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DOPAMINE TRANSPORTER AND TRANSMISSION OF PSYCHOPATHOLOGICAL RISK. A REVIEW OF GENE-ENVIRONMENT INTERPLAY

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Abstract

Research underlines that intergenerational transmission of psychopathological risk results from a complex interplay of genetic and environmental risk factors which predispose child to develop emotional-behavioral problems. Mechanisms of transmission are poorly understood, but few studies have focused on the role played by dopamine transporter (DAT) gene. This review aims to examine mediating mechanism of DAT genotype-environmental interaction (GxE), DAT genotype-environmental correlation (rGE), and methylation status involved in transmission of psychopathological risk. The review of literature was made through researches in university libraries on paper material, and telematics systems research. Studies have evidenced that DAT is implicated in intergenerational transmission of psychopathological risk. Results are mixed regarding its genetic variants, but mechanisms through which this gene can affect both quality of parenting and child development are partially established. Only few studies have examined methylation mechanisms that can be implicated. Findings suggest to involve an improved focus on DAT genotypes, methylation status associated, and their relationship with environment to better understanding child's vulnerability and resilience following exposure to contextual risk factors associated with parental psychopathological symptoms.

Keywords: Psychopathological risk, dopamine transporter, gene-environment, epigenetic.

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1. Introduction

The international research in the field of developmental psychopathology have widely underlined that parental mental illness is one of the most risk factor for child's development and mental health (Breaux, Harvey, & Lugo-Candelas, 2014) that may lead to a wide range of maladaptive outcomes among offspring, including both internalizing and externalizing problems (van der Pol et al., 2016). Moreover, it has been suggested a stability of psychopathology from childhood to adolescence and adulthood (Nivard et al., 2015), thereby leading to the transmission of psychopathological risk over the course of successive generations. Despite these findings, our knowledge of underpinning multiple mechanisms that may mediate the relationships between parental psychopathological risk and child development are less clear.

2. Problem Statement

In the last few decades, integration of different disciplines and the great progress in new technologies that have made possible the study of individual susceptibility genes, have allowed to increase complexity of our knowledge of interactive processes that occur between genetic and environmental variations, and of their dynamic interplay in shaping individual risk for psychopathology (Hyde, Bogdan, & Hariri, 2011).

The Developmental Psychopathology theoretical framework offers a valid model for examining the intergenerational transmission of psychopathological risk, who is considered as the result of dynamic and reciprocal interactions between risk factors of different nature, from genetics to environment systems, which act cumulatively, predisposing child to develop emotional-behavioral problems (Tronick & Hunter, 2016). Parental psychopathological symptoms may influence children mental health (a) through predisposition to vulnerability genes (Cicchetti, 2016) because parents share approximately 50% of their genes with their biological offspring (Kim et al., 2009), and/or (b) through exposure offspring to higher adverse and non supportive environment, including poor parenting (Cimino et al., 2016), interparental conflict and (Breslend et al., 2016) a lower socio-economic status (Piotrowska et al., 2015).

Recent studies focused on biological vulnerability-environmental interactions and on their involvement in the transmission of psychopathological risk, have evidenced that poor parenting (i.e., ineffective and unresponsive caregiving) is one of the primary mechanism by which risk from a parent with psychopathological difficulties is transmitted to the child (Davies, Cicchetti, & Hentges, 2015). Regarding genetic factors, genes influencing the dopaminergic system are postulated to be the most important candidate genes for child's psychopathological risk, especially in externalizing area (Li et al., 2016), which act as moderators in associations between maladaptive parenting and child negative outcomes (Del Giudice, Ellis, & Shirtcliff, 2013). In other words, both the continuity of environmental risks associated to parental psychopathology and genetic factors may predispose children to develop psychopathological symptoms (Silberg, Maes, & Eaves, 2012), and these factors may behave effects in both unidirectional (i.e., from parents to children) and bidirectional ways (Cents, 2016).

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2.1. Dopamine transporter

Dopamine is an important monoamine, released predominantly from the ventral tegmental area (VTA) of the brain, that acts as a neuromodulator and is involved in a variety of cognitive, affective, and motivational processes, including reward (Schultz, Carelli, & Wightman, 2015), aggression (Schlüter et al., 2013), and cognitions (Nevalainen et al., 2015). Genetic studies have also evidenced that the release of dopamine is associated with behavioural exploration, increasing the motivation to explore and facilitating cognitive-behavioural processes functional in exploration (DeYoung, 2013), which are central processes in the middle-childhood. Moreover, due to the key role of the dopamine in promoting affiliative behaviours, both in humans (Johnson & Young, 2015) and animals (Numan, 2007), many genes involved in the functioning of dopaminergic system have been studied within gene-environment (GxE) research. The availability of dopamine at the synaptic level is regulated by the dopamine active transporter (DAT), a solute carrier protein on presynaptic neurons, which pumps dopamine from neuronal extracellular space into intracellular compartments after release (McHugh & Buckley, 2015). Expression of the DAT protein is shaped by genetic variation of DAT1 gene and thus, it plays a key role in the regulation of dopaminergic neurotransmission, because although exist many dopamine receptors (encoded by genes such as DRD2 and DRD4), exist only one dopamine transporter (Vaughan & Foster, 2013). DAT1 has a 40 base pair variable number tandem repeat polymorphism (VNTR) located in the 3'-untranslated region (3'UTR) of chromosome 5p15.3 of the dopamine transporter gene (SLC6A3). Generally, the 40 base pair sequence is repeated in a ranging from 3 to 11 repeat, although it has been highlighted that the most common polymorphism are 9- or 10-repeat (Faraone et al., 2014). Given the central role of dopamine in regulation of mood and behaviour, it's not surprising that several studies have evidenced that DAT1 is the major candidate gene in the pathogenesis of externalizing problems in childhood. In particular, genetic association studies have linked DAT1 gene to ADHD (Fernandez-Jaen et al. 2015; Sokolova et al. 2015; Thissen et al. 2015, Giana et al., 2015), conduct disorder (Lahey et al., 2011), and pediatric bipolar disorder (Mick et al., 2008). Regarding genetic variants of DAT1, the pioneering study of Cook et al., (1995) have reported a significant association between ADHD and the 10-repeat allele of DAT1. Afterwards, several researchers have examined this association, reporting inconsistent results (Joyce et al., 2009; Giana et al., 2015). Some in vivo studies have also suggested that individual with at least one 9-repeat allele have significantly increased DAT activity (Spencer et al., 2012). In contrast, Single-photon emission tomography (SPECT) studies didn't confirm previous associations between DAT1 genotype and DAT activity in the brain (Costa et al., 2011).

3. Research Questions

The recent evidence that both genetic and environmental influences contribute to child's development outcomes suggests that the key to understand underlying processes involved in intergenerational transmission of psychopathological risk is a clarification of how genes and environments operate together as protective and/or risk factors for child's adaptive functioning. Although mechanisms by which parents can transmit psychopathological difficulties to their children are poorly

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understood, a few studies have examined genetic disruption of dopamine transporter and its implication in psychopathological risk.

4. Purpose of the Study

This review aims to examine the role of dopamine transporter in transmission of psychopathological risk, within gene-environment interplay framework. In particular, we intend to examine mediating mechanism of genotype-environmental interaction (GxE), and genotype-environmental correlation (rGE) involved in transmission of psychopathological risk, considering the specific role played by dopamine transporter (DAT) gene. Finally, we'll discuss epigenetic mechanism of DNA methylation through which environmental influences can alter the expression of the genome.

5. Research Methods

The review of international literature was made through researches in university libraries on paper material, and telematics systems research. Particularly useful database were ProQuest, PsyArticles, PsyInfo, PubMed, together with the use of Scopus index to verify the papers' scientific relevance. Articles, published in English, were identified using the terms: gene-environment interplay, gene-environment interaction, gene-environment correlation, epigenetic, methylation, dopamine transporter, children psychopathological risk, parental psychopathological symptoms, intergenerational transmission.

6. Findings

Gene-environment studies have underlined that intergenerational transmission of psychopathological risk may be influenced by DAT and its complex interplay with environment provided by parents. In the field of research examining gene-environment interplay, developmental psychopathologists have long been interested to correlations between genes and environments to underline children' developmental processes, because these dual sets of risk for psychopathology are often associated each other (Cicchetti, 2016). In particular, these processes comprising gene-environmental interaction (GxE), gene-environmental correlation (rGE), and epigenetic gene regulation (Boyce & Kobor, 2015). Although finding are mixed regarding DAT genetic variants, mechanisms through which this gene can affect both quality of parent-child interactions and child emotional-behavioural functioning are partially established.

6.1. DAT Genotype-environment interaction

Gene-environment interactions refers to genetic moderation (i.e., genetic polymorphisms) on differences in individuals' sensitivity to particular environmental experiences (Pyeritz, 2015), which are conditional upon each other. Particularly, GxE occurs when (a) the effect of an environmental factor (e.g., early adverse experiences, stress, parental psychopathological symptoms, poor parenting) on the development of altered physiological, emotional or behavioral responses (e.g., internalizing and externalizing symptoms) depending by individual differences in genetic disposition (i.e., genotype), or (b)

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conversely, the effect of the genetic variation on emotional-behavioral functioning (developmental outcomes) is conditional on the presence of specific social context condition (Uher, 2014).

With specific regard to DAT1, few studies have confirmed its key role in childhood psychopathological risk, but findings are mixed regarding its genetic variants. A study by Li and Lee (2013) have examined interaction between maltreated children and DAT1, reporting a more severe ADHD symptoms in offspring homozygous for the 10-repeat allele, compared to children with at least one 9-repeat allele. In contrast, in a cross-sectional study of boys between 5 and 17 years old with ADHD, Sonuga-Barke et al. (2009) found that maternal expressed positive emotion was predictive of a lower externalizing symptoms in offspring, but only for children with 9-repeat allele. These results were replicated in a longitudinal study by Lee et al. (2011), that reported predictive association between both negative and positive parenting, at 4-5 years of age, and future children' conduct disorder symptoms, primarily for children with two copies of the 9-repeat allele of the VNTR. More recently, Lahey et al., (2011) reported a stronger association between positive quality of parenting and the development of conduct problems among children with 9-repeat allele.

Moreover, genetic influences seem to predict also quality of caregiving and its transmission across generation. In particular, a few studies have evidenced a GxE interaction between parent's DAT1 genotype and the quality of parenting. For example, a study by Lee et al. (2010) have found a significant association between the presence of 9/10 genotype of maternal DAT1 gene with both negative parenting and children disruptive behaviour. Mothers with the 9/10 genotype had more difficulties in parenting, showing a higher frequency of verbal commands in comparison to mothers who carried the 9- or 10-repeat allele. Moreover, the correlation between maternal DAT1 and maladaptive parenting was stronger in the presence of children with higher disruptive behaviour during the same parent-child interaction task, suggesting a moderating role played by infant difficultness in the parental genetic vulnerability to parenting impairments (Cicchetti, 2016).

6.2. Beyond GxE: The role of DAT genotype-environment correlations

In contrast to gene-environment interactions, gene-environment correlation (rGE) encompasses any situation in which an individual's genetically influenced traits in turn influence individual's exposure to particular environmental risk factors, and could make those environments themselves heritable (Wilkinson et al., 2013). These genetic mechanisms involve rGE's in three ways: passive, active and evocative. In passive rGE, parents pass on their genes to their child a susceptibility to psychopathology and provide environment that their offspring experience, both of which influence children' development (Rutter, Moffitt, & Caspi, 2006). The second, active (or selective) rGE, refers heritable and genetically influenced personal characteristics that are involved in the processes by which individuals shape and select their own environments, and that will provide risk or protective features. Finally, evocative (or reactive) rGE concerns to genetically influenced characteristics of children which may influence the response from the social environment and environment provided by parents, for example, eliciting a poor quality of parenting (Knafo & Jaffee, 2013). Thus, some researches of GxE interactions could be biased by rGE. In others words, some of the associations between children's DAT genes and adverse outcomes could be mediated by genetics influences on early parent-child relationships. Specifically, DAT1 gene

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could influence children behaviours that, in turn, could evoke maladaptive parenting (Hayden et al., 2013).

In the literature on rGE and children psychopathological risk there is a dearth of studies that have investigated the specific role played by DAT. For example, a study by Hayden et al. (2013) in a sample of 365 children, examined whether children' DAT1 genotypes (10/10, 9/9 or 9/10 polymorphisms) are associated with their exhibited negative emotionality (used as a measure of psychopathological risk) during a standardized parent-child interaction tasks and with quality of parenting (used as a measure of environment risk factor). They found that DAT1 9-repeat polymorphism was associated with children negative emotional expressed toward their parents. On the other hand, parents of children with a DAT1 9-repeat variant shown a lower quality of parenting (i.e., more hostility and less guidance and engagement during the task) than parent of children with other variants. Moreover, these gene-environment associations were partially mediated by negative affect shown by children toward their parents, evidencing the presence of evocative rGE involved in children's psychopathological risk. More recent, Rehan et al. (2016), in a large sample of male and female twins and their siblings, examined the possible associations between DAT1 polymorphism and childhood experiences of abuse, evidencing that individuals with 9-repeat genotype variant was less susceptible to experiences of abuse. These findings suggest that the DAT1 variant may affect a temperamental trait or a behaviour associated to some adverse experiences, either through passive or evocative rGE.

6.3. Epigenetic: the role of methylation status of DAT promoter gene

Despite number of studies in gene-environmental interactions and gene-environment correlations have increased our knowledge of mechanisms responsible for transmission of psychopathological difficulties from parents to children, underlining the genetic moderation of environmental influences (van IJzendoorn, Bakermans-Kranenburg, & Ebstein, 2011), disparities of results in traditional genetic studies of the DAT1 suggest to consider also epigenetic mechanisms which may influence DAT regulation. Indeed, it has been evidenced that child's emotional-behavioural functioning is shaped not only by interactive effects of genetic vulnerability and environmental risk, but also by the environmental pressure to regulate gene expression through epigenetic mechanisms (Roth, 2013). In other words, in addition to genetic polymorphisms, epigenetic factors also may influence gene expression and mediate the effects of specific environmental risk factors on child psychopathological difficulties (Ikegame et al. 2013). Epigenetic can be defined as any process that alters the regulation of genetic function, gene expression and, consequently, protein levels, without altering the genomic DNA sequences (Breiling & Lyko, 2015). Specifically, Waddington (1942) coined this term to refer to the modification of genotype into a phenotype. These mechanisms are potentially heritable but environmentally modifiable, especially by early stressful experiences which can influence neurobiological substrates until adulthood through their effects on molecular regulators that interact with the DNA molecule (Lopizzo et al., 2015).

Developmental researchers have reported various environmental risk factors that may have important consequences for child's neurocognitive development in terms of epigenetic changes induced, including abuse, maltreatment and neglect experiences, are in foster care, a low level of SES, parental psychopathological symptoms, exposure to persistent parental conflict, and poor parenting (Thompson,

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2014). During critical stages of development, the brain is especially responsive to stressfull experiences (McLaughlin et al., 2015), because there is a neural plasticity highly dependent on experience (Takesian & Hensch, 2013). Moreover, it has been established that biological effects of early adversity experiences may influence not only brain development but also (auto) immunologic functioning, autonomic reactivity, the capacity to tolerate or cope with stress, and cognitive processes (i.e, memory, learning and thinking) (McEwen, 2012). Among epigenetic processes, methylation is one of the most extensive studied epigenetic mechanism in the context of early adverse experiences. It is considered as a key process to explain the long-lasting effects on gene transcription and/or translation and the resultant changes in physiology (e.g., neuronal plasticity and functioning), cognition and emotional-behaviour functioning (Roth, 2013). Methylation of DNA is a covalent modification of the cytosines that are adjacent to CpG sites in mammals. When methylation changes occur in gene-promoter regions, they alter gene expression, reducing binding of transcription factors to regulatory elements, and resulting in gene silencing (Yang et al., 2013).

The role played by DNA methylation in development outcomes has been widely investigated, principally in the context of psychopathological difficulties related to exposure to early adverse experiences (Grayson et al., 2006), including major depression (Dell'Osso et al., 2014) and post-traumatic stress disorder (Rusiecki et al., 2016). However, a growing body of study have suggested that epigenetic modifications can occur in response to a various contextual signals, not only in utero and in early infancy (van Heesbeen et al. 2013), but throughout the development (Moore et al., 2013). Regarding methylation status of DAT1 gene, data from animal studies have evidenced that environmental adverse experiences during embryonic phase trigger modifications in DAT level and also found significant association between hypermethylation of the DAT gene and greater availability of DAT (Rajala et al., 2014). Despite the previous premises, a small body of studies have focused on methylation status of DAT promoter in humans, who may mediate effects of environmental risk factors known to contribute to an increased psychopathological risk in children (Schuch et al. 2015). For example, Swanson et al. (2007) have shown significant association between exposure to tobacco smoke in utero and increased risk to develop externalizing problems. Xu et al. (2015) examined the promoter methylation of DAT1, DRD4 e DRD5 in a sample of 100 children (50 with ADHD and 50 non-ADHD control children) founding a methylation only of CpG site 1's of the DRD4 promoter. A more recent study by Ding et al. (2016) have reported that less DNA methylation of a sequence within the promoter region of DAT1 was correlated with children' symptom response to a methylphenidate treatment (MPH). Specifically, they have found a significant association between a lower state of methylation of DAT1 and reduced of hyperactivity–impulsivity and oppositional-defiant symptoms, after treatment with MPH. To date, to our knowledge, no other studies have examined methylation status of DAT in childhood and its possible associations with psychopathology

7. Conclusion

Gene-environment interplay framework in the field of developmental psychopathology seems to prove fruitful in increasing our knowledge of child psychopathological risk. Studies considered in this review have focused on understanding of DAT genotype-environment interaction (G×E), DAT genotype-

environment correlation (rGE), and epigenetic mechanisms, with specific regard to methylation processes. Findings are poor and inconsistent, suggesting to involve an improved focus on DAT genotypes, DNA methylation associated, and their relationship with environment to better understanding child's vulnerability and resilience following exposure to contextual risk factors associated with parental psychopathological symptoms.

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