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Childhood traumatic events and the dopaminergic theory of psychosis: A mini-review of studies investigating gene – environment interactions

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Abstract
There is great body of evidence showing a relationship between childhood adversity and psychosis onset. Genetic factors moderate the association between childhood adversity and psychosis risk potentially by influencing biological and/or psychological reaction following exposure to adversity. In this review, we discuss studies identifying the specific genetic variants known to affect dopamine levels involved in this interaction. Our review shows that the catechol-O-methyltransferase (COMT), dopamine D2 receptor (DRD2), AKT1 gene play a key role in mediating the relationship between childhood adversity and development of psychosis. We have also found conflicting findings on the impact of dopamine genes on the relationship between childhood adversity and development of psychosis, suggesting that other genetic and environmental factors should be taken into account. We here discuss the implications of our findings and future directions.

Keywords Dopamine · Polygenic risk · Trauma · Psychosis · Schizophrenia · Stress · Gene-environment interaction

Introduction

The dopamine hypothesis of schizophrenia is the leading and longest standing theory of schizophrenia pathophysiology, stating that characteristic symptoms such as hallucinations, delusions and abnormal cognitive functioning are caused by a synergistic imbalance of dopamine neurotransmission in cortical and subcortical brain regions (Howes & Kapur, 2009; Kimura et al., 2021; Takao et al., 2021). Dopamine system dysregulation can be influenced by both genetic and environmental factors (van Os et al., 2008). In addition to the dopamine hypothesis, several studies have also shown that glutamatergic dysfunction also underpins the development of schizophrenia symptoms (Gruter et al., 2015; Loureiro et al., 2021; McCutcheon et al., 2020; Serafini et al., 2013). At the molecular level, schizophrenia and related disorders could be related to impairment in microRNAs, which plays a role in synaptic function (Serafini et al., 2012). Impairment in microRNAs also impacts dopamine function, and thus may explain the development of schizophrenia symptoms (Kim et al., 2007; Schaefer et al., 2007).

One of the widely researched environmental factor in the recent years that has been shown to be increasing risk of psychosis is trauma experienced in childhood (Stanton et al., 2020). Childhood trauma and other types of stressful experiences are now well established as a significant risk factor for the development of psychosis (Janssen et al., 2004; Kessler et al., 2010; Matheson et al., 2013; Read et al., 2009; Varese et al., 2012). Exposure to adverse events in childhood is associated with around 2 to fourfold increased risk of psychosis (Morgan & Gayer-Anderson, 2016). A history of childhood trauma has been shown to be more frequent in individuals at ultra-high risk (UHR) of psychosis (Kraan, van Dam, et al., 2015; Kraan, Velthorst, et al., 2015), individuals with psychotic-like experiencing (Boyda & McFeeters, 2015;

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Gaweda et al., 2020; Lu et al., 2020; Mazur et al., 2018; Metel et al., 2020; Misiak et al., 2018; Nelson et al., 2018; Sommer et al., 2010) and first episode psychosis patients in comparison to healthy controls (Mondelli et al., 2010). Moreover, childhood traumatic experiences tend to co-occur such that being exposed to one type of adversity increases the risk of exposure to another, with a cumulative effect of trauma on psychosis (Shevlin et al., 2008). Moreover, people with childhood interpersonal trauma are at higher risk of experiencing adulthood interpersonal trauma (Stain et al., 2014). There is also strong evidence that childhood abuse and other life events, such as cannabis use (Moustafa et al., 2017), together increase the likelihood of developing psychotic experiences (Morgan et al., 2014).

Childhood trauma has been associated with a poorer premorbid adjustment, which is defined as achievement of developmental goals during different periods of life (Haahr et al., 2018; Stain et al., 2014), a longer duration of untreated psychosis (Aas et al., 2016; Haahr et al., 2018), slower improvement rates (Aas et al., 2016), worse treatment response and poorer social functioning (Stain et al., 2014). Moreover, early adverse events correlate with more severe symptomatology in psychotic patients (Aas et al., 2016). Higher levels of childhood trauma have been associated with more severe attenuated and more persistent positive symptoms (Daalman et al., 2012; Kraan, van Dam, et al., 2015), mainly auditory verbal hallucinations and delusions (Duhig et al., 2015; Read et al., 2005). It has also been demonstrated that early childhood adversities may lead to the development of delusions and hallucinations in a dose–response relationship (Muenzenmaier et al., 2015).

Since dopamine dysregulation due to adversity is postulated to be important in the pathogenesis of psychosis (Howes et al., 2004, 2017) and the impact of early childhood trauma on adult mental health outcomes is hypothesized to be modulated by common genetic variants (Weaver, 2007), there are numerous studies in recent years investigating the interaction between dopamine and childhood adversity. For example, one study found positive symptoms in schizophrenia is related to childhood trauma and increase dopamine levels in the ventral striatum (Dahoun et al., 2019); the same relationship was not reported for negative symptoms in schizophrenia in the same study (but for different result see Ruby et al., 2014). Interestingly, similar findings were also reported in relation to glutamate. For example, Loureiro et al. (2021) found that trauma in childhood impacts the functioning of Glutamate Ionotropic Receptor NMDA Type Subunit 1(GRIN1) in schizophrenia.

The aim of our paper is to review research on the interaction between functionally-relevant polymorphisms associated with dopaminergic neurotransmission and adverse childhood experiences that lead to the development and symptomatology of psychosis. Specifically, below, we discuss how catechol-O-methyltransferase (COMT), dopamine D2 receptor (DRD2), AKT1 mediates the relationship between childhood adversity an development of psychosis, respectively. To conduct this study, our search strategy included the following combination of two key words. The first was schizophrenia, and the second was either trauma, childhood trauma, or dopamine. We have searched previous studies using Pubmed, Google Scholar, and PsychoInfo.

The catechol-O-methyltransferase (COMT) gene

The COMT gene plays an important role in the metabolism of dopamine in the central nervous system. A single nucleotide polymorphism (SNP) in the COMT gene (rs4680) causes an amino acid change from valine (Val) to methionine (Met) at position 158 (Val158Met) with a 3- to fourfold higher enzymatic activity in the Val homozygotes in comparison with the Met homozygotes (Chen et al., 2004) that is associated with a reduction of dopamine levels in the prefrontal cortex (PFC) and the mesolimbic hypodopaminergic state (Akil et al., 2003). The COMT SNPs, especially rs4680, have repeatedly been identified as associated with schizophrenia as shown by the systematic review and meta-analysis (Gonzalez-Castro et al., 2016a, 2016b) and more recent data (Ahmadi et al., 2018; Morozova et al., 2019). In this section, we show that there are conflicting results regarding the impact of COMT gene on mediating the relationship between childhood adversity and development of psychosis.

There are numerous studies showing that the COMT polymorphism moderates the effect of stress on psychotic experiences in healthy individuals. It has been shown schizophrenia patients who are Met homozygotes show significantly increased psychotic reactivity to stress in comparison with carriers of other genotypes; however, there was no gene-stress interaction among healthy control subjects (Collip et al., 2011). Similarly, among patients with cannabis misuse problems who experience psychotic symptoms, Met homozygotes had the largest increase in psychotic experiences in reaction to daily stress, while this effect was not observed among healthy cannabis users (van Winkel et al., 2008). It has been demonstrated that there is an interaction between variation in the COMT and the methylenetetrahydroflate reductase (MTHFR) genes (encoding a crucial enzyme involved in the methylation of DNA) that moderates psychotic response to environmental daily stress (Peerbooms et al., 2012). In the Peerbooms et al. (2012) study, Met homozygotes displayed the largest increase in psychotic symptoms in reaction to self-assessed everyday stressful situations; however, this association was conditional on the MTHFR 677 T/T genotype (Peerbooms et al., 2012). There was a gene-environment interaction among healthy young men during a semi-experimental stress

exposure showing individuals with the Val allele having increased level of psychotic symptoms in comparison with the Met homozygotes (Stefanis et al., 2007); future studies should investigate whether the same results hold true fo female participants. One study on adult female twins showed that the Val allele carriers displayed more feelings of paranoia in response to stress compared to the Met allele carriers (Simons et al., 2009).

Various gene-environment interactions have been reported for the COMT Val158Met in moderating a risk for psychosis, including traumatic childhood experiences and stressful life events. Savitz et al. (2010) showed that the COMT Val158Met is associated with schizotypal personality severity in Val/Val individuals who were exposed to childhood trauma. They also found that there is an interaction between the COMT Val158Met and childhood trauma in the general population in relation to the risk of psychotic symptoms (Kelleher et al., 2013; Ramsay et al., 2013; Vinkers et al., 2013). In two studies, the Val homozygote individuals who experienced childhood trauma were more likely to report psychotic symptoms (Kelleher et al., 2013; Ramsay et al., 2013). However Vinkers et al. (2013)show that Met homozygotes demonstrated more severe expression of psychotic symptoms in individuals who did not use cannabis and that the Val homozygotes showed the highest levels of psychotic symptoms in relation to cannabis use.

Moreover, several studies have investigated genetic factors moderating the relationship between childhood trauma and psychosis (Debost et al., 2017; Green et al., 2014; Ira et al., 2014). Positive symptom severity was greater in individuals with the COMT Met allele and had experienced physical abuse. However, the negative symptoms severity in the COMT Met carriers was greater only in the presence of emotional neglect. A significant interaction was reported in the same study between genotype and emotional neglect in increasing the severity of negative symptoms among the COMT Met homozygotes (Green et al., 2014). However, individuals with childhood trauma who are COMT Val homozygotes have higher risk of developing schizophrenia (Debost et al., 2017). One important study reported the influence of both childhood experiences and recent stress on psychosis symptomatology (Ira et al., 2014). The authors have demonstrated that low maternal care and recent stressful life events were associated with higher level of positive symptoms at the onset of psychosis among first episode psychosis patients. Moreover, this association was strongest among Val homozygotes (Ira et al., 2014). In a study investigating the interaction between childhood trauma and two genetic polymorphisms influencing the regulation of mesolimbic dopaminergic neurotransmission (the COMT Val158Met and the MTHFR C677T), a three-way interaction has been shown (Debost et al., 2017). The risk of schizophrenia increased in a dose-dependent manner per functionally active COMT Val and MTHFR T allele, consequent upon exposure to childhood adversity.

The interaction between the COMT Val158Met and childhood trauma has been shown to influence cognitive performance as well as brain structure and function (Tian et al., 2020). Healthy participants who are COMT Val homozygotes and reporting low parental care exhibited lower performance on dopamine related-decision making test, such as reward and punishment learning (He et al., 2012) which has been found to be related to positive symptoms among psychotic patients (Struglia et al., 2011). In healthy participants, there was no significant interaction between the COMT Val158Met polymorphism and childhood traumatic events on executive functions (Klaus et al., 2017). However, in schizophrenia, a significant interaction between genotype and physical abuse was associated with better executive function in the Val homozygotes, relative to those of the same genotype with no history of abuse (Green et al., 2014).

There are also few studies not affirming the interaction between trauma and the COMT polymorphism. In a non-clinical and also an early psychosis sample, interaction between the COMT polymorphism with early life adversity and everyday life situational stress on the real life expression of psychotic experiences did not reach statistical significance after controlling for several variables (Cristobal-Narvaez et al., 2017). Moreover, no interaction between the COMT Val158Met polymorphism and childhood maltreatment in predicting schizophreniform disorder at the age of 26 years was found (Caspi et al., 2005). There is also a study showing that no evidence for the COMT Val158Met genotype by childhood adversity interactions for the presence of psychotic disorder in the first episode psychosis patients (Trotta et al., 2019).

The interaction between the COMT Val158Met polymorphism and environmental stressors in modulating psychotic symptoms has been documented in several studies, some of them indicating the association between Val homozygosity and increased odds of psychotic symptoms (Debost et al., 2017; Ira et al., 2014; Ramsay et al., 2013; Simons et al., 2009; Stefanis et al., 2007), while other studies suggest the involvement of the opposite allele (Collip et al., 2011; Peerbooms et al., 2012; van Winkel et al., 2008). Discrepancies in studies could be partly due to differences in the demographics of the samples, type of psychotic outcomes or intensity of the stressors studied (Simons et al., 2009; van Winkel et al., 2008). It has been suggested that both COMT Val158Met alleles may be vulnerable to, or benefit from, specific environmental stressors (Stefanis et al., 2007; van Winkel et al., 2008). Moreover, this inconsistency may be explained by considering that other genetic variants may moderate the effect of variation in the COMT on stress reactivity, as demonstrated by some studies (Alexander et al., 2011; Hoffmann et al., 2018; Peerbooms et al., 2012). It

cannot also be excluded that this inconsistency is related to the complexity of interactions between variation in the COMT gene and a history of traumatic life events. Indeed, a recent study of non-clinical adults revealed that the level of psychotic-like experiencing is significantly higher among individuals with a history of traumatic life events who are the COMT Met allele compared to the Val homozygotes (Kotowicz et al., 2019). Interestingly, this association was significant only in those with high level of cognitive biases.

The dopamine D2 receptor (DRD2) gene

The DRD2 gene encodes type-2 dopaminergic receptor (D2R). There are few highly researched DRD2 variants. The DRD2 polymorphism (rs1076560) regulates the expression of the dopamine receptor long and short isoforms, responsible for dopamine synthesis and release in the frontal cortex (Zhang et al., 2007) and basal ganglia (Cathiard et al., 2021; Frank et al., 2007; Markett et al., 2017; Valli et al., 2019). Another DRD2 polymorphism (rs12364283) results in enhanced gene expression, which may exacerbate already elevated striatal dopamine transmission in patients with schizophrenia (Bertolino et al., 2009). In turn, the DRD2 rs1801028 polymorphism is responsible for the replacement of serine to cysteine production. Some of these DRD2 variants have also been shown to impact schizophrenia-associated intermediate phenotypes such as disrupted prefrontal-striatal activity (Bertolino et al., 2009; Vink et al., 2016). Genetic variations of DRD2 have been found to be associated with schizophrenia (Betcheva et al., 2009; Glatt et al., 2003; Gonzalez-Castro, et al., 2016a, 2016b; Ripke et al., 2013) and DRD2 is one of the Psychiatric Genomics Consortium (PGC2) genome-wide association study (GWAS) hits (Schizophrenia Working Group of the Psychiatric Genomics, 2014).

Studies have reported that DRD2 gene is associated with risk to develop schizophrenia (Hussain et al., 2020) as well as response to medication (Zhang et al., 2015). There is one study showing that the DRD2 polymorphisms (rs17601612 and rs6589386) are associated with subclinical psychotic experiences that are related to chronic and severe stress (Bruenig et al., 2014). However, one study did not provide evidence of a possible role of the DRD2 (rs1076560) polymorphism in modifying the association between childhood adversity and the onset of psychosis in first-episode psychosis patients (Trotta et al., 2019). However, there are studies showing that the DRD2 gene polymorphism (rs1076560) increases the likelihood of having psychotic disorder in the context of cannabis use (Colizzi, et al., 2015a, 2015b; Colizzi, et al., 2015a, 2015b) which is in line with the evidence of schizophrenia patients with comorbid substance dependence having abnormal postsynaptic dopamine D2 receptor function (Thompson et al., 2013). There is one study exploring the moderating effects of dopaminergic polymorphisms (COMT and DRD2) and childhood adversity on brain morphology in schizophrenia-spectrum disorders (Hoffmann et al., 2018). A significant two-way interaction between dopaminergic risk allelic load and childhood adversity was found for the left putamen volumes in structural MRI (Hoffmann et al., 2018).

One study on healthy participants has demonstrated that DRD2 (C957T) polymorphism influences performance on executive functions, and this effect is mediated via the impact of childhood traumatic events (Klaus et al., 2017). Another study demonstrated no significant effects of interactions between DRD2 polymorphism (rs6277) and a history of traumatic life events on psychosis proneness in non-clinical adults (Kotowicz et al., 2019). However, the DRD2 rs6277 C allele was associated with significantly higher levels of psychotic-like experiencing in this study.

In short, prior studies show that there are conflicting findings on the impact of DRD2 polymorphism on the relationship between childhood adversity and the development of psychotic episodes. Further, it is not exactly known how DRD2 polymorphisms and childhood adversity impacts the prefrontal cortex and basal ganglia, which should be investigated in future studies.

The AKT1 gene

Variations in the AKT1 gene polymorphisms have been linked to dopamine-associated prefrontal cortex (Tan et al., 2008), striatal function (Shumay et al., 2017), and DRD2 gene (Tan et al., 2012; Zai et al., 2008). AKT1 encodes a protein kinase (protein kinase B, PKB) that plays a role in cascade mediating dopamine signaling in the striatum. Further, AKT1 facilitates dopamine and growth factor signaling (Beaulieu et al., 2009). Several studies have provided evidence of a decrease in AKT1 mRNA activity levels in the prefrontal cortex and hippocampus, as well as in peripheral blood levels of individuals with schizophrenia (Emamian et al., 2004; Thiselton et al., 2008) and dopamine receptor antagonists have been found to increase brain AKT1 levels in animal models (Li et al., 2007). For a detailed review of molecular mechanisms underlying the role of AKT pathway in schizophrenia (Emamian, 2012). Importantly, variations in the AKT1 gene (14q32.32) have been associated with a risk of developing schizophrenia in different populations (Bajestan et al., 2006; Emamian et al., 2004; Ikeda et al., 2004; Mathur et al., 2010; Schwab et al., 2005; Thiselton et al., 2008; Xu et al., 2007) as well as schizophrenia and related disorders (Karege et al., 2012; Thiselton et al., 2008).

Bruenig et al. (2014)reported higher subclinical psychotic experiences were associated with stress and AKT1 rs2494732. To our knowledge, there is only one study

investigating the interaction between AKT1 gene polymorphisms and childhood trauma (Trotta et al., 2019). This study, however, did not provide any evidence regarding a possible role of the AKT1 rs2494732 polymorphism in modifying the association between childhood adversity and the onset of psychosis in first episode psychosis patients. However, some prior studies have reported an interaction between the AKT1 rs2494732 polymorphism and cannabis use in relation to the development of psychosis. Specifically, carriers of C/C genotype were most likely to develop psychotic illness after smoking cannabis (Di Forti et al., 2012; van Winkel et al., 2011). Moreover, cannabinoids have been shown to activate the AKT1 signaling downstream of dopamine D2 receptors (Bhattacharyya et al., 2012) and the interaction between the AKT1 (rs2494732) and the DRD2 (rs1076560) polymorphisms on psychosis risk among cannabis users have also been shown with likelihood of developing psychosis especially increased in participants who carry risk allele of both genes (Colizzi, et al., 2015a, 2015b).

In sum, prior results have shown that the AKT1 gene interacts with the DRD2 gene, together impacting the relationship between childhood adversity and the development of psychosis.

Conclusions, limitations and future directions

Although the hypothesis that monogenic determinants can explain the etiology of psychotic disorders was abandoned several years ago (Miller et al., 2018; Nieratschker et al., 2010; Wang et al., 2018), the recognition of interactions between genetic factors and environmental insults renewed our understanding of psychosis. Interactions between variation in dopaminergic genes and psychosocial stress can play a role in the etiology of psychosis. Our review shows that there are conflicting results relating to how dopamine genes mediate the relationship between childhood adversity and development of schizophrenia. Our review suggests that other genetic and environmental factors should be taken into account. These environmental and genetic factors could be interacting with each other in a complex fashion, leading to the development of schizophrenia.

Our study has some limitations. For example, our study did not specify which type of childhood trauma may mediate the relationship between different dopamine genes and the development of schizophrenia. Several studies have shown different childhood trauma (e.g., parental neglect, sexual assault, etc.) have different impacts on the brain, behaviour, and development of clinical disorders (Garami et al., 2019; Huang et al., 2012; Schorr et al., 2020). Another limitation of our interview is investigating how other potential environmental factors (e.g., cannabis use) may mediate the relationship between dopamine genes and the development of schizophrenia. Along these lines, it is also possible that there are interactions among several environmental factors, and these interactions may mediate the relationship between dopamine genes and the development of schizophrenia. For example, it has been found that childhood trauma leads to cannabis abuse, and that both childhood trauma and cannabis abuse are risk factors for the development of schizophrenia (Frydecka et al., 2020).

However, our review has shown that there are inconsistent results of studies in this field, suggesting that various caveats and complexities need to be taken into consideration by future studies. Firstly, it is now increasingly being acknowledged that simple interactions between single gene variants and the measures of stress are insufficient to explain a risk of various psychosis outcomes. Consequently, testing more complex models with various phenotypes that are intermediate constructs between mental health and overt psychosis (e.g., cognitive biases, anomalous self-experiences and psychotic-like experiencing) are warranted. This point is also relevant to environmental factors which need to be precisely measured. The impact, duration and timing of stress exposure should be routinely recorded by future studies, as stress plays a key role in the development of several clinical disorders, including schizophrenia and its related disorders (Moustafa, 2021).

Moreover, the development of experimental sampling methodologies can provide grounds for collecting real-time data regarding the levels of stress on symptomatic manifestation. This paradigm can further improve our understanding of genetic determinants underlying responses to stress. However, increasing the complexity of tested models and sample size always drives the risk of insufficient statistical power. For instance, detecting an interaction of moderate effect size for the genotype that is present in only 5% of the population would require 5200 participants to provide the power of 80% (Uher, 2014). Another point is that detecting interaction often does not indicate direction of causality, even in longitudinal studies and thus various scenarios need to be considered (Misiak et al., 2018).

Future computational modeling work should investigate the complex relationship between childhood adversity, dopamine genes and the development of psychotic episodes. While there are prior computational models of dopamine genes and their relationship to psychosis (Moustafa & Gluck, 2011; Moustafa et al., 2017), we are not aware of any models that specifically study the relationship between childhood trauma, dopamine, and psychosis. Future models should simulate interactions among prefrontal cortex, hippocampus, and basal ganglia as well as the role of dopamine in these brain regions as well as how childhood trauma impacts their structure and function. Such models can help provide treatment for psychosis and schizophrenia, guided by complex understanding of their risk factors.

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Data Availability Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical statement The study was approved by the Ethics Comittee of Wroclaw Medical University (KB-59/2015).

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