of psychosis and schizophrenia, a fervent area of research has been to identify and locate potential predisposing genes (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014). Over the years, several putative candidates have been identified. Characterization of phenotypes associated with breakpoint regions of translocation chromosomes led to the association of *DISC1* and *NPAS3* with schizophrenia (Kamnasaran et al. 2003, Blackwood et al. 2004). Within the last decade, genome-wide association studies (GWAS) have finally identified genetic

markers statistically associated with schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014). Sequential studies have identified the major histocompatibility complex (*MHC*) locus as having a strong signal, as well as the gene *CACNA1C*, which encodes a voltage-gated calcium channel (Purcell et al. 2014, Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014). In addition, microRNAs, involved in transcriptional regulation, have been repeatedly associated with schizophrenia (Lett et al. 2013). One such microRNA gene, *miR-137*, interestingly targets *CACNA1C* as well as two other candidate genes that have independently been associated with schizophrenia, transcription factor 4 (*TCF4*) and dihydropyrimidine dehydrogenase (*DPYD*) (Kwon et al. 2013, Guan et al. 2014). Additionally, GWAS have confirmed genes in the dopamine and glutamatergic systems, such as the gene encoding the dopamine D2 receptor (*DRD2*), as being of relevance to schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014).

Neurobiological Dysfunction

The first neurobiological theories arose from the finding that antipsychotic medications had a common mechanism of action at dopamine D_2 receptor sites (Seeman et al. 1976). As such, it was theorized that an excess of dopamine was the root cause of psychosis and schizophrenia (Basu 2007, Read et al. 2009). In 2003, Kapur suggested that positive symptoms of psychosis are attributed to abnormally heightened dopaminergic neurotransmission, resulting in aberrant attachment of salience and meaning to random stimuli (Kapur 2003). This theory has been refined over time to describe various areas of the brain in which dopamine function has been disrupted, with elevated dopamine neurotransmission in areas such as the ventral striatum and limbic areas, and reduced dopaminergic functioning in other regions including the prefrontal cortex (Murray et al. 2008).

Subsequently, researchers have begun to investigate the effect of other neurotransmitters (NTs) such as glutamate and serotonin, and the interplay between these neurotransmitters and dopamine (Pilowsky et al. 1992, Carlsson et al. 1999, Basu 2007, Stone et al. 2007, Kantrowitz et al. 2010, Egerton et al. 2014, Tang et al. 2014).

Recent research indicates inflammation may have a pathogenic role in the onset of psychosis. Inflammation is a complex biological response to harmful stimuli, and the role of pro-inflammatory cytokines is essential to this response, affecting the brain as well as the rest of the body, which may contribute to physical and mental health conditions (Fan et al. 2007, Miller et al. 2013). In this context, a low-grade systemic type of inflammation is postulated to be secondary to stress, occurring over a lengthy time span (Mondelli 2014, Rohleder 2014). Several inflammatory biomarkers have been associated with mental disorders such as depression, bipolar disorder and psychosis. In particular, elevated levels of serum interleukin-6 (IL-6), a pro-inflammatory cytokine, tumor necrosis factor alpha (TNF-**α)** and C-reactive protein (CRP) have been associated with schizophrenia (Fan et al. 2007, Potvin et al. 2008, Miller et al. 2011, Zajkowska et al. 2014). In fact, some studies have suggested that the level of inflammation may affect the presentation of the psychotic episode and may be associated with more severe psychopathology (Fan et al. 2007, Stojanovic et al. 2014). Research on first episode psychosis and inflammatory processes, indicates a positive correlation between increased inflammatory cytokines and the presence of psychosis (Mondelli et al. 2011 Borovcanin et al. 2012, Garcia-Rizo et al. 2012, Di Nicola et al. 2013). In addition, IL-6 levels were elevated in 9 year old children who at 18 years reported psychotic experiences and psychotic disorder (Khandaker et al. 2014). Moreover, the *MHC* locus is of course central to the immune system and thus inflammatory response.

Other theories discuss brain morphology implicated in people experiencing psychosis. For example, some studies have shown abnormal dendritic spine morphology, enlarged ventricles and lower overall cortical volume (Reveley et al. 1984, van Haren et al. 2012). Additionally, disruption of myelin development and oligodendrocyte function has been implicated in the etiology of psychosis and schizophrenia (Davis et al. 2003, Zhang et al. 2012, Mighdoll et al. 2015). The association of dysmyelination with schizophrenia has lead to candidate gene studies regarding white matter phenotypes with interest in the neuregulin1-tyrosine kinase receptor ErbB4 (*NRG1-ErbB4*) and oligodendrocyte/myelin (OM) system genes (Voineskos 2015).

Limitations of biological theories

In summary, while there is much evidence to support a biological basis for psychosis, these concepts do not adequately explain *how* and *why* a person may become psychotic, why one person may be more vulnerable than another, or why a person may be more vulnerable at a particular time in their lives (Read et al. 2009). Genetic heritability has been shown to explain a portion of the susceptibility to a psychotic episode, but we must herein consider environmental factors, such as stress and adverse life events, and the resultant underlying effect on relevant genes and neurodevelopmental and neurobiological function (van Os et al. 2010, van Nierop et al. 2013). Of interest, stressful experiences have been associated with and may have contributed to many of these neurobiological bases for psychosis. For example, the dopaminergic system has been shown to be hyper-responsive in times of stress (Mizrahi et al. 2012). Additionally, the immune system and inflammatory response are highly related to stressful events (Black 2002).

Adverse Childhood Experiences

Adverse Childhood Experiences (ACEs) are very common throughout the world. Some studies have estimated that approximately 40% of the general population, over several countries with varying economic status, have experienced adversity as a child (Kessler et al. 2010), while other studies have suggested that the incidence of ACEs may be even higher, over 50% (Felitti et al. 1998, Rosenman and Rodgers 2004). ACEs can be defined by three categories: childhood abuse (emotional, physical and sexual), childhood neglect (emotional and physical), and household dysfunction (domestic violence, substance abuse, mental illness, parental discord or loss, and crime) (Felitti et al. 1998).

ACEs have been shown to have lasting consequences in adulthood, affecting general health and well-being (Felitti et al. 1998, Dube et al. 2003, Anda et al. 2006). Moreover, ACEs do not generally occur in isolation but tend to cluster together; having experienced one ACE puts a person at increased risk for more ACEs (Dong et

al. 2004). In addition, the number of ACEs experienced appears to have a dose-response relationship later in life: the more ACEs experienced, the higher the risk for social and health issues later in life, either in a linear, or even in an exponential fashion (Felitti et al. 1998, Anda et al. 2006, Kelly-Irving et al. 2013).

ACEs and Psychosis

A meta-analysis of childhood adversities and risk for psychosis found strong associations between ACEs and emergent psychosis (OR = 2.78) across several research designs (Varese et al. 2012). In case-control analyses only, the authors found that those who had experienced psychosis were 2.72 times more likely to have experienced childhood adversities than controls. They also found that the estimated attributable risk of ACEs contributing to psychosis later in life was 33% (Varese et al. 2012). Additionally, van Nierop, Janssens et al. (2013) found that all transitions to psychosis were associated with at least some exposure to environmental risks, with the greatest effects in their sample being attributable to having experienced childhood trauma (OR = 34.4).

The aforementioned dose-response relationship of ACEs appears to also remain true for greater risk of psychosis (Heins et al. 2011). In a study comparing patients with psychosis to siblings and controls, patients had an OR of 4.53 of having experienced trauma, while siblings of patients had an OR of 1.61 when compared to controls and an OR of 2.60 when compared to their siblings. This indicates that the patients may bave experienced more trauma than their siblings (Heins et al. 2011). Hainsworth, Starling et al. (2011) compared patients with psychosis who had been exposed to traumatic childhood experiences to those who had not. They found that those who had traumatic experiences, particularly those with a history of sexual assault, showed a significant increase in positive psychotic symptoms (Hainsworth et al. 2011).

In terms of mechanism, some studies suggest that environmental effects early on in life may change the way genes react and therefore influence risk for psychosis (Murray et al. 2008). Many studies suggest that those at high risk for psychosis have a heightened sensitization to stress following childhood trauma and abuse via changes in hypothalamic-pituitary-adrenal axis (HPA) functioning (Elzinga et al. 2008, Holtzman et al. 2012, McCrory et al. 2012). Later in life, the sensitized HPA pathway may be one route whereby genetic vulnerability plays out in a susceptibility to psychosis following recent adverse events in an individual's life.

Stressful Life Events

Adverse life events, or stressors, have been shown to have great impact on many facets of physical and mental health (Brown and Harris 1978, Salleh 2008). Stress may be positive or negative both in nature and in the impact it has on an individual (Paykel et al. 1980). Certain adverse life events have particular importance for long-term threat in regard to ill-health (Brugha et al. 1985). The onset of a psychotic episode appears to incorporate several risk factors, both genetic and environmental, with recent life stressors working synergistically with these to result in the onset of psychosis (Lataster et al. 2012).

Life events and the timing of onset of psychosis

It is important to determine how and when a stressful event may trigger a psychotic event. A recent study looked at life events and rated their severity over the year prior to a first episode psychosis compared to stressful events in the year prior to interview in a control group. Patients reported a higher number of stressful life events of moderate/severe threat than controls, and as number of events increased, so did the odds of onset of psychosis (Beards et al. 2013). Another study assessed stressful events over the year prior to onset of the psychotic episode and looked specifically at the timing, independence, threat and intrusiveness of each event (Raune et al. 2009). Although adverse events were frequent over the year prior, they found that adverse events were considered most stressful and intrusive in the three months prior to onset of the psychotic event. Bebbington and colleagues, in data collected over the 6 months prior, similarly found a greater amount of adverse life events in the three months preceding the onset of psychosis when compared to a healthy sample group from the general population (Bebbington et al. 1993).

Relapses of psychosis can also be linked to stressful life events. For example, patients interviewed during or shortly after relapse reported an increase in moderately threatening life events, especially in the preceding 4 weeks (Fallon 2009).

Vulnerability to Stress (HPA axis)

The HPA axis has been implicated in faulty reactions to stressors and may therefore be important in later poor health outcomes. In a normal functioning HPA axis, cortisol binds to glucocorticoid receptors (GRs) in the hypothalamus and pituitary in a negative feedback loop, resulting in inhibition of the production of both corticotropin releasing hormone (CRH) from the hypothalamus and adrenocorticotropic hormone (ACTH) from the pituitary, thus maintaining the system in equilibrium. In some cases, people who have been exposed to extreme stressors in early life, such as abuse, may have a lower release of cortisol, in accordance with a "dampened" HPA axis response, resulting in a less effective physiological response, leading to relatively poor coping with stress (Collip et al. 2009). In other cases, the feedback loop may not work properly, resulting in increased CRH, ACTH and cortisol in the body, which is also detrimental and will thereby affect the health of the individual (Caufriez et al. 2002, Spiegel et al. 2004, Wolff et al. 2012).

Alterations in the HPA Axis and Psychosis

Several studies have shown altered HPA axis functioning may be involved in the onset of psychosis. Some studies have attempted to measure salivary cortisol levels to determine how the HPA system might have been altered. One study suggested that those at above average genetic risk for psychosis have a higher baseline level of cortisol in daily life (Collip et al. 2011). These authors also noted heightened cortisol reactivity following negative experiences throughout the day, and increased psychotic experiences associated with the cortisol spike (Collip et al. 2011). Another study suggested that the overall stress response is blunted and cortisol levels in response to stress are lower in

psychosis (Lovallo et al. 2012). It is possible that the HPA axis is altered in psychosis such that the baseline cortisol level is already high, and therefore the cortisol response appears blunted, even though it is raised during a psychotic event (Collip et al. 2011). A 2013 review corroborated that onset of psychosis is associated with a generally hyperactive HPA axis along with blunted HPA axis response to stressors (Borges et al. 2013). In addition, a recent meta-analysis detected a trend for a larger pituitary volume in first episode patients and individuals at ultra high risk (UHR) for psychosis who later transitioned to psychosis than healthy controls, suggesting that the pituitary gland may be enlarged prior to a psychotic break (Nordholm et al. 2013).

It has also been suggested that stressful life events may "sensitize" an individual to future stressors through epigenetic mechanisms (Collip et al. 2009). For example, many studies have shown that early childhood adversities have a lasting effect on an individual's health and well being acting through the HPA axis (Read et al. 2009, Varese et al. 2012). These, as mentioned, along with other early life adversities and vulnerabilities, such as genetic vulnerabilities and pre- and peri-natal events, may also interact and affect the HPA axis via epigenetic processes (Murray et al. 2008, Read et al. 2009). Meaney and colleagues have demonstrated that animal models exposed to poor maternal care (i.e., low levels of licking and grooming of rat pups) have altered HPA development and activity in the hippocampus and the medial prefrontal cortex lasting into adult life (Weaver et al. 2004, Champagne and Curley 2009). This animal model also shows dysregulated gene transcription via epigenetic changes to the glucocorticoid receptor gene promoter, leading to a disruption of the negative feedback system in a later stressful event (Champagne and Curley 2009). Interestingly, such epigenetic changes are heritable; this provides a mechanism whereby adverse events occurring in another generation may be relevant. Nonetheless, it has been suggested that early childhood, a critical period for the development of a normal stress response, may be a good target for intervention and prevention efforts, such as coping skills, as a means to possibly prevent later illnesses and avoid maladaptive stress responses in adolescence and early adulthood (Fish et al. 2004).

Psychosis Symptomatology and Life Events

Some research has suggested that particular stressful life events and types of childhood trauma may be associated with the specific symptomatology of a psychotic illness, with a degree of conflicting data to date. Due to the heterogeneous nature of the presentation of a psychotic illness, this is potentially an exciting area of research, as determining a psychological pathway to psychosis may influence and bolster treatment for early psychosis and even point to possible prevention strategies (Raune et al. 2006, Beards and Fisher 2014). Determining pathways by which specific adversities may result in specific symptoms may additionally help illuminate the etiological course of psychosis.

Several studies have suggested that the form of adversity experienced as a child may have an effect on the symptomatology of later psychosis (Ucok and Bikmaz 2007, Heins et al. 2011, Bentall et al. 2012). Childhood sexual abuse has been associated with more severe positive symptoms of psychosis (Ucok and Bikmaz 2007, Heins et al. 2011). Also, childhood emotional abuse has been associated specifically with hallucinations and delusions of mind reading (Ucok and Bikmaz 2007). Another study looked for associations of sexual trauma, physical abuse, bullying, and/or being brought up in institutional care with reports of paranoid beliefs and auditory hallucinations as measured by the 2007 Adult Psychiatric Morbidity Survey (Bentall et al. 2012). Interestingly, they found that sexual abuse was associated with auditory hallucinations, and moreover, that hallucinations were associated specifically with childhood rape only when paranoia was controlled for with an OR of 8.9. Paranoid symptoms were specifically associated with growing up in institutional care with an OR of 11.08, once hallucinations were controlled for. Physical abuse was associated with both types of symptoms, but bullying showed no significant effect on symptomatology. They also found that individuals were especially vulnerable to any kind of psychosis when exposed to more than one adversity in early life (Bentall et al. 2012). On the other hand, a recent study out of the Netherlands found that childhood trauma was related to psychotic symptoms without specificity for type of trauma or nature of symptoms, but did note particular importance for traumatic experiences with intention-to-harm life events (van Nierop et al. 2014).

Adult life events are also implicated in the onset of psychosis; however, this is relatively understudied territory (Beards et al. 2013). For example, relatively recent intrusive life events were associated with the development of persecutory delusional thoughts in psychosis. Stressful life events involving loss were negatively associated with grandiose delusions, and life events involving occurrences of a dangerous nature appeared to be associated with depressive delusions (Raune et al. 2006).

Recent reviews on the topic are more concerned about the mechanism and pathway by which a particular traumatic event may later influence the psychotic illness (Beards and Fisher 2014, Bentall et al. 2014). Stressful life events may act through the various biological bases of psychosis discussed earlier, such as through abnormal dopamine functioning and/or HPA axis dysfunction (Bentall et al. 2014). In their review, Bentall and colleagues (2014) discuss several potential mechanisms for which specific forms of childhood adversity may influence later psychotic symptoms such as thought disorder, auditory verbal hallucinations, and persecutory delusions. For example, among other possible pathways, they propose that childhood sexual abuse results in auditory verbal hallucinations working through a dissociative psychological process (Bentall et al. 2014).

Beards and Fisher (2014) also argued that recent life events may play a role in mediating the development of psychotic symptoms (subclinical and first episode psychosis), following previous childhood traumatic events. Additionally, the risk of psychosis following particular childhood traumatic events may be mediated by adversity in adulthood, and the two types of adversity may act synergistically (Morgan et al. 2014).

Preventative and Resiliency Measures

Coping responses have been shown to be relevant to the likelihood of the onset of psychosis. Phillips and colleagues (2011) compared healthy controls to a group of participants at UHR for psychosis. They found that the UHR group reported that they were more distressed by life events and utilized different coping strategies than the healthy group (Phillips et al. 2012). They suggested that future treatment could focus on stress management and improving coping skills to help prevent the

conversion to psychosis in the UHR group. Other studies suggested that protective factors, such as self esteem and social support may play a part in creating better coping strategies for individuals at UHR for psychosis, and indeed distress with psychotic symptoms has been shown to be moderated by improved quality of life and healthy social relationships (Pruessner et al. 2011, Lim and Gleeson 2014). Psychosocial interventions aimed at promoting resiliency and reducing stress may prove valuable in improving outcomes.

Conclusions

There is conclusive evidence that life adversities play a part in the onset of a first psychotic episode. As the etiology of psychosis is complex and in many cases seems to require existing vulnerabilities, such as a genetic predisposition and/or exposure to early childhood trauma or abuse, more recent (proximal) adverse life events may be a major precipitating factor for a first psychotic episode. In terms of proximity, the three month period prior to onset (or one month prior to relapse) of a psychotic illness would appear to be the most relevant.

It is also interesting to note that the type of trauma or adverse event may be important in the course and presentation of psychosis, and may therefore inform treatment. Thus we suggest that clinicians to review life adversities with their patients and see if these link to specific psychotic symptoms.

Current and future research could focus on the mechanisms by which these stressful life events exert their effect in affected individuals, and how different vulnerabilities and triggers interact with each other to produce a psychotic illness. We should also investigate interventions, such as psychoeducation for those at high risk for psychosis, to enable individuals at risk to better manage stressors, in an effort to *prevent* the occurrence of the psychotic illness regardless of any predisposing factors already present.

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