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Influence of interactions between genes and childhood trauma on refractoriness in psychiatric disorders

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ABSTRACT

Psychiatric disorders are excellent disease models in which gene–environmental interaction play a significant role in the pathogenesis. Childhood trauma has been known as a significant environmental factor in the progress of, and prognosis for psychiatric illness. Patients with refractory illness usually have more severe symptoms, greater disability, lower quality of life and are at greater risk of suicide than other psychiatric patients. Our literature review uncovered some important clinical factors which modulate response to treatment in psychiatric patients who have experienced childhood trauma. Childhood trauma seems to be a critical determinant of treatment refractoriness in psychotic disorder, bipolar disorder, major depressive disorder, and post-traumatic stress disorder. In patients with psychotic disorders, the relationship between childhood trauma and treatment-refractoriness appears to be mediated by cognitive impairment. In the case of bipolar disorder, the relationship appears to be mediated by greater affective disturbance and earlier onset, while in major depressive disorder the mediating factors are persistent, severe symptoms and frequent recurrence. In suicidal individuals, childhood maltreatment was associated with violent suicidal attempts. In the case of PTSD patients, it appears that childhood trauma makes the brain more vulnerable to subsequent trauma, thus resulting in more severe, refractory symptoms. Given that several studies have suggested that there are distinct subtypes of genetic vulnerability to childhood trauma, it is important to understand how gene–environment interactions influence the course of psychiatric illnesses in order to improve therapeutic strategies.

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1. Introduction

Both genetic disposition and environmental factors contribute to the development of psychiatric disorders, especially severe disorders such as schizophrenia, bipolar disorder (BD), severe depression, and post-traumatic stress disorder (PTSD) (Uher, 2014).

Childhood trauma has been regarded as the most important environmental determinant of the occurrence of psychiatric illness. In fact, stress and maltreatment in the early life are thought to interact with genomic traits and can alter neurodevelopment (Brietzke et al., 2012). Childhood trauma is associated with development of psychiatric illness and more generally with poor functioning and cognitive deficits (Lee and Hoaken, 2007). Furthermore, in individuals who have experienced maltreatment psychiatric disorders present with more severe symptoms and more comorbidity, and the response to treatment is worse (Alvarez et al., 2011; Nanni et al., 2012). On this basis one can speculate that interactions between genes and childhood trauma influence progress and prognosis in psychiatric disorders as well as their occurrence.

"Refractoriness" is an important concept in clinical psychiatry. The word "refractory" can be used to imply greater resistance (Souery et al., 1999) and it has been suggested that the terms "refractory" and "resistant" can be used interchangeably (Berlim and Turecki, 2007). Treatment resistant patients have more severe symptoms, greater disabilities, higher suicidal risk and lower quality of life than non-treatment resistant patients (Kane et al., 1988; Mamo, 2007; Hassan and De Luca, 2015), making treatment refractoriness an important issue which deserves greater clinical attention.

In this article, we review the literature on how interactions between genes and childhood trauma affect refractoriness in psychiatric disorders. We focus on four themes: 1) gene–environment interactions involved in mental illness, 2) the effects of childhood stress and trauma on psychopathology, 3) gene–childhood trauma interactions in psychiatric disorders and 4) gene–childhood trauma interactions with respect to refractoriness in several psychiatric disorders.

Abbreviations: 5-HTTPLR, 5-hydroxy-tryptamine transporter-linked polymorphic region; APOE-ε4, Apolipoprotein 4; BD, Bipolar disorder; BDNF, Brain-derived neurotrophic factor; MAOA, Monoamine oxidase A; MDD, Major depressive disorder; MMN, Mismatch negativity; MTHFR, Methylenetetrahydrofolate reductase; PACAP, Pituitary adenylate cyclase-activating polypeptide; PTSD, Post-traumatic stress disorder; SNP, Single nucleotide polymorphism; αCaM kinase II, α-calcium/calmodulin-dependent protein kinase.

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2. Gene–environment interactions in severe psychiatric disorders

Both genetic disposition and environmental factors are important in the development of psychiatric disorders, particularly severe psychiatric disorders such as schizophrenia, BD and severe depression (Uher, 2014). It is because the overall contribution of genetic influence might be stronger for those severe mental disorders (Shih et al., 2004), and a number of environment exposures appear to be responsible for substantial proportion of cases of severe mental illness (Varese et al., 2012; Uher, 2014). The large "heritability gap" – the difference between twin study heritability and molecular single nucleotide polymorphism (SNP) heritability – in severe mental disorders indicates that gene–environmental interactions may account for large proportion of cases (Uher, 2014). Several researchers have used proxy methods (e.g. adoption studies; twin studies) to assess gene–environment interactions, but such methods are also limited because of unequal familial relatedness and because specific environmental factors may interact with specific genetic variants. In this regard, the investigation of the interactions involving specific molecular genetic variants is important to explain the causal relationships developing to severe mental illness (Uher, 2014).

A gene–environment interaction is involved when two different genotypes respond to environmental variation in different ways. It can be defined as the dependence of the effects of an environmental factor on an individual's genotype and vice versa (Duncan and Keller, 2011). Recent studies have demonstrated specific gene–environment interactions in severe psychiatric disorders including psychosis, BD, MDD and PTSD (Fig. 1). Although a number of environmental factors are thought to play a role in psychiatric disorders, it has been suggested that childhood trauma has a critical impact on brain development which produces permanent functional changes that may increase the risk of developing mental health problems (Heim and Binder, 2012).

3. The influence of childhood stress and trauma on psychopathology

Psychological trauma is the unique individual experience of an event or enduring conditions, in which the individual's ability to integrate his/her emotional experience is overwhelmed, or the individual experiences a threat to life, bodily integrity, or sanity (Pearlman and Saakvitne, 1995). Childhood trauma could be regarded as psychological trauma which the individuals have experienced during his/her childhood. Childhood abuse is defined as the "physical and mental injury, sexual abuse, negligent treatment, or maltreatment of a child under the age of 18 years by a person who is responsible for the child's welfare under circumstances which indicate that the child's health or welfare is harmed or threatened" (Child Abuse Prevention and Treatment Act, 2010). In this study, childhood trauma includes any difficult conditions that affects physically and psychologically to children such as accidents, natural disaster and childhood abuse.

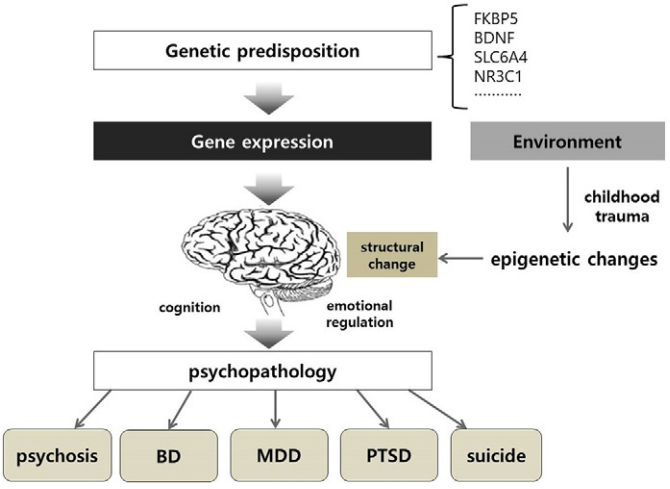

Fig. 1. Gene–childhood trauma interactions affect gene expression. The gene expression affected by a specific gene–environmental interaction leads to structural and functional changes in the brain including changes in cognition and emotional regulation. These changes mediate genetic predisposition to psychopathology associated with psychosis, mood disorders and post-traumatic stress disorder.

Childhood stress and trauma can produce long-term changes in brain development (Kaufman et al., 2000). Neuroimaging studies suggest that experience of trauma in early life may lead to structural as well as functional changes in the brain (Bremner, 2006). Childhood stress is also associated with adult psychopathology via its effects on specific brain systems (Mello et al., 2003). Fig. 1 shows how childhood trauma can lead to adult psychopathology.

The brain regions most consistently reported to be affected by childhood trauma are the corpus callosum and hippocampus (Teicher and Samson, 2013). There have also been reports linking childhood adversity to structural changes in anterior cingulate cortex (Cohen et al., 2006a, b), orbitofrontal cortex (Hanson et al., 2010), dorsolateral prefrontal cortex (Tomoda et al., 2009) and the striatum/basal ganglia (Dillon et al., 2009). These brain regions are all associated with emotional regulation, however most studies report that childhood maltreatment is not associated with volumetric changes in the amygdala (Andersen et al., 2008; Teicher and Samson, 2013), which is one of the regions critically involved in emotional regulation. Smaller amygdala volumes have, however, been observed in patients with borderline personality disorder or PTSD and a history of childhood trauma (Brambilla et al., 2004; Veer et al., 2015).

There are also reports of correlations between childhood trauma and cognitive functioning. In particular, some studies have reported negative correlations between childhood maltreatment and general cognitive abilities, memory or executive function in psychotic patients (Schenkel et al., 2005; Aas et al., 2011; Shannon et al., 2011). Parlar et al. (2014) reported that women with PTSD showed reduced ability to identify the social cognitive perspective of others compared with patients who did not have any history childhood trauma.

It has also been reported that children with a history of childhood abuse are more likely to have difficulties with emotion regulation than children without such a history (Shipman et al., 2000, 2005). Children who had suffered abuse showed deficits or delays in understanding and regulating emotions and tended to anticipate negative reactions to display of sadness and anger (Shipman et al., 2000). Childhood trauma has also been associated emotional non-acceptance (Gratz et al., 2007) and it has been reported that childhood trauma can lead to emotional avoidance and suppression (Krause et al., 2003).

A number of studies have shown that adults with a history of childhood trauma are vulnerable to various psychiatric disorders, such as affective disorders, psychotic disorders, anxiety disorders, substance abuse, PTSD and suicidal behavior (Brietzke et al., 2012). Emotional dysregulation is implicated in many psychiatric disorders, but it is the central feature of BD (Garno et al., 2005; Dvir et al., 2014). In patients with a history of childhood trauma BD tends to manifest earlier and produce more severe symptoms (Kauer-Sant'Anna et al., 2007; Etain et al., 2008). Exposure to childhood trauma has also been associated with development of major depressive disorder (MDD) (Felitti et al., 1998). One study reported that risk for depression increased dose-dependently with the number of adverse childhood experiences (Anda et al., 2002). The course of MDD is also worse in patients with a history of childhood adversity: onset tends to be earlier and the duration of the illness tends to be longer than in patients without a history of early adversity (Nanni et al., 2012). Childhood trauma also increases the risk of developing psychosis, including hallucinations and delusions (Freeman and Fowler, 2009; Alvarez et al., 2011; Galletly et al., 2011). In one study about 94% of patients with schizophrenia retrospectively reported childhood trauma (Kilcommons and Morrison, 2005), and childhood maltreatment is reported to be caused about 33% of cases of psychosis (Varese et al., 2012). Importantly, psychotic symptoms have been associated

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