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A review of vulnerability and risks for schizophrenia: Beyond the two hit hypothesis

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Abstract

Schizophrenia risk has often been conceptualized using a model which requires two hits in order to generate the clinical phenotype—the first as an early priming in a genetically predisposed individual and the second a likely environmental insult. The aim of this paper was to review the literature and reformulate this binary risk-vulnerability model. We sourced the data for this

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narrative review from the electronic database PUBMED. Our search terms were not limited by language or date of publication. The development of schizophrenia may be driven by genetic vulnerability interacting with multiple vulnerability factors including lowered prenatal vitamin D exposure, viral infections, smoking intelligence quotient, social cognition cannabis use, social defeat, nutrition and childhood trauma. It is likely that these genetic risks, environmental risks and vulnerability factors are cumulative and interactive with each other and with critical periods of neurodevelopmental vulnerability. The development of schizophrenia is likely to be more complex and nuanced than the binary two hit model originally proposed nearly thirty years ago. Risk appears influenced by a more complex process involving genetic risk interfacing with multiple potentially interacting hits and vulnerability factors occurring at key periods of neurodevelopmental activity, which culminate in the expression of disease state. These risks are common across a number of neuropsychiatric and medical disorders, which might inform common preventive and intervention strategies across non-communicable disorders.

1. Introduction

Schizophrenia continues to impose a significant burden on global society. Data from the 2010 Global Burden of Disease Study suggests that mental and behavioral disorders account for a global disability adjusted life year (DALY) burden of 7.4% of the total, of which schizophrenia forms 0.6% of this (Murray et al., 2012). The modern theory of the development of schizophrenia has been built upon the neurodevelopmental theory, first elaborated upon by seminal papers by Weinberger and Murray and Robin almost thirty years ago. The initial neurodevelopmental theory speculated that a prenatal event could disrupt the normal maturation process of the brain which ultimately culminated in the clinical syndrome of schizophrenia later on during life, suggesting a “single hit” theory of schizophrenia (Weinberger, 1987; Murray and Lewis, 1987). As more research into the neurodevelopmental model occurred, it became apparent that such a static model was unable to explain features such as the longitudinal changes in brain volume that occur in schizophrenia (McGrath et al., 2003; Velakoulis et al., 2000). Research then began to focus on delineating the subsequent ‘second hits’ that were felt to be necessary to explain this gap in the neurodevelopmental model. However, as yet more work has gone into determining the nature of these second hits, it is becoming increasingly apparent that a two hit model is also inadequate to fully explain the considerable neuroanatomical heterogeneity present in schizophrenia (Gogtay et al., 2011; Pantelis et al., 2005). The notion that the timing of the hits during neurodevelopment causes differing outcomes, where early hits cause more widespread abnormalities as opposed to later hits causing more specific changes, has been previously explored as an extension of the original model (Pantelis et al., 2003). We propose that the notion of binary first and second hits oversimplified the model of schizophrenia pathogenesis and, based on modern epidemiology and neurobiology, we propose that a multi-hit threshold model interacting with key neurodevelopmental milestones might better represent the complex genetic, social and environmental interactions that have been explored as contributing to the development of schizophrenia.

Early developmental factors contributing to the neuroprogression of schizophrenia have been discussed elsewhere (Davis et al., 2014). There have been many potential non-genetic

"second hits" proposed within the literature that act at differing periods of neurodevelopment (Owen et al., 2016). It may be that instead of being "second hits" per se, which implies that each factor occurs in a pre-specified binary sequence analogous to the development of malignant cells in cancer, given the complex interaction these factors have within a genetically at risk individual with the environment, they instead act as vulnerability factors. Such vulnerability factors likely have a relatively weak individual effect, but acting in concert at specific critical points of neurodevelopment in a genetically susceptible individual they may have sufficient magnitude to impact the development of the clinical syndrome of schizophrenia.

Factors suggested in the literature to be potential vulnerability factors include nutrition, perinatal vitamin D exposure, infection with human endogenous retroviruses (HERVs), smoking, intelligence quotient and social cognition, cannabis use, childhood trauma and social defeat.

This paper will provide concise summaries on selected vulnerability factors, with an exploration of the neurobiology of such factors involved in the complex causal chains to conceptualize a modern multiple hit theory for the pathogenesis of schizophrenia. The manuscript also explores prevention strategies which may serve to ameliorate the effects of some of these potential vulnerability factors.

2. Methods

Data for this review was sourced from electronic databases PUBMED, and was not limited by language or date of publication. The manuscripts were selected for relevance to the topics reviewed.

3. Cannabis and the endocannabinoid system

The use of cannabis is a potential vulnerability factor which is theorized to most likely to occur during the adolescent period. Cannabis use may represent one of the later non-genetic insults predisposing an individual to schizophrenia. According to the 2010 Global Burden of Disease study, cannabis usage worldwide is estimated to occur in 0.2% of the population; this is a figure that has stayed relatively constant since 1990, although the actual number of users has increased due to population growth (Degenhardt et al., 2013). There has also been an increase in cannabis potency due to changes in cannabis strains (Swift et al., 2013). Recent longitudinal studies suggest that there is up to a 40% greater risk of psychosis in individuals who have ever used cannabis, a value which persists even after controlling for such variables as premorbid personality traits, cigarette smoking, occupational function and poor social integration. There is also evidence of a dose-effect relationship between cannabis use and schizophrenia risk (Monteleone et al., 2014; Manrique-Garcia et al., 2012). Cannabis usage in adolescence has additionally been proposed to induce first episode psychosis at a younger age, with some authors suggesting that cannabis usage can induce the onset of psychosis up to 2.7 years earlier than in those who develop psychosis without a history of cannabis usage (Donoghue et al., 2014).

While evidence supporting the association between cannabis usage and the development of psychosis in susceptible individuals is relatively robust, the ongoing effects of cannabis usage on the course and symptoms of patients suffering from schizophrenia is less clear. Much of the literature surrounding ongoing cannabis usage in schizophrenia suggests that such co-morbid substance use is associated with worse outcomes including longer periods of hospitalization, higher relapse rates and less medication adherence (Malchow et al., 2013). On the other hand, a number of studies suggest that compared to non-users with schizophrenia, cannabis use may be associated with better cognitive and social functioning in schizophrenia; these are factors associated with positive clinical outcomes in psychosis (Koola et al., 2012; Lev-Ran et al., 2012). It has been argued that cannabis using patients have no significant difference in psychopathology or quality of life measures compared to non-using patients, even after adjustment for confounders such as length of illness and baseline illness severity (van Dijk et al., 2012). This may be due to the fact that cannabis can decrease blood concentrations of psychiatric medications such as antipsychotics, thus preventing some side effects related to negative and cognitive symptoms. However, it may aggravate positive symptoms, which is suggested by a higher incidence of relapse and re-hospitalization (van Dijk et al., 2012).

Evidence regarding the possible effect of cannabis use on the structural integrity of differing brain regions is inconclusive. The hippocampus is often reported to be structurally abnormal in schizophrenia, and some groups have demonstrated that chronic cannabis use in otherwise healthy individuals is associated with a smaller hippocampal and amygdala volumes and subclinical positive symptoms (Solowij et al., 2013; Yucel et al., 2008), as well as white matter tract reductions on diffusion tensor imaging in the region of the hippocampus (Zalesky et al., 2012). A recent study in these subjects also demonstrated that cannabis specifically affected medial temporal lobe structures (Lorenzetti et al., 2015), suggesting that cannabis use impacts hippocampus and amygdala structures specifically in normal individuals.

Patients with first episode psychosis who are regular cannabis users have a greater overall volume reduction during 5-year longitudinal follow-up, as opposed to individuals with schizophrenia who are non-users, with the greatest loss of volume pertaining to grey matter (Cohen et al., 2012a). In contrast, other authors have found larger brain volumes within both the right and left hippocampus in adolescents suffering from schizophrenia and comorbid cannabis use (Kumra et al., 2012). Other studies found increased grey matter density within the left dorsolateral prefrontal cortex and have suggested this alteration may in part explain the observation between cannabis use and cognitive function in those with schizophrenia (Schnell et al., 2012). Some of these conflicting findings of the effects in psychosis may in part stem from the observation that structural brain changes in schizophrenia may in fact represent a core feature of the illness, with volume loss within the thalami, hippocampus and prefrontal regions being already present in individuals who are at increased risk of developing schizophrenia, and that cannabis use is associated with further volume reductions and the potential transition from ultra-high risk to disease state in genetically disposed individuals (Welch et al., 2013).

4. Childhood trauma

Childhood trauma, including both physical and psychological maltreatment, childhood sexual abuse, parental loss or divorce, parental substance abuse, and poverty (Green et al., 2014), appears to be a potential vulnerability factor for the development of schizophrenia in later life. Meta-analyses suggest that individuals with a history of childhood trauma have nearly three times the risk of developing psychosis, with an estimated population attributable risk of 33% (Sahin et al., 2013). Although the field suffers from some methodological problems, including a lack of a clear definition of what constitutes childhood trauma, in general the findings suggest that the more severe the childhood trauma, the more severe the subsequent symptomatology which accompanies the illness (Braehler et al., 2013). Also, most studies were retrospective and therefore cannot defectively disentangle cause and response relationships. Interestingly, children with a family history of schizophrenia or those who display antecedents of schizophrenia were more likely to be exposed to major negative life events and daily stressors compared to their peers (Cullen et al., 2014). Importantly, a recent meta-analysis suggested that no one particular type of trauma confers greater risk of psychosis compared to others (Green et al., 2014).

Childhood trauma also appears to be associated with worse positive symptoms in individuals suffering from schizophrenia compared to those who have no history of childhood trauma, and childhood trauma is additionally associated with non-remission of positive symptoms (Cohen et al., 2012b). This non-remission of positive symptoms has been suggested to be in part due to increased hypothalamic pituitary adrenal (HPA) axis activity and cortisol secretion in patients with a history of trauma, although such a hypothesis is at present inconclusive (Corcoran et al., 2012). A study of children with either a family history of schizophrenia or those who displayed antecedents of schizophrenia showed no difference in pituitary volume on neuroimaging of children aged between 11 and 14 years in comparison to a control group, which suggests that HPA axis hyperactivity may develop later within the pathogenesis of schizophrenia (Cullen et al., 2015).

Brain derived neurotrophic factor (BDNF) is another potential candidate explanation for the proposed link between childhood trauma and the development of schizophrenia. Whilst the evidence in relation to BDNF in individuals suffering from schizophrenia remains somewhat inconclusive, recent systematic reviews have suggested that serum BDNF levels are decreased in both drug-naïve and medicated patients with schizophrenia (Fernandes et al., 2014). Exposure to trauma also appears to decrease the expression of BDNF messenger ribonucleic acid (mRNA) within some areas of the brain including the hippocampus and some have suggested that the hippocampal volume deficits seen within schizophrenia may be in part due to this decreased expression of BDNF (Bennett and Lagopoulos, 2014). Interestingly, BDNF mRNA expression in response to trauma was increased in the basal lateral amygdala, which may in part account for the inconsistent alterations seen in this region in imaging studies of schizophrenia patients with a history of childhood trauma.

In accordance with several other lines of evidence, maltreated children appear to demonstrate smaller intra-cerebral volumes in comparison to healthy controls, leading some authors to speculate that the volume reduction often observed in early schizophrenia may in

part be due to the contribution of childhood trauma (Green et al., 2014). Volume reductions within the left hippocampus, a commonly reported finding in both first episode and patients with chronic schizophrenia, has also been reported in adult survivors of childhood abuse without psychosis (Picken and Tarrier, 2011). Other groups have suggested that the finding between a history of abuse and reduced hippocampal volume may only observed for male patients (Samplin et al., 2013). There has also been some suggestion within observational retrospective studies that amygdala volumes may be altered in schizophrenia in those patients with a history of childhood trauma, however this finding has not been reliably replicated (Hoy et al., 2012). In contrast to these findings, others have found that high-risk individuals with larger hippocampal volumes were more likely to develop psychosis than individuals with smaller or normal hippocampal volumes, and other prospective studies report no difference between schizophrenia and appropriately age-matched controls (Brambilla et al., 2013; Phillips et al., 2002). The noted aberrations may be secondary to inflammatory changes in this region during acute illness episodes (Cropley et al., 2013; Cropley and Pantelis, 2014). At present it remains unclear as to whether childhood trauma drives some structural brain changes seen in schizophrenia or if the noted changes antedate the development of psychosis and are simply a result of the traumatic process itself. Despite these unanswered questions, childhood trauma does appear to confer a significant vulnerability occurring early in life that may predispose to the later development of schizophrenia in the presence of other potential insults

5. Social defeat

Social defeat, where social defeat is defined as losing a confrontation amongst any type of hostile dispute amongst humans, is a theory that is proposed by some to underlie part of the observed associations between vulnerability factors for schizophrenia development such as being part of a migrant population or having an urban upbringing. It needs to be noted that urbanicity is a however a broad proxy of many risk factors. Social defeat may act across multiple potential periods of neurodevelopment. The main crux of the argument for social defeat being a hit in schizophrenia is that social stressors, which are often perceived to be worse amongst marginalized and excluded social or ethnic groups, may potentiate an individual’s underlying genetic and other environmental risk for developing schizophrenia. Indeed people with mental health disorders often present a more vulnerable and socially excluded population who are more likely to be affected by discrimination, human rights violations or poverty, and exposed to other environmental risks (Susser and Patel, 2014). In addition, despite documentation of the effectiveness of a range of interventions from pharmacological to social, and the recent movement toward championing global mental health as a serious global disease burden, the majority of the world’s populace continues to have minimal to no access to such interventions (Patel and Saxena, 2014). In a similar way to childhood trauma, it appears that the more severe the social stressors an individual is exposed to the more likely they are to develop a psychotic disorder. Some authors have shown that the risk of schizophrenia is highest amongst immigrant groups who experience the least social integration, and subsequently are also likely to have the most poverty, alienation and social uprooting (Li et al., 2012). Similarly children from a different ethnic background were found to have a higher risk of subsequent psychosis if they were in schools

with a higher percentage of native students (van Nierop et al., 2014). The social defeat theory may intertwine with that of childhood trauma, as some authors have proposed that early social adversities including trauma may induce negative schemas about the self, which later translates into an increased risk of psychosis (Stowkowy and Addington, 2012) (Fig. 1).

6. Nutrition

The hypothesis that malnutrition, specifically maternal malnutrition before and during pregnancy, is a potential vulnerability in the pathogenesis of schizophrenia mainly comes from three major studies of famine and the subsequent increases in cases of schizophrenia seen thereafter. Analysis of data obtained from two major famines, one being the Dutch Hunger Winter of 1944 and 1945, and the other occurring in China during 1959–1961 has demonstrated a close to 2-fold increase in the rate of schizophrenia in the offspring of mothers born during this period (McGrath et al., 2011; Xu et al., 2009). Several theories have been put forth as to why maternal malnutrition may increase the risk of schizophrenia in the offspring. One of the most widely hypothesized is that of a micronutrient deficiency, specifically the micronutrients vitamin D (see below), folate and/or iron may be involved. There is some evidence that increased third trimester plasma levels of homocysteine (a surrogate marker of decreased folate levels) and maternal anaemia are associated with a 2-fold and up to 4-fold increased risk of schizophrenia in the offspring even after controlling for variables such as ethnicity and education (McGrath et al., 2011). There remains a lack of longitudinal studies that look at the effects on long term neurocognitive outcome of supplementation of the aforementioned micronutrients, with studies reporting discordant results including improvement and no change (McGrath et al., 2011). Another potential theory is that micronutrient deficiency, and in this case specifically folate, may induce epigenetic changes in methylation patterns in maternally imprinted genes. Long term follow up of offspring born during the aforementioned famines have shown reduced methylation for the insulin-like growth factor 2 (*IGF2*) locus, a maternally imprinted gene with a crucial role during early development as well as ongoing cognitive processes throughout life (Kirkbride et al., 2012). Another potential cause comes from the finding of decreased neural aborization of serotonergic and dopaminergic neurons in the hippocampus and prefrontal cortex respectively of prenatally malnourished rats, an interesting observation given decreased neural aborization is postulated to occur during the pathogenesis of schizophrenia. Maternal diet before and during pregnancy may also be related to the risk for schizophrenia via its impact on metabolic conditions, such as overweight and gestational diabetes during pregnancy (Van Lieshout et al., 2011; Van Lieshout and Voruganti, 2008). At present it remains unclear whether it is protein-energy malnutrition itself which is the potential vulnerability factor for schizophrenia, its associated micronutrient deficiencies, or unhealthy dietary patterns that confer the vulnerability.

7. Vitamin D

Low levels of serum vitamin D, particularly during in utero development and infancy, have been suggested to underlie some of the other observed environmental vulnerability factors linked to the development of schizophrenia. These include seasonality of birth and difference in latitude and subsequent psychosis risk. Interestingly, low levels of vitamin D

are proposed to underpin part of the increased risk for schizophrenia in migrant populations (as opposed to social defeat mentioned above, although it may be that the two are not mutually exclusive). This finding is more pronounced in darker skinned immigrants who subsequently emigrate to a higher latitude which risks lower vitamin D (Graham et al., 2014). It is somewhat problematic to apply this as a blanket statement however, as others have suggested that this observed association between low vitamin D in infancy and subsequent schizophrenia may only be true for those with lower levels of 25-hydroxyvitamin D and not the fully active form (1,25-dihydroxyvitamin D) (McGrath et al., 2010a). This led some to speculate as to whether variations within gene encoding proteins involved in vitamin D activation may be in part responsible for the observed effects of 25-hydroxvitamin D. Also interesting is the suggestion that this risk may be non-linear. Neonates with serum vitamin D levels in the lower quintile range have been suggested to have a 2-fold increased risk for schizophrenia (McGrath et al., 2010b). In support of this, long term observational data from a Finnish birth cohort study has suggested that mothers who used vitamin D supplementation of at least 2000 IU conferred an up to 77% risk reduction of subsequent schizophrenia for male infants as opposed to mothers who had no or supplementation of less than 2000 IU a day (McGrath et al., 2004). In contrast, another study suggested that the increased risk of developing schizophrenia among those with low vitamin D levels during infancy may bear little relation to maternal vitamin D levels prenatally (McGrath et al., 2010b). Vitamin D deficiency is likely to act as vulnerability factor for the development of schizophrenia and may underlie some of the observed environmental differences in risks for this disorder.

8. Infection induced activation of HERVs

Some environmental hits through activation of HERVs may act as vulnerability factors for the development of schizophrenia, although this data are premature and require further development (Arias et al., 2012; Krause et al., 2010; Yolken and Torrey, 1995). HERVs that exhibit similar characteristics as exogenous retroviruses constitute 8% of the human genome (Blikstad et al., 2008). Although HERV protein serves important functions in normal human physiology, recent understanding suggests that there is pathogenic potential of HERVs and the pathogenicity of these elements is mediated by the interactions between hereditary and environmental factors (Christensen, 2010; Young et al., 2013). The endogenous retroelements are responsive to external stimuli including environmental factors such as infectious agents and ultraviolet (UV) radiation (Hohenadl et al., 1999; Sutkowski et al., 2001). Genetic and/or epigenetic modulation of HERV elements at a particularly vulnerable development stage may lead to variable patterns of neurodevelopment and upon exposure to subsequent environmental triggers, such patterns may translate to a schizophrenia phenotype. Microbes that lead to immune cell activation through transcription of immune-related host genes may cause global modulation of endogenous retroelement transcription (Young et al., 2014). Certain copies of the HERV elements are activated by some infectious agents. For example, *T. gondii* and the influenza virus may activate HERV-W elements within human cell lines (Frank et al., 2006; Li et al., 2014; Nellaker et al., 2006). Several studies including a meta-analysis have indicated an increased prevalence of antibodies against *T. gondii* in schizophrenia (Torrey et al., 2007, 2012). The envelope protein released

due to pathogenic activation of HERVs has been demonstrated to have the ability to activate innate immunity and induce the production of pro-inflammatory cytokines. This appears to be mediated through the cluster of differentiation 14 (CD14)/toll like receptor 4 (TLR4) pathway (Rolland et al., 2006). In addition, a study has also revealed significant correlation between group specific antigen (GAG) or envelope (ENV) antigenemia and C-reactive protein levels in schizophrenia (Perron et al., 2008). Elevated levels of HERV transcripts have been detected within red blood cells, plasma, cerebrospinal fluid and neural tissue of patients with first episode psychosis (Huang et al., 2006; Karlsson et al., 2001, 2004; Yao et al., 2008). Further, antibodies to retroviral proteins have been shown to be elevated in individuals with recent onset-psychosis (Dickerson et al., 2012). Recent studies in multiple sclerosis have demonstrated that simultaneous presence of endogenous retrovirus and herpes virus antigens have a profound impact on cell mediated immunity and may also translate into increased production of proinflammatory cytokines (Brudek et al., 2004,2008).The pathogenic glycoproteins of HERVs have been postulated to cause neuroinflammation as well as neurodegeneration (Antony et al., 2007; Perron and Lang, 2010), with one study finding that antibodies to HSV1 were associated with grey matter abnormalities (Whitford et al., 2012). Based on these observations, it is possible that environmental activation of HERVs can influence the onset and progression of schizophrenia by becoming a driver of the inflammatory process, although at present such data remains in relative infancy compared to other risk factors for the development of schizophrenia

9. Smoking

Smoking is known to influence the risk for other disorders, particularly depression (Pasco et al., 2008). A recent meta-analysis has suggested that smoking is both a vulnerability factor for schizophrenia and is associated with an earlier age of onset, with prospective studies showing a more than doubling of the risk for de-novo psychosis among daily smokers (Gage and Munafo, 2015). Smoking is also associated with cortical thinning, which is partially reversible with cessation (Karama et al., 2015). Theoretically, smoking along with other addictions may alter the regulatory set point of the dopaminergic and cholinergic neurotransmitter system, which are implicated in schizophrenia pathogenesis. Indeed, gene wide association studies (GWAS) have suggested that common variants in the cholinergic/nicotinic systems may be associated with the development of schizophrenia (McGrath, 2015; Young and Geyer, 2013). Data from animal models suggest that prenatal exposure to smoking increases risk for a psychotic phenotype in adulthood (Zugno et al., 2013). There is also some epidemiological data suggesting maternal smoking, but not paternal smoking, increases risk among offspring At illness onset, smoking is more prevalent among those with schizophrenia than among non-psychotic individuals (Samele et al., 2007), although the direction of this relationship is uncertain. There is some suggestion that tobacco use may be associated with (possibly subsyndromal) psychosis, given data from two large cross-sectional population surveys suggesting that both age of first tobacco use and daily use of tobacco are associated with psychotic like experiences (Rossler et al., 2015; Saha et al., 2011).

10. Intelligence quotient

A lower premorbid levels of intelligence quotient (IQ) is an often quoted potential vulnerability factor, although little is known about the mechanism for the association between the two or whether lower premorbid levels of IQ predict worse outcomes of illness. It is likely to be a mediating factor earlier in life. In a similar fashion to vitamin D, the risk of lower IQ and the risk of developing schizophrenia appears to be non-linear, with children aged 7 whose IQ is more than 2 standard deviations below the mean showing an eight times greater risk of developing schizophrenia than those with average IQ Also important to note is the lack of observed risk reduction for children who had an above average IQ further strengthening the suggestion that the link between IQ and schizophrenia is non-linear (Schulz et al., 2014). Despite this proposed non-linear relationship, it is unknown whether a lower premorbid IQ predicts a worse outcome, with inconsistent findings - particularly in longitudinal studies of first-episode psychosis (Leeson et al., 2009).The recent Dunedin cohort however suggested that there is substantial neuropsychological decline from the premorbid to the post onset period in schizophrenia, however this decline varied across various mental functions (Meier et al., 2014). However some authors have found no evidence of deterioration in IQ after a 10 year follow-up period. In contrast to the above findings, one study conducted in a Finnish population suggested that better performance at school may be linked to the subsequent development of schizophrenia, suggesting that a high IQ may also be a risk factor. There has also been a suggestion that people with schizophrenia with a higher IQ may represent a subtype of the disease spectrum who may suffer less negative symptoms (Cernis et al., 2015). Another systematic review has suggested that premorbid deficits in cognitive functioning including intelligence quotient (IQ), (see below) and behavioral, emotional and social problems within middle childhood and early adolescence identifies a cohort of children at risk for schizophrenia disorders in later adult life (Laurens et al., 2015). Overall the neurobiological link between these two factors remains to be fully elucidated.

11. Social cognition

Social cognition is a related but independent construct to IQ involving the perception, interpretation and processing of social information, which has received attention as a potential vulnerability factor contributing to the manifestation of schizophrenia. Social cognition refers to how people think about themselves and others in the social world (Penn et al., 2008). Preliminary findings point to relative stability of social cognition from the early through to the later stages of psychosis (Green et al., 2012). Social cognition provides phenotypic clues regarding underlying pathophysiology and is strongly related to functioning and disability in psychiatric disorders (Fett et al., 2011). It includes the domains of emotion recognition, theory of mind, and attributional style. In particular, the domain of emotion recognition has been extensively studied in people with schizophrenia, where Individuals with schizophrenia display deficits compared with nonclinical control participants (Couture et al., 2006; Edwards et al., 2002; Kohler et al., 2010). The greatest deficits are evident in the perception of negative emotions (compared with positive emotions). The deficit in emotion recognition is relatively stable over time and can be observed independent of the acute phase of the disorder. Notably, impairments in emotion

recognition are present early in the course of psychotic illness (Amminger et al., 2012; Pinkham et al., 2007).

Impaired emotion recognition has been related to social dysfunction in people with schizophrenia (Hooker and Park, 2002), as well as in putatively prodromal individuals (Amminger et al., 2013). Impaired emotion recognition may therefore contribute to social impairment in people with schizophrenia, and may precede the onset of illness (Cannon et al., 2008; Nelson et al., 2013). However, whether it is a moderator, meditator or marker of risk remains uncertain. In social situations, inaccurate decoding of emotional expression may be a source of stress and a barrier to social interactions and communication (Bediou et al., 2007). Stress could exacerbate symptoms in people with schizophrenia, and possibly also play a role in the onset of frank psychosis in high-risk individuals (Phillips et al., 2006). Inaccurate decoding of emotions may also serve as a building block in delusion formation (Blackwood et al., 2001). This view is supported by a study that investigated emotion recognition as predictor of transition to psychosis in ultra-high risk individuals (Allott et al., 2014), showing that poorer identification of “neutral” emotion predicted transition. According to these findings, the positive symptoms of psychosis may arise because people read meaning where there is none.

The nature of the dysfunction underlying emotion recognition deficits in schizophrenia and other psychoses is only partially understood. Biological theories of psychosis note the tendency to misinterpret benign or ambiguous social cues. In psychosis, increased dopamine is observed in the mesolimbic pathway, with dopamine being a key neurochemical determinant of the significance of environmental cues to human motivations (Kapur, 2003). Abnormal increases in this neurotransmitter are proposed to lead to “aberrant salience” of environmental cues (Kapur, 2003). Thus, increased dopamine synthesis in prodromal individuals may influence the perceived salience of environmental cues, and in this instance, a tendency to interpret neutral faces as emotionally meaningful. Concordantly, recent findings show that elevated dopamine synthesis in prodromal individuals is correlated with the severity of psychotic (but not anxiety or depressive) symptoms (Howes et al., 2009) and also predicts later psychotic disorder transition (Howes et al., 2011).

12. Prevention strategies

Given the substantial economic, societal and global health impact that schizophrenia has, there have been recent attempts looking at preventing the onset of disease. Intervention during the prodromal stage or disease onset and during the critical period of the early years of illness has the potential to reduce the severity and impact of the subsequent disease state. This is particularly important if schizophrenia is conceptualized to involve the cumulative effect of a number of potential hits and vulnerability factors, as it provides multiple potential early therapeutic intervention targets. There is also a growing understanding that the appearance of the ultra-high risk stage seen during emerging adulthood often builds on latent vulnerability from earlier in life (Seidman and Nordentoft, 2015). It needs to be emphasized that risks for schizophrenia overlap with those for other psychiatric and non-communicable disorders, and feasible preventive approaches need to be integrated as part of a whole of health approach. Such interventions to potentially reduce the risk of non-communicable

disorders including schizophrenia in vulnerable persons at risk may range from the care of pregnant patients with psychoses who may benefit from prenatal care and social support and family centered programs, to preemptive cognitive remediation and early intervention for children at risk. (Liu et al., 2015). Additionally, having a systemic approach which allows for multiple referral sources being established through networking with general practitioners, community mental health workers and school officials allows for the earlier recognition and referral of persons within the early phase of a psychotic disorder (Ho et al., 2005).

There is now a substantial evidence base regarding indicated prevention, with 11 randomised controlled trials to date in the ultra-high risk (UHR) prodrome. A recent meta-analysis concluded that preventative interventions aimed toward people at an ultrahigh risk of first episode psychosis are effective in reducing the risk of transition to psychosis by 50% in the first 12 months (van der Gaag et al., 2013). In addition, a previous randomised controlled trial has suggested that in people with an ultra-high risk of psychosis, early intervention with cognitive behavioral therapy may be safer and at least as efficacious as low dose anti-psychotic medications in this setting (McGorry et al., 2013). The use of omega 3 poly-unsaturated fatty acids for twelve weeks has been suggested to prevent the transition to a full-threshold psychotic disorder in younger adults in an at-risk mental state, a finding which is now the subject of a major replication study (Markulev et al., 2015). Data from the London Child Health and Development Study, which looked at 9–11 year old children identified a subset of children who are suggested to be at a greater risk of psychosis who report higher rates of psychotic like experiences, greater exposure and responsivity to stressors, and impairments in general intelligence may allow intervention at a younger age than has previously been employed with early adolescents (Laurens and Cullen, 2015).

There has also been investigation into the possible effects of the prevention of cannabis use in regards to subsequent conversion into schizophrenia. It has been estimated the number needed to prevent, that being the number of heavy cannabis users which would need to stop in order to prevent one episode of psychosis, is around 2800 in males aged 20–24 and 4700 in males aged 35–39, with female equivalent numbers being double both of these estimates (Brown and McGrath, 2011). However heavier use in the context of subthreshold psychotic symptoms would be a more cost effective target for intervention. It’s worth noting that current programs not aimed at psychiatric endpoints may indeed have efficacy in this domain; existing public health smoking campaigns and the Australian Royal Commission into Institutional Responses to Child Sexual Abuse being exemplars (Berk et al., 2014). A 2010 Cochrane review concluded that regular exercise programs are feasible in patients suffering from schizophrenia and have shown promising effects on both physical health, symptoms and cognition, as long as they have adequate intensity and duration (Gorczynski and Faulkner, 2010). Recently, some novel interventions have been developed that show promise in promoting physical activity and engagement in young, first episode patients with schizophrenia through the use of internet enabled mobile devices and interactive exercise applications (Killackey et al., 2011). Given the potential impact early life stressors and/or maternal under or over-nutrition may have on the subsequent pathogenesis of schizophrenia, it has been postulated that the delivery of health education, smoking cessation, substance use, nutritional and lifestyle interventions for women during the antenatal period may have

long term benefits on diverse neurocognitive outcomes (Jacka and Berk, 2014; O'Neil et al., 2014). Others have shown that in order for a clinically meaningful risk-prediction for conversion to psychosis at first presentation to occur several investigative modalities including clinical interviewing, neurocognitive testing, structural imaging and electrophysiological testing would have to be performed In order to give a meaningful risk weighted profile (Clark et al., 2015). Specific structural abnormalities have been proposed to predict transition to psychosis. These include greater thinning of the grey matter, which is most pronounced within the pre-frontal cortex, as well as greater disrupted thalamo-cortical functional connectivity at baseline (Cannon, 2015), which may provide potential prognostic clues as to the risk of future progression within high risk populations. In order for any of the above early therapeutic interventions to be effective however, preventative paradigms need to be integrated within mental health in partnership with other medical disciplines and health promotion agencies (O'Neil et al., 2015). A greater understanding of the potential hits and vulnerability factors which work together to drive the pathophysiology of schizophrenia will be required in order to make such preventative programs feasible.

13. Conclusion

We have presented a summary of selected risk factors which demonstrate the considerable heterogeneity and complexity that the neuropathogenesis of schizophrenia displays. It is likely that multiple hits, with some conferring a greater risk than others, operate within a genetically primed individual across key periods of neurodevelopment to culminate in the clinical syndrome of schizophrenia. It may be that many vulnerability factors which contribute to the overall disease process are yet to be fully elucidated, just as many of these hits may have a small effect size which will make their detection and understanding of their overall contribution to the disease state a difficult task. It is likely, using the Framingham risk model for cardiovascular disease as an analogy, that these risks are cumulative and interactive, both with each other, and with critical periods of neurodevelopmental vulnerability. The genetic and molecular mechanisms underpinning such an association are only just beginning to be discovered, and we are likely to see further advances in understanding the complex interactions between these environmental factors and genetic influences in the pathogenesis of schizophrenia.

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Abbreviations

BDNF	Brain derived neurotrophic factor
CD14	cluster of differentiation 14
ENV	envelope
GWAS	genome wide association studies
GAG	group specific antigen
HERVs	human endogenous retroviruses
HPA	hypothalamic pituitary adrenal
IGF2	insulin-like growth factor 2
IQ	intelligence quotient
mRNA	messenger ribonucleic acid
TL4	toll like receptor 4
UHR	ultra-high risk
UV	ultraviolet

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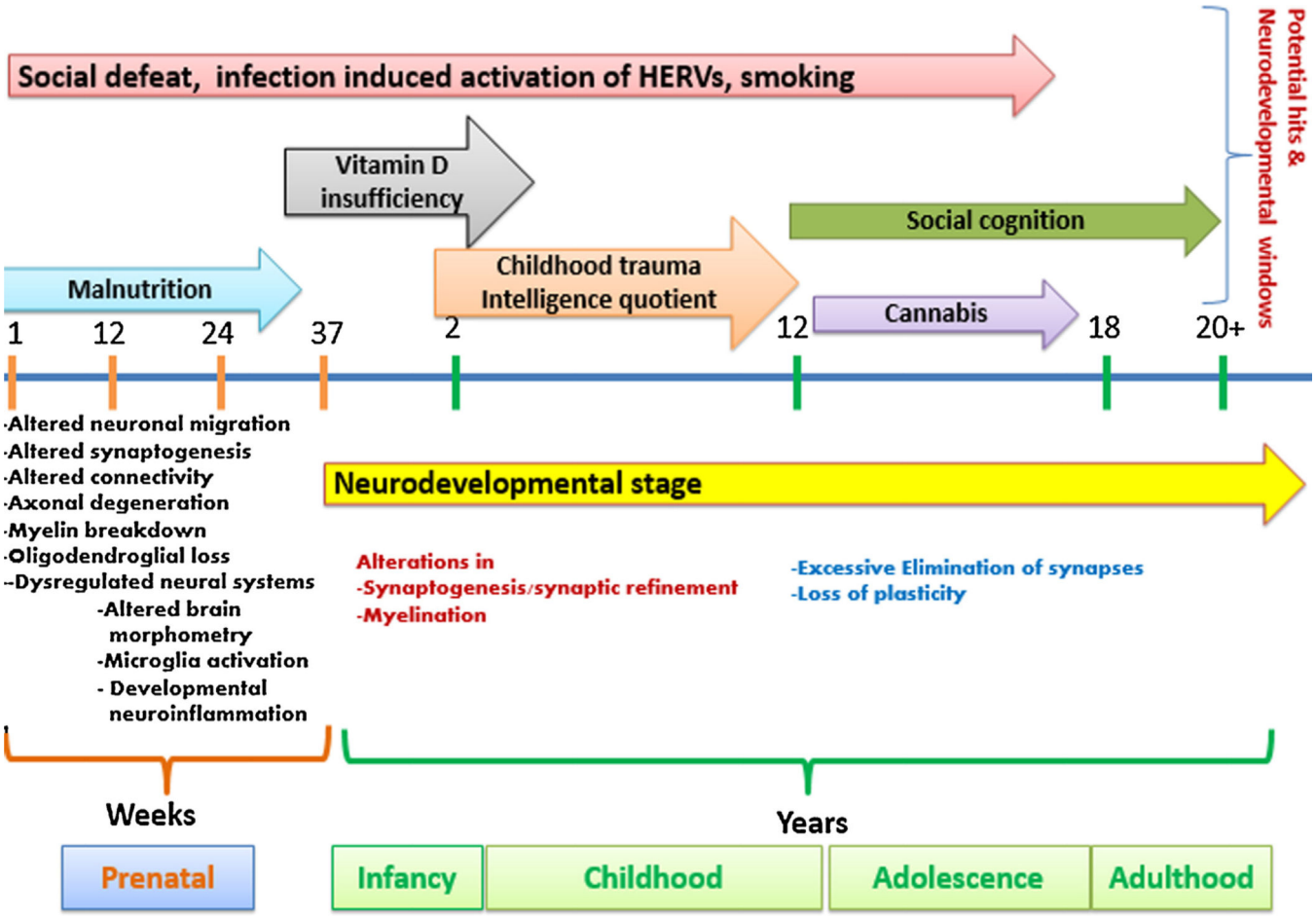

Fig. 1.

Neurodevelopmental windows across a multiple hit theory of schizophrenia. Schizophrenia may be conceptualized as a process which involves multiple vulnerability factors across numerous neurodevelopmental windows. Some hit such as under and over-nutrition are thought to act during early developmental periods, whereas others such as cannabis and social cognition act later with the neurodevelopmental period.