My dopamine has been busy: Research on gene by environment interactions in child externalizing behavior

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1 GENERAL INTRODUCTION

CHAPTER 1

GENERAL INTRODUCTION

There is consensus that parents play a pivotal role in how their children develop and function (Karreman, Van Tuijl, Van Aken, & Dekovic, 2006; Rothbaum & Weisz, 1994). Many of the behavioral skills young children and adolescents learn are highly dependent on the quality of parenting they receive and evoke (Miner & Clarke-Stewart, 2008; Stormshak, Bierman, McMahon, & Lengua, 2000). In fact, parenting is considered to be one of the strongest potentially modifiable risk factor that contributes to the development of child externalizing behavior (McCart, Priester, Davies, & Azen, 2006). Yet more recent research suggests that not all children are equally sensitive to their environment and, thus, to the parenting they receive. A growing body of recent evidence demonstrates that genes might have something to do with this phenomenon (Belsky & Pluess, 2009, 2013). Indeed, some studies suggest that children carrying a genetic "polymorphism" seem to be more sensitive to quality of parenting than children without such a polymorphism (Belsky & Van IJzendoorn, 2015; Van IJzendoorn & Bakermans-Kranenburg, 2015). The word polymorphism comes from the Greek roots "poly" (many) and "morphe" (form). It implies that some individuals have a variation in a single gene (i.e., DNA sequence) that is relatively common in the population, being prevalent in at least 1%. Such a variation in a gene might alter neurobiological processes in the brain that possibly make children more sensitive to their environment (Matthys, Vanderschuren, & Schutter, 2013).

It is specifically this interaction between a gene and the environment (i.e., G × E) that is thought to shape externalizing behavior. However, G × E findings have raised criticism and serious concerns regarding mixed findings and replications, making it difficult to draw conclusions (Dick et al., 2015; Duncan & Keller, 2011; Jaffee, Price, & Reyes, 2013; Weeland, Overbeek, de Castro, & Matthys, 2015). One important challenge is to fill in the details in neurobiological processes that link genes and environment to child externalizing behavior (Moore & Depue, 2016; Salvatore & Dick, 2015). By addressing specific neurobiological components related to environmental sensitivity, studies would contribute to a better understanding of G × E interactions (Chorpita & Daleiden, 2009; Tolan, Dodge, & Rutter, 2013). Another relevant challenge pertains to G × E confounders (Keller, 2014). Many G × E studies use correlational designs (Riley, 2008) that do not permit causal inferences and are unable to rule out alternative interpretations in terms of gene-environment correlations (i.e., *r*GE). Longitudinal and experimental studies can overcome these concerns by design (Bakermans-Kranenburg & Van IJzendoorn, 2015). The aim of this thesis is to clarify G × E interactions in child externalizing behavior based on multiple genes influencing the dopamine system. First, we conducted a longitudinal study to predict G × E over time and to statistically account for passive *r*GE. Second, an intervention study was carried out to experimentally manipulate the environment, thereby increasing statistical power, ruling out any *r*GE confounding, and reducing environmental measurement error.

Externalizing behavior in children

Mild levels of externalizing behavior (e.g., aggression, oppositional behavior,

disobedience) are considered to be typical behavior in young children. However, some children show high levels of externalizing behavior that, when left untreated, might worsen with age and might develop into persistent patterns of serious anti-social behavior (Campbell, Shaw, & Gilliom, 2000). In fact, stable high or increasing levels of externalizing behavior in early childhood might be a sign of incipient severe externalizing behaviors in adolescence, including delinquency (Fergusson, Boden, & Horwood, 2014; Miettunen et al., 2014; Moffitt, 2003). Such forms of externalizing behavior carry substantial social and economic costs to individuals and society (Raaijmakers, Posthumus, Van Hout, Van Engeland, & Matthys, 2011; Scott, Knapp, Henderson, & Maughan, 2001). Moreover, families may experience adverse effects of the child's externalizing behavior and might be hindered in their daily functioning, resulting in marital discord, parental stress, and productivity losses (e.g., Mackler et al., 2015). Not surprisingly, then, the developmental legacy of externalizing behavior underscores the need to learn more about the causes of externalizing behavior in childhood.

Parenting behavior and externalizing behavior

Extensive evidence supports the notion that environmental characteristics, such as parenting behavior, are related to child externalizing behavior (Karreman et al., 2006; Rothbaum & Weisz, 1994). *Negative parenting behavior*, like harsh and inconsistent discipline, limited use of praise, and lack of attention to appropriate behaviors are associated with higher levels of externalizing behavior in young children (e.g., Patterson, DeBaryshe, & Ramsey, 1989; Pettit & Bates, 1989; Shaw, Keenan, & Vondra, 1994) and adolescents (Hoeve et al., 2009; Steinberg, Lamborn, Darling, Mounts, & Dornbusch, 1994). Although mild levels of externalizing behavior can be considered typical in early childhood, parents' ineffective reactions might inadvertently result in more conflicts, leading to a fertile ground for children to become generally oppositional. As such, these children may learn to ignore demands that are unrewarding or unpleasant, thereby triggering a coercive exchange with their parents (e.g., Patterson, 1982; Scaramella & Leve, 2004). *Positive parenting behavior*, in contrast, is associated with decreases in externalizing behavior (e.g., Stormshak et al., 2000). Indeed, parents with a greater capacity of positive parenting qualities, including the use of tangible rewards, praise and other positive reinforcements, appear to be able to respond to externalizing behavior in a more predictable and consistent manner, thereby ameliorating early emerging problems and allowing their children to return to adaptive functioning (e.g., Gardner, Ward, Burton, & Wilson, 2003; Sandler, Schoenfelder, Wolchik, & Mackinnon, 2011). Thus, negative parenting may serve as an environmental risk factor in the development of externalizing behavior, but positive parenting may also serve as a protective factor.

Gene-×-Environment interactions

Behavioral genetic studies suggest a genetic contribution to the development of externalizing behavior in children. Such research has traditionally used twin and adoption studies, showing that the heritability of externalizing behavior ranges between 40% and 60% (Hicks, Foster, Iacono, & McGue, 2013; Rhee & Waldman, 2002). However, the emergence and persistence of externalizing behavior appears to be explained best by the interaction of genes with environment (e.g., Rutter, 2012). That is, children's likelihood to develop externalizing behavior as a consequence of negative parenting behavior, depends in part on their genetic make-up. Specifically, genes related to dopaminergic brain functions would seem to play a role because of its link with reward-based learning and reward sensitivity (Bakermans-Kranenburg & Van IJzendoorn, 2011). Several dopaminergic polymorphisms—like the *DRD2* A1, *DRD4* 7-repeat, *DAT1* 10-repeat, *MAOA* low-activity, and the *COMT* val—may contribute to differential sensitivity in responsiveness to parenting behavior and thereby to child externalizing behavior (e.g., Boardman et al., 2014; Ficks & Waldman, 2014; Wagner et al., 2010; Windhorst et al., 2015; Yang et al., 2007). These findings, however, have not always been straightforward (Dick et al., 2015; Jaffee et al., 2013) and have proven to be difficult to replicate (Duncan & Keller, 2011). This difficulty with replicability may in part be caused by the fact that previous studies are typically cross-sectionally designed and/or used a limited single candidate gene approach. In this regard, the use of (1) longitudinal and experimental designs, (2) the creation of polygenetic indices based on multiple genes influencing a specific biological system (i.e., systems approach), and (3) linking the biological system to environment and child behavior would help to draw stronger conclusions about how G × E interactions relate to externalizing behavior.

Longitudinal and experimental designs

Longitudinal G × E studies use repeated-measurements that allow the investigation of how externalizing behavior unfolds over time and whether parenting behavior indeed *predicts* change in such behavior. However, although longitudinal G × E studies are invaluable sources for information they cannot rule out alternative explanations for detected G × E. One explanation lies in passive *r*GE. Passive *r*GE refers to the notion that the child's exposure to the environment (parenting quality) is not random but rather influenced by his or her parents who carry the same genetic polymorphism (Dick, 2011; Horwitz & Neiderhiser, 2015). Longitudinal G × E studies could account for passive *r*GE in order to investigate whether interactions really constitute G × E evidence or are confounded by *r*GE. In addition, e*xperimental G × E studies* have advantages relative to longitudinal G × E studies due to their randomized experimental character: (1) this eliminates any concerns about *r*GE because in a randomized design, participants' genes cannot be correlated with the (manipulated) environment, (2) experimental studies work with standardized environmental conditions that reduce environmental measurement error, and (3) experimental studies provide considerably more statistical power because the environmental variance is increased and—especially in the case of intervention studies—often use "at risk" samples (Bakermans-Kranenburg & Van IJzendoorn, 2015).

A dopamine-related systems approach

Until now, single candidate G × E studies have found only modest G × E effects (e.g, Dick et al., 2015).
Moreover, results of these studies have generally not been consistently replicated in follow-up studies (Duncan & Keller, 2011; Jaffee et al., 2013). However, it may be that the functional contribution of genes are polygenetic in nature – with each polymorphism of each gene making only a small contribution (Chen et al., 2011). The cumulative consideration of multiple genes, via polygenetic indices, may collectively account for significant polygenetic effects (Nikolova, Ferrell, Manuck, & Hariri, 2011). Thus, the creation of polygenic indices that use multiple genes influencing a specific biological process may be a more accurate measure of children's latent differential sensitivity to parenting behavior. In addition, different genes may also impact different aspects of the dopamine system by either affecting the amount of dopamine released (i.e., receptors), recaptured (i.e., transporters) or degraded (i.e, enzymes) (Chen et al., 2011). Such further functional distinctions have not been considered much in G × E research but could potentially provide new information about how specific dopaminergic processes depend on genetic variability and how this, in turn, determines children's behavioral responses to positive and negative parenting behavior.

Linking the dopamine system to parenting and externalizing behavior

Dopamine is a neurochemical that modulates, via dopamine signaling, reward processing (Schultz, 2002). Therefore, dopamine appears to be critical in reward sensitivity and reward-based learning (e.g., Pessiglione, Seymour, Flandin, Dolan, & Frith, 2006; Schultz, 2010). In simplistic terms, dopaminergic neurons in the ventral tegmental area/substantial nigra provide information about whether the environmental stimulus is rewarding (reward salience) and, if so, the nucleus accumbens mediates the rewarding effect and provides information about whether or not specific behavior should be repeated (reward-based learning) (Dichter, Damiano, & Allen, 2012; Wise, 1996). The *DRD2 A1*, *DRD4 7*-repeat, *DAT1* 10-repeat, and *COMT* val polymorphism (but not *MAOA* low-activity) have been related to less dopamine signaling and impaired reward processing, resulting in reduced reward salience and reward-based-learning (Comings & Blum, 2000; Schultz, 2002). Indeed, decreased dopaminergic functioning has been observed in young children and adolescents showing severe externalizing behaviors (Matthys et al., 2013). As a consequence, children with decreased dopaminergic functioning may lack motivation to obtain ordinary and/or delayed rewards, making it difficult to learn adequate social behavior. Moreover, these children may actively seek stronger rewards in their environment to overcome a condition of stimulus deprivation (Buckholtz et al., 2010). Thus, negative parenting might contribute to the affectively unpleasant condition of under stimulation, thereby increasing the child's motivation to change this condition by seeking stimulation. For these children, positive parenting, in contrast, might promote social learning processes and prevent

stimulation seeking (Matthys, Vanderschuren, Schutter, & Lochman, 2012).

Diathesis-stress, differential susceptibility, and vantage sensitivity

Traditionally, differential sensitivity in responsiveness to parenting has been cast in *diathesis-stress* terms (e.g., Zuckerman, 1999), stipulating that some "vulnerable" children are more likely than others to develop problematically in response to adverse environmental context only. More recently though, a *differential susceptibility* theory has been put forward (Belsky, Bakermans-Kranenburg, & Van IJzendoorn, 2007; Belsky & Pluess, 2009, 2013; Boyce & Ellis, 2005; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & Van IJzendoorn, 2011), which postulates that those most vulnerable to adversity may also benefit the most from environmental enrichment. A related but different perspective is the *vantage sensitivity* framework (Pluess & Belsky, 2013; Pluess, 2015), which stipulates that some children as a function of their very personal characteristics, may exclusively be responsive to environmental enrichment. These frameworks need to be considered in G × E research to better understand how G × E interactions work in response to both positive and negative parenting behavior.

Genetic moderation of intervention efficacy

There is much interest in whether the experience of environmental enrichment that brings about decreases in child externalizing behavior is due to the same genetically induced qualities related to negative changes brought about by adverse environmental influences (i.e., differential susceptibility). This hypothesis can be investigated in intervention studies that use parents as primary agents for positive change in parenting behavior (Bakermans-Kranenburg & Van IJzendoorn, 2015). Indeed, so called G × I (gene-by-intervention) research suggests that some children who may be more sensitive to adverse environmental influences, based on the allelic variants, may also be more sensitive to intervention-induced enrichment (Belsky & Pluess, 2009, 2013). However, more research on genetic moderation is required to investigate heterogeneity in intervention response, but also to investigate specific neurobiological processes allowing for genetic variability in response to induced positive parenting changes. Since the Incredible Years (IY; Webster-Stratton, 2001) parent intervention is one of the most effective behavioral parent training programs to prevent and/or ameliorate externalizing behavior in young children (Menting, Orobio de Castro, & Matthys, 2013), IY is the specific focus of this thesis regarding the investigation of genetic moderation of intervention efficacy.

Aims and outline of this thesis

The aim of this thesis is to examine genetic variability in susceptibility to negative and positive parenting behavior in a sample of children at risk for maintaining or developing externalizing behavior. First, a longitudinal study was carried out on an

existing dataset involving adolescents. Second, an experimental intervention study was carried out to intervene in early emerging externalizing behavior in young children. Rather than focusing only on single dopaminergic candidate genes as a potential moderator of intervention effects, we adopted a systems approach by creating a dopaminergic polygenetic index.

In **chapter 2**, we report on a longitudinal study in which we investigated the moderating role of the *DRD2* and *DRD4* in the longitudinal association between parental psychological control and parental support on the one hand and the development of delinquent behavior on the other hand, accounting for passive *r*GE. Indeed, high psychological control and low parental support have been studied as important predictors in the development of delinquency (Hoeve et al., 2009). We predicted that for *DRD4 7*-repeat carriers high perceived psychological control and low support would be more strongly related to the presence and development of delinquent behavior, when compared to their peers without such a polymorphism. Because of inconsistent effects in the *DRD2* literature, in particular on delinquent behavior (e.g., Guo, Roettger, & Shih, 2007; Vasilyev, 2011), we explored whether either the *DRD2* TaqI A1 or A2 allele would be associated with higher risk for the presence and development of delinquent behavior.

Left untreated, early externalizing behavior may worsen with age and tend to persist over time (Vaughn, Salas-wright, Delisi, & Maynard, 2013). This underscores the need for early intervention to ameliorate such early emerging problems. In **chapter 3**, we describe the study protocol for project ORCHIDS (Observational Randomized Controlled Trial on Childhood Differential Susceptibility), which is designed to examine heterogeneity in IY intervention effectiveness. In this study protocol we delineate the hypotheses about genetic moderation of intervention effects. The inclusion of genes in experimental intervention-based studies is fraught with difficulties and raises ethical questions. In **chapter 4** we make some of these ethical questions explicit by discussing whether it is ethically responsible to withhold an effective treatment; to what extent or under which circumstances genetic data should be disclosed; whether researchers should be allowed to collect genes of both children and parents; and what costs and benefits of personalized interventions are based on (genetic) screening.

Heterogeneity in responses to intervention effects may be due to genetic variation (Belsky & Van IJzendoorn, 2015; Van IJzendoorn & Bakermans-Kranenburg, 2015). Since responsiveness to positive parenting change may depend on reward sensitivity/salience and reward-based learning (Matthys et al., 2013), it may very well be that some of the determinants of variation in intervention response depend on variance in dopaminergic genes. In **chapter 5**, we examine the effectiveness of the IY parent intervention program and potential moderators (i.e., initial severity of externalizing problem behavior, child gender, social economic status, family composition, and number of sessions parents attended), following the ORCHIDS design presented in chapter 3. The IY program was offered as an indicated preventive intervention in

order to reduce externalizing behavior in young children. In this study, we predicted that parents assigned to the intervention group would improve more in positive parenting behavior than those assigned to the control group and that their children would show greatest decreases in externalizing behavior.

In **chapter 6**, we used the ORCHIDS study to investigate genetic moderation of intervention efficacy by creating a dopaminergic polygenetic index. Genes were selected on our a priori defined hypotheses (see chapter 3). We predicted that children scoring highest on a dopaminergic polygenic index (*DRD2* A1, *DRD4 7*-repeat, *DAT1 10*-repeat, *MAOA* low-activity, and the *COMT* val allele) would show the greatest decrease in externalizing behavior in response to the IY intervention and that this would be especially so when parents evinced substantial rather than limited improvement in their positive parenting behavior. As all children were screened to have relatively high levels of externalizing behavior—presumably indicating an at risk group—we predicted that in the control group those children scoring high on the dopaminergic index would demonstrate greatest increases in externalizing behavior.

In **chapter 7**, we elaborate on the findings presented in chapter 6, by decomposing the dopaminergic polygenetic index into receptors (*DRD2*, *DRD4*), transporters (*DAT1*), and enzymes (*MAOA*, *COMT*). This because these genes play a different role in dopamine signaling by respectively either modulating the amount of dopamine released (via neural signaling), recaptured, or degraded (Chen et al., 2011). As such functional distinctions have not been considered much in G × E research, we explored the proposition that one or more of the three dopaminergic subsets might be responsible for the polygenic moderation of IY efficacy.

In **chapter 8**, the results described in the previous chapters are summarized and discussed. In addition, the role of the dopaminergic system in a differential-susceptibility-related manner is discussed as well as recommendations for further G × E research.