How do genes get outside the skin? Mechanisms underlying Gene×Environment interactions in child externalizing problems

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1.
General introduction

Child Externalizing Problems in the Era of Genetics

Externalizing problems refer to behavior patterns, including-amongst others-oppositional, disruptive, hyperactive, and aggressive behaviors, which have negative effects on children's social environment and impair their daily functioning. Although childhood externalizing problem behaviors are relatively common, an early onset of such behavior is known to be a strong predictor of comorbid developmental difficulties and of psychopathological outcomes later in life (Jokela, Ferrie, & Kivimäki, 2009; Von Stumm et al., 2011). Therefore, it is important to intervene when this behavior develops. In order to effectively do so, we need to know which factors contribute to the development and maintenance of externalizing problems. Externalizing problems are a very heterogeneous cluster that can be preceded by many different developmental trajectories (Frick, 2012). Studies conducted within different scientific disciplines identified important predictors of externalizing behavior, among which environmental, neurobiological, and genetic risk factors. All of these risk factors are well supported by empirical data. Meta-analytical studies have shown that—amongst others—harsh parenting strategies (e.g., coercive control, corporal punishment, Gershoff, 2002; a lack of parental responsiveness, Rothbaum, & Weisz, 1994), deficits in executive functioning (Schoemaker, Bunte, Espy, Deković, & Matthys, 2014), and variance in dopamine and serotonin related genes (Byrd & Manuck, 2014; Ficks & Waldman, 2014) are all salient predictors of the development of externalizing behaviors problems.

Parenting

Parenting is one of the most well-studied and documented contributors to the development of child externalizing problems, as well as an important target for interventions aimed at reducing this behavior (for an overview see Tolan & Leventhal, 2013). Negative parenting techniques, such as inconsistent discipline, harshness, and psychological control, have been positively related to child negative and externalizing behavior (e.g., Bor, Sanders, & Markie-Dadds, 2002; Collins, Maccoby, Steinberg, Hetherington, & Bornstein, 2000; Ge, Brody, Conger, Simons, & Murry, 2002; Karreman, Van Tuijl, Van Aken, & Dekovic, 2006; Rothbaum & Weisz, 1994). Whereas, positive parenting techniques, such as appropriate discipline, responsiveness, and limit setting have been related to less externalizing and more socially desirable behavior (e.g., Zahn-Waxler, Iannotti, Cummings, & Denham, 1990). Moreover, besides actual parenting behavior parental affect, such as warmth, acceptance and joy, and on the other hand irritability, rejection, and anger, might be key mechanism in the development of externalizing problems. Specifically, parental negative affect might contribute to escalating coercive interaction patterns within families that maintain child externalizing problems (Duncombe, Havighurst, Holland, & Frankling, 2012; Granic, O'Hara, Pepler, & Lewis, 2007; Isley, O'Neil, Clatfelter, & Parke, 1999; Rudy & Grusec, 2006).

However, parental behavior and affect might not have an equally large impact on the development of externalizing problems in all children. We know that children differ in how (strongly) they react to what goes on around them (Belsky & Pluess, 2009). Specifically, we know that children differ in their reactivity to certain parenting behaviors (e.g., Pluess & Belsky, 2010; Scott & O'Connor, 2012). These individual differences already express themselves at an early age and might be partly heritable. Over the last decade we have learned much about how children's genes contribute to such differences in reactivity to parenting (see for overviews Bakermans-Kranenburg & Van IJzendoorn, 2011; Belsky & Pluess, 2009; Van IJzendoorn, Belsky, & Bakermans-Kranenburg, 2012). Specifically, much attention was paid to the contribution of candidate genes that might influence dopamine and serotonin regulation and in turn contribute to individual differences in reactivity to the environment.

(Candidate-)Genes

The term 'candidate gene' refers to a specific gene that may be directly, and/or in interaction with the environment, related to psychopathology (including the *DRD4, DRD2, DAT1, 5-HTT, MAOA* and *COMT*). These genes have common variations, polymorphisms, which influence the expression of this gene. Specifically, studies have been interested in Single Nucleotide Polymorphisms (SNP's), a variation in a single nucleotide (i.e., DNA building block), and Variable Number Tandem Repeat Polymorphisms (VNTR's), a variation in which a short nucleotide sequence is repeated a variable number of times between individuals. An example of a SNP is a polymorphism of the *COMT* gene, coding for the *catechol-O-methyltransferase* enzyme, which breaks down neurotransmitters such as dopamine. The *COMT* Val/Met polymorphism results in a valine (i.e., Val, high activity) to methionine (i.e., Met, low activity) mutation. An example of a VNTR is a polymorphism of the serotonin transport gene *(*SLC6A4). This gene codes for serotonin transporters involved in the active clearance and termination of synaptic serotonin and has a linked polymorphic region: The *5-HTTLPR*. The *5-HTTLPR* polymorphism has two common variants typically defined as a "short-allele" (i.e., S-allele, low expressing) comprising 14 copies and a "long-allele" (i.e., L-allele, high expressing) comprising 16 copies.

Candidate Gene-by-Environment Interactions

There is increasing evidence that environmental and genetic risk factors work together in shaping behavior and development (Rutter, 2007; 2012; Rutter et al., 2003; Rutter, Moffit & Caspi, 2006). Therefore, the nature versus nurture debate has been put to rest and has made way for research on the interplay between nature and nurture. For example, we know that

specific risk factors might be more important for some children than for others. Genes can function as a predisposition for how strongly children respond to environmental adversity and environmental risk factors can "get under the skin" and alter children's neurobiological functioning. Nevertheless, these predictors have long been studied separately, leaving a trail of disconnected clues on how differential pathways to externalizing behaviors are shaped. One effort to change this is the investigation of candidate-gene-by-environment interactions (cG×E), which has created both a lot of excitement and criticism.

Theoretically, cG×E interactions can be seen as representations of the differential impact of the environment on child behavior and can take different "forms". One hypothesis on such a specific form has gained a lot of scientific attention: The differential susceptibility hypothesis (Belsky, 1997). The differential susceptibility hypothesis states that some individuals are more susceptible to environmental conditions in a "for better and for worse" manner, where the most "susceptible" individuals are disproportionately affected by both positive and negative environmental conditions. Such a crossover interaction distinguishes itself from other forms of interaction-effects, including "dual risk" and "vantage sensitivity". Duals risk arises when we assume a cumulative risk of environmental and child factors, where the most "vulnerable" individuals are disproportionately affected in an adverse manner by a negative environment but do not also benefit disproportionately from positive environmental conditions. Vantage sensitivity arises when we assume a cumulative beneficial effect of environmental and child factors, where the most ''sensitive" individuals are disproportionately affected in a vantage manner by a positive environment but do not also suffer disproportionately from negative environmental conditions (Pluess, 2015; Pluess & Belsky, 2013). To date, most studies on externalizing behavior focus on the cumulative negative effects of environmental risk, such as harsh parenting, and child characteristics, such as carrying the low activity allele of the *MAOA* gene. Therefore, these studies are unable to rule out that found cG×E represent differential susceptibility rather than dual risk. From an empirical perspective, this might mean that we wrongly label susceptible children as merely vulnerable. From a clinical perspective, this might mean that we miss important information on individual differences in susceptibility to environmental enrichment in the form of interventions (i.e., what works for whom), possibly causing under- or overestimation of intervention effectiveness.

Limitations of the Current Literature

Over the last decade and a half many interactions between, specifically dopaminergic and serotonergic, candidate genes and the environment have been reported in predicting externalizing problems (see for an overview, Bakermans-Kranenburg & Van IJzendoorn, 2011;Belsky & Pluess, 2009; Duncan & Keller, 2011; Van IJzendoorn et al., 2012; Van

IJzendoorn et al., 2011). Although these findings are very intriguing, they also raised much criticism. The field has been plagued by replication issues, publication bias, and critiques on the study designs used to test cG×E. One of the most important critiques is that most studies use a correlational design, which does not permit causal inferences and leaves us unable to rule out alternative explanations for the interactions found. For example, genotype and environment might be confounded (i.e., gene-environment correlation or *r*GE). Because children and parents partly share their genetics, harsh parenting and child externalizing behavior might be explained by the same (inherited) underlying genetics. Alternatively, children might evoke specific parenting strategies due to certain biological tendencies. Such alternative explanations can only be ruled out using an experimental design, in which children are randomly assigned to a certain environmental condition. Moreover, by manipulating the environment such designs increase differences between children in different experimental conditions and in turn power to detect possible cG×E interactions.

Besides limitations due to study design, a lack of insight into how cG×E interactions work (i.e., the underlying mechanisms) makes the implications of the earlier findings unclear. At present, looking at cG×E findings is like looking at a "black box", in that we are only aware of what goes in and what comes out. Insights into 'how genes get outside the skin', (Reiss & Leve, 2007) are of great empirical and clinical importance. From an empirical perspective, it can increase our knowledge of differential (biological) pathways leading to externalizing problems. From a clinical perspective, this knowledge could be used to tailor interventions by indicating the needed clinical focus, increasing their effectiveness (Matthys, Vanderschuren, Schutter, & Lochman, 2012).

The Current Dissertation

The aims of this dissertation are (1) to create an overview of literature on cG×E between family adversity and polymorphisms of the candidate genes *MAOA*, *DRD4*, *DRD2*, *DAT1*, *5-HTT*, and *COMT* in externalizing behavior problems and to extend previous findings on cG×E using a randomized controlled trial (the ORCHIDS study; Chapters 3-6); (2) to form theoretically based hypotheses on mechanisms underlying cG×E in externalizing behavior problems and; (3) to experimentally test these hypotheses. **Chapter 2** presents a systematic review of the literature on cG×E in externalizing behavior problems. In the same paper extant literature on genetics, (neuro)biology, and psychology will be used to form hypotheses on possible underlying mechanisms. In order to test such mechanisms a randomized trial and an experiment will be conducted using two independent samples. In both samples buccal swaps will be collected from children in order to genotype several candidate polymorphisms.

First, concerning the randomized controlled trial, Chapters 3 through 6 are based on the *O*bservational *R*andomized controlled trial of *CHI*ldhood *D*ifferential *S*usceptibility (ORCHIDS study) in which 387 parent-child dyads will participate in a randomized controlled trial. The trial has been registered in the Netherlands Trial Registry (NTR-TC-3594). Families with children between 4 and 8 years (*M*age = 6.21 years; 55.30 % boys) old will be screened for child externalizing behavior problems. Eligible families (i.e., scoring at or above the 75th percentile of their cohort) will be randomized into a control (i.e., care as usual) or intervention group (i.e., The Incredible Years or IY program). Parent and child behavior will be reported on by parents as well as observed during recorded parent-child interactions. **Chapter 3** presents the study protocol published before conducting the trial. In **Chapter 4** we will answer the question whether IY is effective in decreasing child externalizing problem behavior and negative parenting and increasing child socially desirable behavior and positive parenting, and whether the intervention effects are moderated by putative socio-demographical and intervention-factors. This chapter includes a comprehensive description of our procedure and sample. **Chapter 5** focuses on praise and dopamine related reward sensitivity. In this Chapter we will answer the question whether previously found gene-by-intervention effects (G×I) can be explained by differential effects of parents' use of praise. **Chapter 6** focuses on parental affect and serotonin related emotional reactivity. In this Chapter we will answer the question whether the intervention effect tested in Chapter 3 is mediated by changes in parental affect and behavior. Furthermore, we will test whether these mechanisms of change are more important for some children than others due to their temperament or *5-HTTTLPR* genotype.

Second, concerning the experiment, in **Chapter 7** we will answer the question whether the *5-HTTLPR* polymorphism is related to individual differences in children's general emotional reactivity. To this end, an experimental study will be conducted including 521 parent-child dyads recruited at science center NEMO in Amsterdam. Children aged 7 to 12 (*M*age = 9.72 years; 52.5% boys) will be randomized and exposed to angry, happy or neutral dynamic facial expressions and vocalizations. Children's self-reported affective and measured motor emotional reactivity (*f*EMG measure) will be assessed. Parents will report on the emotional family climate through report on positive and negative parenting behavior.