Hovedoppgave

NTNU
Norges teknisk-naturvitenskapelige universitet
Fakultet for samfunns- og utdanningsvitenskap
Institutt for psykologi

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Current Knowledge of Markers, Mechanisms and Age Differences in Differential Susceptibility Theory

A semi-structured literature study

Hovedoppgave i Psykologi

Juli 2020

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Kunnskap for en bedre verden

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Author Note

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Abstract

This semi-structured literature study aimed to review recent research of some central markers, i.e. genetic markers, temperament and physiological reactivity, and hypothesized neurobiological and adaptive mechanisms of Differential Susceptibility Theory (DST), thereby providing an overview of the research field. Some markers seem to predict an increased susceptibility to environmental influences, for better and for worse. The amount of research supporting DST has increased the last decade, but a lot of studies aimed at testing DST also fail to support the theory. Gene x Environment (GxE) studies, which account for a vast amount of research on DST, have been subjected to criticism, questioning the validity of the findings supporting GxE effects. GxE studies are prone to false positives, and publication bias might also be a problem in GxE studies. However, limitations in research might also hide effects in line with DST. Knowledge of adaptive mechanisms, i.e. why and how differential susceptibility is formed and how it yields an adaptive advantage, is still scarce. However, researchers from various traditions have recently proposed adaptive mechanisms which overlap greatly. There is also little knowledge of neurobiological mechanisms, but various researchers have recently suggested neurobiological mechanisms of DST with overlapping elements, e.g. a lower sensory threshold, epigenetic processes and differences in perception. The present thesis also addresses whether differential susceptibility may be more pronounced in or restricted to a specific age. Currently, evidence is inconsistent, supporting both an age dependent susceptibility and susceptibility throughout the lifespan. In conclusion, many unknowns regarding markers, mechanisms and the importance of age in DST still exist, and further research is needed.

Today, it is widely recognized that children are differentially affected by their environment (Belsky & Pluess, 2013). Consequently, child development happens not only as a result of nature *and* nurture, but from the interaction between the two. However, researchers debate in what manner and to what degree individuals are differentially affected by their environment. It has been argued that research on child development has kept a one-sided, negative focus, concentrating on how children are differentially affected by adversity and hardship, while neglecting to investigate how children differ in reactions to positive rearing (Belsky & Pluess, 2009). Individuals are typically described as vulnerable or resilient, depending on how they react to stress (Belsky & Pluess, 2013; Rutter, 2012). During the past few decades, however, new emerging theories that challenge traditional views of risk and resilience have gained attention. Differential susceptibility theory (DST), first proposed by Belsky (1997), is one such theory. Although some still refer to DST as the differential susceptibility *hypothesis*, an increasing number of researchers now refer to it as differential susceptibility *theory* (DST; Belsky, 2015; Boyce, 2016; Ellis & Del Giudice, 2019). DST hypothesizes that some individuals are more susceptible to the environment, *for better and for worse*, and that *the very same markers* - i.e., genetics, temperament and physiological reactivity - underlie an individual susceptibility to both positive and negative environments, and subsequently positive and negative outcomes. According to DST, individuals formerly perceived as vulnerable could instead be viewed as highly malleable and susceptible to environmental influences (Belsky et al., 2009). Importantly, this implies that susceptible children would not only be protected from harm if raised in a supportive environment, but would also be expected to surpass their peers, potentially showing the least amount of psychological and behavioral problems, and possibly also a high degree of positive outcomes such as empathy, social skills and emotion regulation.

The aim of this thesis is to provide an overview of some central and current evidence of DST, as well as some recent theoretical advances in DST. This will be done by focusing on three important aspects of DST; markers, mechanisms and the possibility of age differences in DST. First, this thesis presents and discusses evidence of proposed *markers* of DST, i.e. individual factors that could imply a heightened susceptibility to the environment. There is still uncertainty surrounding which markers might increase susceptibility for better and for worse, and whether the proposed markers are sufficiently supported by research. Second, this thesis addresses current hypotheses of mechanisms of DST, i.e. neurobiological or adaptive processes which underlie and mediate differential susceptibility. Lastly, recent research and theoretical advances in DST suggest that DST might be more evident in early childhood,

although some research also show evidence of DST in adulthood. (e.g. Cicchetti, Toth, & Handley, 2015). Even though DST could theoretically apply to all age groups, the moderating effect of age has not yet been thoroughly investigated (Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2011). The present thesis aims to address the possible importance of age in DST. Summarizing central and current knowledge of DST will create an overview of the field, possibly unveiling knowledge gaps and guide future research.

Delimitations of the Present Thesis

As outlined above, the aim of the thesis is to give an overview of how current research supports or challenges central elements of DST, as well as current theoretical advances. Such overview will of course compromise in-depth descriptions and discussions. It is beyond the scope of this thesis to write a structured review including all relevant literature. Instead, this semi-structured literature study will elucidate central elements of DST through presenting and discussing examples of central and recent research of the theory. Some of the discussion will be carried out along with the presentation of markers and mechanisms to facilitate understanding.

The presentation of markers is limited to the most studied and known markers, i.e. the most studied genetic variations and the most studied markers of physiological reactivity. There are several hypothesized markers not evaluated in this thesis, e.g., the gene *FKBP5* (VanZomeren-Dohm, Pitula, Koss, Thomas, & Gunnar, 2015; Perez-Perez et al., 2018), prenatal exposure to androgens (Del Giudice et al., 2018), function of corticotrophin-releasing hormone (CRH; Moore & Depue, 2016) and opioid (OP) projection systems (Moore & Depue, 2016).

Even though markers of DST have been assessed by looking at various environmental factors and outcomes, I have chosen not to specify all environmental factors and outcomes in this review. This was done to limit the amount of details, thereby highlighting the main focus; whether DST is supported by research. A thorough evaluation of how discrepant findings may be influenced by type of environment and outcome would be necessary when answering whether and to what degree DST is domain specific or domain general, but that is not the aim of this thesis. However, the question of whether DST is domain specific will be discussed, as it relates to the three research questions elucidated in the current thesis.

Given the scope of this thesis, an in-depth presentation of neurobiological mechanisms at the synaptic or genetic level will not be provided, but some overarching biological explanations of mechanisms in DST will be addressed. The literature of mechanisms included

in the current thesis reviews current theoretical advances of DST, not empirical evidence of mechanisms of DST.

Differential Susceptibility Theory

Differential susceptibility Theory (DST) is a theory of developmental psychology which states that some individuals might be more susceptible to environmental influences, *for better and for worse* (Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2007), because they demonstrate a heightened neurological plasticity to positive as well as negative environments. Apart from the claim that some individuals are more influenced by their environment than others, most elements of the theory are constantly being revised and refined in response to new research findings. Yet, there are some core elements of DST. DST claims that certain *individual characteristics* will make a person more susceptible to environmental influences. These characteristics are referred to as *markers* of DST. What environments DST refer to and what outcomes are defined as "better" and "worse" are not clearly defined. However, environments and outcomes are traditionally limited to psychological, emotional or social. Genetic makeup was initially thought to be the most predictive factor of differential susceptibility (Belsky & Pluess, 2009), i.e. the degree of susceptibility was thought to be rather fixed depending on genetics. Today, researchers acknowledge that differential susceptibility might be shaped by early environmental experiences, dependent on a genetic disposition (Ellis et al., 2011). Indeed, differential susceptibility might even be shaped prenatally (Pluess & Belsky, 2011; Hartman & Belsky, 2018; Conradt et al., 2018; Tung, Morgan, Norona, & Lee, 2017). It is hypothesized that heightened susceptibility might be especially prevalent in individuals who experienced highly stressful or highly protective early environments (Boyce & Ellis, 2005; Ellis & Boyce, 2008).

The differential susceptibility hypothesis was first proposed by Jay Belsky (1997). Belsky, Hsieh and Crnic (1998) argued that many earlier studies implicitly suggested that children were equally affected by their environment and that research was dominated by a negative focus, claiming that some children were especially affected by negative environments only. Belsky proposed, based on theoretical and logical reasoning, that natural selection would not favour a trait that was merely detrimental. Instead, Belsky proposed that children could vary in their susceptibility to rearing influences (1997), for better and for worse. Belsky observed that several studies of the temperament trait *negative emotionality/affectivity*, i.e. children prone to anger, sadness and unsoothability (Rothbart, Ahadi, Hershey, & Fisher, 2001) indicated a "for better and for worse" pattern: Children with a high degree of negative affect seemed to show worse outcomes in stressful environments

but better outcomes in supportive environments, indicating a differential susceptibility effect (Belsky et al., 1998; Belsky, 2005). These observations, along with logical reasoning, led Belsky to propose that some children may be more susceptible to rearing experiences for better and for worse, not merely vulnerable.

Theoretical background of DST. DST has its basis in evolutionary psychology (Hartman & Belsky, 2016; Belsky & Pluess, 2009; Belsky et al., 1998). Belsky and colleagues (1998; 2009) argued that heightened susceptibility to adverse environments would only persist in evolution if it has an adaptive advantage as well. This adaptive advantage was hypothesized to be a more plastic brain, potentially benefiting more from supportive environments. The theory of evolution states that species change over time due to natural selection. A quality or trait that enhances survival will be passed on to later generations. Such traits are referred to as adaptive traits. This implies that the trait has more benefits than downsides for survival, not that it is without costs (Ellis & Del Giudice, 2019). An important aspect of this is that natural selection favours traits that enhance the survival of the species, not merely the individual. Some traits might only be adaptive if present in some, but not all, individuals of the species, which might be nature's way of hedging its bets (Belsky, 1997; Ellis et al., 2011). A group of highly malleable individuals in a species will ensure the survival of the species when faced with an environment that requires the species to adapt. At the same time, the species would be vulnerable if all individuals in a species were vulnerable to hardship and change. Thus, the differential susceptibility hypothesis claimed that differences in susceptibility would strengthen the survival of the species by meeting different demands of the environment.

Markers of DST. Markers of DST are usually classified into three categories, namely genetics, temperament and/or physiological reactivity (Belsky & Pluess, 2009). In the following I will provide a presentation of these three categories and how they apply to research on DST.

Genetics. One of the reasons for individual variations in susceptibility to the environment may lie in genetic makeup. Several genetic variants have been proposed as potential markers of DST (Belsky et al., 2009). Belsky hypothesized that some genetic variants would make an individual more susceptible to the environment, and that susceptibility would increase with a higher number of such "susceptibility genes" (Belsky & Beaver, 2011). Since then, a great deal of research aiming to test DST has focused on genetics. As genetic studies are referred to throughout this thesis, it is necessary to briefly explain some central, genetic concepts.

Genetic variation. Each individual has a different genetic makeup. One common way to study genetic variations is by examining variations in *Single nucleotide polymorphisms* (SNPs) and *Variable number tandem repeats* (VNTRs), which are small parts of a DNA sequence, varying for each individual (Marshall, 1997). All humans possess the same genes, but what makes us different from one another is different genetic variants of the same gene, referred to as alleles (Hartl, 2011). Each individual receives one allele from each parent. A specific genetic variant of a gene often consists of two alleles, and individuals are either homozygous (identical alleles, e.g., AA), or heterozygous (two different alleles, e.g. AG)(Hartl, 2011). Various combinations of alleles have been hypothesized to be linked to DST, as will be outlined below.

Gene by environment. Gene by environment (GxE) studies are inquiries designed to test how genetic variations and environmental factors interact to shape an outcome (Dick et al., 2015). To date, GxE is perhaps the most common design when investigating DST and genetic markers. Early research on potential genetic markers of DST relied heavily on *candidate gene studies*, investigating the effect of a single genetic variation and a specific environmental factor in GxE studies (Dick et al., 2015), also referred to as candidate GxE (cGxE) studies. For this reason, many studies presented later in the section of genetic markers are candidate gene studies.

Polygenic studies. Although cGxE studies are still relevant, an increasing amount of genetic studies now look at polygenic susceptibility effects; the effect of a combined score of several susceptibility genes on a given outcome (Assary, Vincent, Keers, & Pluess, 2018). Each single genetic variation probably contributes a very small amount to a phenotype, while polygenic studies show that susceptibility might increase with more susceptibility genes (Belsky & Beaver, 2011). Evidence from polygenic research is therefore a valuable contribution to evidence of DST markers. Advancement in research methods and new knowledge about the human genome allows researchers to investigate how formerly less known genes are related to psychological and behavioral outcomes, and study the effects of genes combined (Donnelly, 2008; Assary et al., 2018).

Temperament. *Temperament* is another possible marker of DST. Temperament can be defined as "innate individual differences in behavioral and emotional tendencies that appear in infancy and are relatively stable across context and time" (Clauss, Avery, & Blackford, 2015), but may also change with time and environmental exposure (Cruz, Abreu-Lima, Canario, & Burchinal, 2018).The concept of temperament is conceptualized in various ways.

The most important conceptualizations regarding research on DST will therefore be presented briefly.

One common conceptualization of temperament divides the concept into three subdimensions; *negative emotionality/affectivity*, *surgency/extraversion* (i.e. high activity level, impulsivity and high intensity pleasure) and *effortful control* (i.e. low intensity pleasure, attentional focusing and inhibitory control)(Rothbart et al., 2001), with negative emotionality being the most studied in DST. Other researchers have conceptualized temperament on a scale from easy to difficult, measuring various aspects of temperament, i.e. attention, activity, sociability, adaptability and emotional expression, measured with Child Personality Scale (CPS; Dibble & Cohen, 1974). Overall temperament is scored by summing up these aspects of temperament, ranging from high scores indicating easy temperament, to low scores indicating difficult temperament (Cruz et al., 2018).

Temperament was one of the earliest suspected markers of DST, specifically a difficult temperament or children characterized by negative emotionality. Difficult temperament has long been identified as a potential risk factor for developing psychiatric disorders (Bajgarova & Stuchlikova, 2019), but may be a susceptibility factor, not merely a risk factor.

Physiological reactivity. When studying DST through the lens of physiological reactivity, reactivity is measured in physiological systems related to stress, or *stress response systems* (Del Giudice, Ellis, & Shirtcliff, 2011), such as hypothalamic-pituitary-adrenal (HPA) axis activity and autonomic nervous system (ANS) activity. The autonomic nervous system is divided into the sympathetic (SNS) and parasympathetic nervous system (PNS), these systems are involved in increasing and down-regulating arousal, respectively (Allegrini, Evans, Rooij, Greaves-lord, & Huizink, 2019).

Activity of stress response systems is assessed through measuring variables like the stress hormone cortisol (Kalomiris, Phelps, & Kiel, 2019), heart rate (Somers, Ibrahim, & Luecken, 2017) and respiratory sinus arrhythmia, a measure of heart rate variability (Obradovic, 2012). Measuring the level of cortisol is used to capture the activity of the hypothalamic-pituitary-adrenal (HPA) axis, which is activated in response to stress. Every individual differs regarding how much resting cortisol they generate throughout a day (Gunnar & Quevedo, 2007). In addition, individuals differ in cortisol reactivity, i.e. the degree of cortisol released in response to stress or uncertainty (Kalomiris et al., 2019). Both resting cortisol and cortisol reactivity have been studied as markers of DST and are therefore included in the present review of studies. Heart rate (HR) is considered a measure of SNS, or

the balance between SNS and PNS (Zandstra et al., 2018), and is also a hypothesized marker of DST. Lastly, respiratory sinus arrhythmia (RSA) is a proposed marker of DST. RSA is heart rate variability when breathing in and out. It is considered a measure of parasympathetic (PSN) functioning (Somers, Jewell, Ibrahim, & Luecken, 2019).

Mechanisms of DST. While a lot of potential markers of DST have been identified, researchers still ponder what mechanisms might underlie DST, and state the importance of investigating it further (Belsky et al., 2007; Greven et al., 2019; Belsky & van IJzendoorn, 2017). The underlying mechanisms are, at most, only partially understood. "Mechanisms" in the context of DST are studied on several levels, ranging from assessing observable neurobiological processes in the brain (Boyce, 2016) to considering higher order mechanisms, i.e. what motivational or adaptive systems might underlie susceptibility (Ellis & Del Giudice, 2019). This might include how, when and why differential susceptibility could benefit the individual and improve adaptation to environmental demands. In the present thesis, "motivational" or "adaptive" mechanisms are referred to as *adaptive mechanisms*. It should be noted that markers and neurobiological mechanisms are not necessarily separable. Boyce (2016) argues that studying physiological reactivity is in many ways the first step in assessing mechanisms, since there is no clear-cut difference between physiological reactivity and neurobiological mechanisms underlying DST. It is also important to emphasize that DST does not contain a defined set of mechanisms. Rather, researchers continuously investigate possible new mechanisms of DST.

The importance of age in DST. An important but still unanswered question in the DST literature is whether differential susceptibility is evident in childhood only or throughout the lifespan. The brains of young children are highly plastic and fast developing (DeMaster et al., 2019). As DST is a theory of heightened neural plasticity in certain individuals, some researchers have proposed that DST could be more pronounced in early childhood when plasticity is higher. However, other researchers have claimed to find evidence of differential susceptibility in adolescence and adulthood too. In other words, the question of whether and to what degree age matters in DST is uncertain, which will be demonstrated in the current thesis.

The importance of DST research. Further research on DST is important for several reasons. First and foremost, it contributes to the understanding of how individuals may be differentially affected by their environment, which is central to understanding both normal developmental pathways and the development of psychopathology. Investigating DST could also have consequences for how the effect of therapeutic methods is measured. Neglecting a

differential susceptibility effect could hide large treatment effects for some individuals and show false positive effects for others (Belsky, 1997, 2007; Bakermans-Kranenburg & van IJzendoorn, 2015). DST holds that some individuals might benefit a great deal from treatment, and that other individuals might be more resilient and less malleable, and consequently benefit less from treatment. Hence, knowledge of differential susceptibility could possibly help allocate scarce resources in a more effective way. Whether age differences exist in DST is another important theme, because it could have implications for early intervention in childhood: If children in stressful environments are especially susceptible for positive support - but mainly for a short period - this time window should be used as well as possible.

DST in relation to comparable theories. Before presenting current evidence of DST, one important distinction needs to be clarified: The difference between *differential susceptibility theory* and the *concept* of being differentially affected by/susceptible to the environment for better and for worse. This thesis focuses on DST, i.e. the contributions of Belsky and colleagues (1997; 1998), as well as later research that uses the same framework. A defining element of DST is the hypothesis that some individuals are more affected by their environment for better and for worse. However, the recognition that some individuals might be more susceptible to both positive and negative experiences is not exclusive to DST. Two additional theories were developed parallel to DST, sharing the core element that some individuals might be differentially susceptible for better *and* for worse. These theories are Biological sensitivity to Context theory (BSCT; Boyce & Ellis, 2005) and the theory of Sensory Processing Sensitivity (SPS; Aron & Aron, 1997). In addition, recent papers have used other terms like «Environmental Sensitivity» to describe the phenomenon of sensitivity for better and for worse (Pluess, 2015; Moore & Depue, 2016). It should be noted that it is not simple to distinguish DST from differential susceptibility to the environment as a concept. Researchers have sought to integrate the three different theories (Ellis et al., 2011; Boyce, 2016; Pluess, 2015; Greven et al., 2019) into one overarching theory. In addition, DST is constantly being revisited and expanded, integrating empirical evidence from other traditions. In sum, there are substantial overlap between these theories, but there are also certain differences in research focus and definitions, such as whether differential susceptibility is dimensional or not or what markers are the most studied. When presenting findings of markers, the present thesis focuses on DST exclusively.

Most research on the *concept* of differential susceptibility use DST as a term and framework when investigating potential markers. Notably though, researchers from other

traditions have made important contributions to the understanding of potential mechanisms of differential susceptibility and the relative importance of age, arguably more than Belsky. I will therefore include contributions from other research traditions, using other terms than DST, when presenting potential mechanisms and discussing how age might be relevant when studying DST. However, all the presented perspectives on mechanisms share the notion that individuals may be susceptible for better and for worse, and thus will contribute to understanding potential mechanisms in DST.

DST challenges existing views of risk and resilience. Diathesis-stress theory/dual-risk theory (Monroe & Simons, 1991; Zuckerman, 1999) had long governed research on child development, claiming that some children were more vulnerable than others if they possessed certain risk factors. Children less affected by adversity were typically considered resilient (Rutter, 2012). Diathesis-stress theory suggests that supportive environments can help vulnerable individuals reach the same level of healthy development as their less vulnerable counterparts, but not excel if being reared in a supportive environment. Instead of viewing resilience as a protecting factor, DST hypothesized that resilience could be a consequence of a less susceptible brain (Belsky & Pluess, 2013). Resilient individuals were regarded as more fixed (i.e. less affected by their environment), making resilient individuals less affected by negative experience as well as benefitting less from positive environments. Moreover, factors that within diathesis-stress theorizing was described as «risky», i.e. genes or temperament, could instead be regarded as possibility factors (Belsky et al., 2009), allowing the susceptible individuals to have even less emotional and behavioral problems than their less susceptible counterparts, given a supportive environment. Factors previously viewed as risk factors would make the individual more flexible, and thus function as a potentially beneficial factor.

Lastly, some research testing DST has demonstrated that some individuals seem to be more susceptible to positive experience than others, while being less susceptible to negative experience. This has been named vantage sensitivity (Pluess & Belsky, 2013). Vantage sensitivity is mentioned throughout this thesis when presenting research findings contrasting DST and in the discussion.

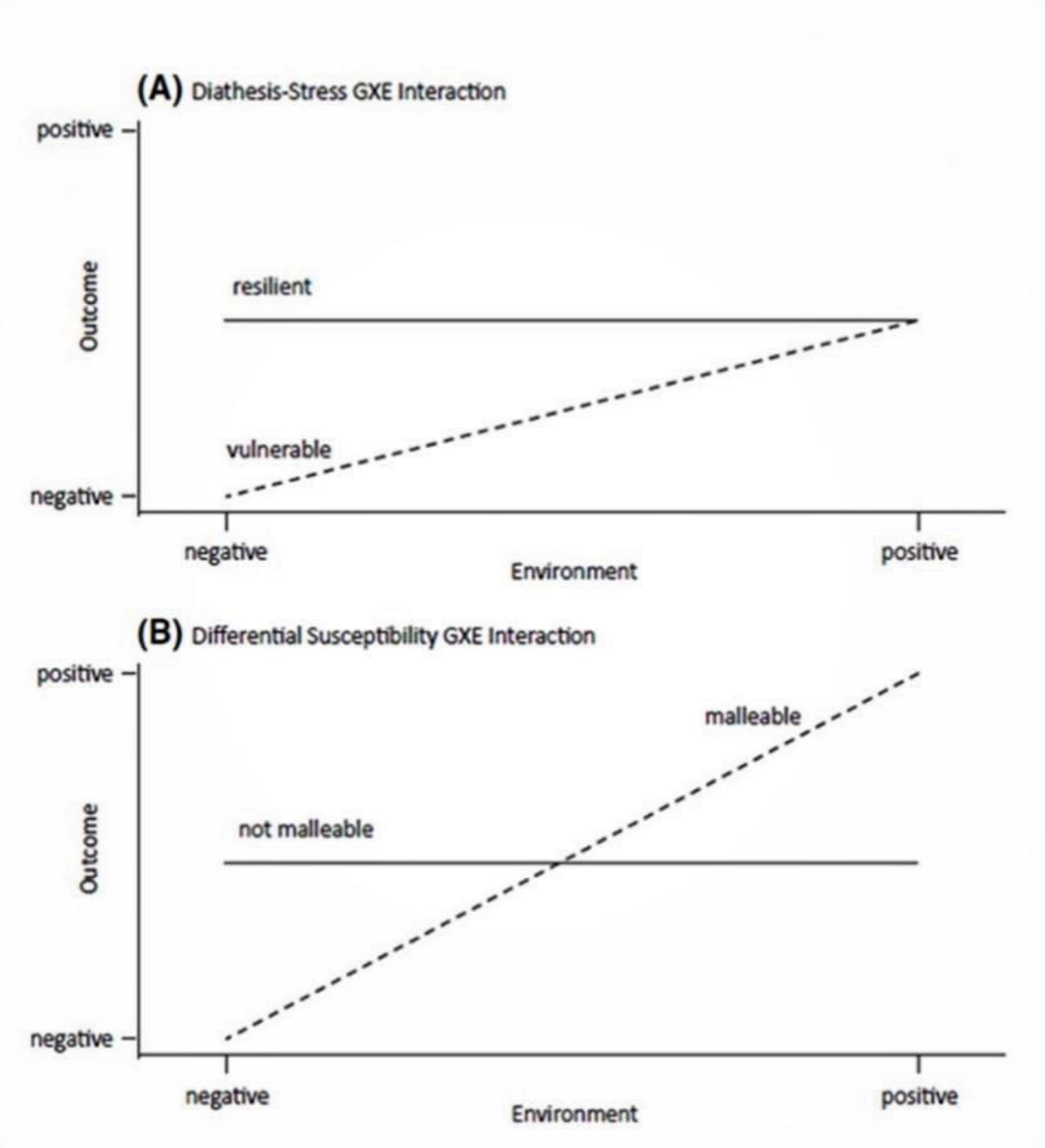


Figure 1 GxE interactions of diathesis-stress patterns and differential susceptibility patterns (The figure is retrieved from Belsky, Pluess & Widaman, 2013, with permission from the Journal of Child Psychology and Psychiatry).

Summary and aims of the current thesis

DST grants important perspectives on development and psychopathology, possibly challenging existing views of risk and resilience. Knowledge of this theory may have important implications for research and treatment practices. This thesis aims to give an overview of some central elements of DST and advancements in research by answering three research questions. The research questions that I will attempt to answer are as follows: *"To what degree does current evidence support proposed markers of DST?", "What are current evidence and hypotheses of mechanisms in DST?" and "What are current evidence and hypotheses of the importance of age in DST?".*

Method

The broad scope of this thesis, as well as the research questions above, guided the search for relevant literature. As noted, a full review of all relevant literature would be too vast, hence only a selection of papers was included, based on the procedure outlined below.

Search Process, Inclusion and Exclusion Criteria

Web of science was used as database. Compared to many other fields, the research body of DST is relatively small. Because of this, as many potentially relevant articles as possible were included from the initial search. "Differential susceptibility" was applied as keyword in the first search. Only papers clearly not related to this specific developmental psychology theory were excluded at this stage, such as studies related to immunology, microbiology, applied microbiology and agronomy. The search was limited to papers published after 1997, as this was the year the term "differential susceptibility" was first used by Belsky (1997). Only articles published in English were included in the present work.

After excluding the fields of immunology, microbiology, applied microbiology, agronomy, and articles written before 1997, the search yielded 2369 hits. As a second step, studies focusing on somatic disease, problems related to old age, criminology or other environmental areas like climate change and pollution were manually excluded based on the title or abstract of the papers, which resulted in a total number of 923 potentially relevant papers. In a third step, two more searches were conducted, one for "biological sensitivity to context" and one for "sensory processing sensitivity", because both these theories have made important contributions to DST, especially mechanisms. This yielded 44 and 74 additional hits, and this total number of 1041 papers were used as a pool of research from which relevant papers were selected.

Selection of Relevant Articles

After creating a database of all potentially relevant articles, specific searches for each research questions were carried out. For instance, each included marker was searched for individually. To exemplify, I will use the gene *DRD4* to demonstrate how searches for markers and mechanisms were carried out. When assessing the genetic marker *DRD4*, abstracts that contained the words "*DRD4*" or "Dopamine receptor *D4*" were searched for. This yielded 42 hits in total. I also searched the abstracts of these 42 papers for "review". Of the 42 studies, 7 studies were reviews. It should be noted that most of the studies had small samples and were carried out in the first half of the last decade. This is true for research on most markers. For instance, only 7 of the articles on *DRD4* were published in 2016 or later. Evidence of other genetic markers, physiological reactivity, i.e. cortisol, heart rate and respiratory sinus arrhythmia, temperament and mechanisms were searched for in a similar way. Notably, a few papers were also identified later, mostly from references in other papers, and mostly regarding potential mechanisms of DST.

Most research on DST has focused on children and, to a lesser extent, adolescents. Hence, most research presented in this thesis is focused on children and adolescents. However, in order to address the third research question, which assesses differences in differential susceptibility depending on age, the thesis is not restricted to one age group. A few studies on adults are also included to demonstrate potential age differences.

Some research on DST markers have been summarized in more recent reviews and meta-analyses. Even though some reviews and meta-analyses of DST exist, there are not enough of them to limit this thesis to these few. Candidate GxE (cGxE) studies are therefore included to give more examples of research concerned with DST. The most recent cGxE studies are prioritized over older studies, but some older studies have been included when the research base of a marker is scarce.

In addition to present studies that supported DST, I wanted to demonstrate that the evidence of DST to date is diverse and contradictory. I therefore also included studies that attempted and failed to find evidence of DST.

Results

To what Degree does Current Evidence Support Proposed Markers of DST?

Markers of DST have been much more empirically tested than mechanisms. DST holds that a marker moderates the relationship between environmental influence and outcomes in a for better and for worse manner. Consequently, testing whether a marker influences how and to what degree individuals are affected by their environment is at the core of DST research. The first research question will be answered by presenting evidence of the

three categories of markers, i.e. genetics, temperament and physiological reactivity, as well as discussing the limitations of the included studies.

Candidate GxE studies.

Dopaminergic gene variants. The dopaminergic system is related to reward sensitivity, attention and motivation (Belsky & Pluess, 2009), and certain genetic variants of the dopaminergic system are associated with psychiatric disorders (Moore & Depue, 2016). This has made some dopaminergic genes hypothesized markers of susceptibility (Bakermans-Kranenburg & van IJzendoorn, 2011), in that dopaminergic variation potentially grants a heightened susceptibility for reward cues and positive experience in addition to potential risk associated with some gene variants (Moore & Depue, 2016).

DRD4. One of the most extensively researched genetic variations in relation to DST is the 7-repeat polymorphism of the dopamine receptor *D4* (*DRD4*). Several studies have found support for DST in interactions between various environments and outcomes, moderated by *DRD4* (Bakermans-Kranenburg & van IJzendoorn, 2006; Levitan et al., 2017; Silveira et al., 2016), as well as a review that included various environmental predictors and different aspects of prosocial behavior (Jiang, Chew, & Ebstein, 2013). However, other studies have failed to find evidence of DST, and instead found contradicting evidence. For instance, one study found evidence for diathesis-stress rather than DST (King et al., 2016). Windhorst and colleagues (2015) found evidence for DST in 14 months old children, but not at 36 or 48 months. One study found evidence of vantage sensitivity in 7-repeat carriers (Cho, Kogan, & Brody, 2016). These results demonstrate various possible moderating effects of the *DRD4 7*-repeat allele.

DRD2. Dopamine receptor *D2* has also been studied as a potential marker of DST. Perhaps the most studied polymorphism in *DRD2* is TaqIA (Cao et al., 2018). Carriers of the A1 (T) allele of the TaqIA polymorphism have been hypothesized to be more susceptible than A2 allele carriers. Several studies have supported the TaqIA A1 allele as a susceptibility marker (Lee, Brooks-Gunn, McLanahan, Notterman, & Garfinkel, 2013; Zhang et al., 2015; Fine et al., 2016). However, other studies have failed to find GxE effects of the A1 allele (Villani et al., 2018; Cao et al., 2018). Hence, evidence is inconclusive.

DAT1. The 10-repeat allele of the *DAT1* gene, also known as SLC6A3, is also a potential susceptibility marker. Several studies have showed evidence of differential susceptibility in individuals with the *DAT1* 10-repeat allele (e.g. Villani et al., 2018; Stogner, 2015). Another study found indications of vantage sensitivity to school environment in 10-repeat carriers (Fine et al., 2016). Yet another study found no evidence for differential

susceptibility of the *DAT1* gene, and rather found evidence for the diathesis-stress model (Davies, Cicchetti, & Hentges, 2015). Research on the 10-repeat allele of *DAT1* demonstrate that it might moderate environmental influence, but the manner in which it does is uncertain.

MAOA. The monoamine oxidase A (*MAOA*) gene, coding for the MAOA enzyme, is also a proposed potential marker of DST, especially the low (L) activity *MAOA*-uVNTR allele in male carriers. The attention was brought to *MAOA* as a potential moderator of environmental influence in GxE studies by Caspi and colleagues (2002). They found *MAOA* to moderate the relationship between environmental influence and antisocial personality traits. The *MAOA* gene has ever since been extensively studied in relation to antisocial behavior, as evident in a review by Nilsson, Aslund, Comasco, & Oreland (2018), which suggests that variants of *MAOA* may heighten susceptibility to the environment for better and for worse.

The *MAOA* gene is located on the X-chromosome, hence females have two alleles while males have only one (Nilsson et al., 2018). Reviews have found indications of how *MAOA* might demonstrate sex differences in DST. Specifically, male carriers of the low (L) activity allele show heightened susceptibility, while female carriers of the high (H) activity allele show heightened susceptibility (Weeland, Overbeek, Castro, & Matthys, 2015; Nilsson et al., 2018). Another study found similar sex differences, demonstrating that boys with the L allele were more susceptible to their mother's engagement and stress than their H carrying counterparts, supporting DST (Liu et al., 2017). This effect was not present in girls. The relationship found resembled diathesis-stress rather than DST. These findings demonstrate that sex differences in DST might exist.

COMT. The *COMT* gene coding for enzyme Catechol-O-Methyltransferase (COMT), has been studied as a potential marker of DST, especially the Val158Met polymorphism (Cao, Cao, & Chen, 2019). The Met allele has in several studies been supported as a marker of DST (Kok et al., 2013; Zhang, Cao, Wang, Ji, & Cao, 2016; Laucht et al., 2012). However, studies have yielded different findings regarding which allelic variant should be considered a marker of susceptibility. Some studies have found evidence for Val/Val homozygous being more susceptible to the environment, for instance in the development of aggression (Hygen et al., 2015; Tuvblad et al., 2016), whereas others have found indications of sex differences concerning which allele is a susceptibility marker (Sulik et al., 2015), showing that Met/Met is a susceptibility marker for boys, while girls carrying the Val allele were more susceptible.

In 2019, Cao and colleagues carried out a meta-analysis of GxE studies researching the *COMT* Val158Met, in which they included the studies mentioned above. However, the meta-analysis showed no evidence of DST in Val homozygous or Met allele carriers (Cao et

al., 2019). One limitation of the study is that the authors did not control for potential sexual dimorphism, even though several studies indicate a sex difference for which allele is a susceptibility marker.

Serotonergic gene variant (5-HTTLPR). The neurotransmitter serotonin is involved in many different functions in the brain and is for instance known for being related to emotion-regulation (Aslund & Nilsson, 2018). The 5-*HTTLPR* polymorphism is one of the most studied potential genetic markers of DST.

Several studies show support for DST when investigating the short allele (S) of *5-HTTLPR* (Pluess, Belsky, Way, & Taylor, 2010; Baptista, Belsky, Mesquita, & Soares, 2017; Viddal, Berg-Nielsen, Belsky, & Wichstrom, 2017). One study even demonstrated that an intervention that started prenatally would increase the likelihood for secure attachment between mother and child, but only for the children who possessed one or two of the S allele of the *5-HTTLPR* (Morgan et al., 2017). The study supported DST, as S allele carriers in the control group were also the least likely to develop secure attachment.

Even though several studies show evidence of differential susceptibility for the S allele, other studies do not. In a large meta-analysis from 2017 (n=38802), consistent of European participants, Culverhouse and colleagues (2017) investigated the hypothesized interaction effect between stressful life events and depressive symptoms, with the S allele in *5-HTTLPR* as a moderator. They found no significant interaction effects. Another study (Mesquita et al., 2015) investigated children who were SS homozygous growing up in families or institutions. The results supported diathesis-stress, not DST. One study found sex differences; males homozygous for the Long (L) allele and females homozygous for the S allele were susceptible for better and for worse (Aslund & Nilsson, 2018). A meta-analysis from 2012 (van IJzendoorn, Belsky & Bakermans-Kranenburg) found support for DST only when investigating Caucasian participants, and diathesis-stress in other ethnicities. In summary, the S allele of the *5-HTTLPR* gene has been extensively studied, but the findings are still somewhat inconclusive, and findings may be moderated by other factors like sex or ethnicity.

Brain-derived neurotrophic factor. Brain-derived neurotrophic factor (*BDNF*) gene has also been studied as a potential DST marker. Studies have found that Val allele carriers demonstrate a differential susceptibility pattern to mother's warmth-reasoning on symptoms of anxiety and depression (Chen, Yu, Liu, Zhang, & Zhang, 2015; Zhang et al., 2016). However, other studies have found evidence of the Met allele as the strongest susceptibility marker (Miu et al., 2017; Meyer et al., 2018), while another study found no moderating effect

of *BDNF* (Mesquita et al., 2015). Like other studies of genetic variants, different allelic variants are supported as markers of susceptibility.

The oxytocin receptor gene. Oxytocin has been associated with social and reproductive behavior (Flasbeck, Moser, Kumsta, & Brüne, 2018). Variations in the oxytocin receptor (*OXTR*) gene, especially the SNP rs53576, have been a hypothesized marker of differential susceptibility. Some studies have found evidence for the A allele of rs53576 being a susceptibility marker (Hammen, Bower, & Cole, 2015; Flasbeck et al., 2018; Hygen et al., 2017). In contrast, one study found evidence for GG homozygotes being more sensitive than A carriers, demonstrating that social problems was a stronger moderator of the relationship between relational aggression and depression in GG homozygotes than in A carriers (Kushner, Herzhoff, Vrshek-Schallhorn, & Tackett, 2018). This study supported diathesis-stress, not DST, but the authors emphasize that they did not test for supportive and protective factors and suggest that GG homozygous might as well be susceptible for better and for worse. Another group of researchers investigated two other SNPs related to the oxytocin gene; rs4813625 and rs2770378 (Olofsdotter, Aslund, Furmark, Comasco, & Nilsson, 2018). They found evidence for DST linked to rs4813625, while variations in rs2770378 more closely resembled diathesis-stress. Again, there is great uncertainty surrounding which alleles and polymorphisms may influence susceptibility, and in what way.

Beyond single genes.

Genome wide association studies. Genome-wide association studies (GWAS) apply a relatively new design investigating millions of genetic variations in association with various phenotypes simultaneously (Donnelly, 2008), as opposed to research designs such as cGxE. One limitation in cGxE studies is that a few included genetic variants are selected based on hypotheses of genetic variants that are already much studied (Assary et al., 2018), and cGxE studies commonly lack testing of less known genetic variants that might be markers of DST. Consequently, potential genetic markers might go unnoticed just because they were never suspected as markers. The main advantage in GWAS is the ability to test for many genetic variations, not having to select a few candidates, thereby overcoming selection bias. GWAS now allows researchers to test the majority of known SNPs simultaneously.

There are still some limitations of GWAS regarding DST. GWAS measures main effects of each SNP on a phenotype, i.e. whether a SNP predicts an outcome regardless of environment, and thereby does not allow for investigating GxE interaction effects (Keers et al., 2016). DST hypothesizes that proposed markers of DST, e.g. SNPs, do not show consistent main effects, because the effect varies depending on environmental experience

(Keers et al., 2016). For this reason, researchers of DST need to utilize GWAS findings in a manner that will allow for testing the moderation of environmental influence.

In addition, GWAS measures the effect of each individual SNP, hence the effect sizes are often very small (Donnelly, 2008). GWAS does not assess interaction effects between multiple genes or how a combination of genes might increase the likelihood of an outcome. To measure previously mentioned polygenic effects, the findings from GWAS need to be formed into polygenic scores, also referred to as polygenic susceptibility scores (Belsky & van IJzendoorn, 2017).

Evidence of DST from GWAS. In 2016, Keers and colleagues conducted the first GWAS investigating DST. The study measured within-pair variability in monozygotic twins, overcoming the limitation of main effects in GWAS studies, since variations in phenotype in monozygotic twins are thought to be a good measure of non-shared environmental effects. It is therefore hypothesized that susceptibility genes would increase the difference in a measured outcome in monozygotic twins, because highly susceptible individuals are more affected by their non-shared environment (Keers et al., 2016). Further, Keers and colleagues created a polygenic susceptibility score out of the results of the identified SNPs. This score was investigated as a moderator of parenting and intervention effects on emotional problems. The results revealed indications of treatment-specific outcomes, more specifically that children with a high polygenic susceptibility score benefited more from intensive individual Cognitive Behavioral Therapy (CBT) than group-based CBT or brief parent-led CBT. These differences were not found in children with low polygenic susceptibility score, indicating that knowledge of DST could help tailor treatments to be more effective for specific genotypes (Keers et al., 2016). Another study by Lemery-Chalfant, Clifford, Dishion, Shaw, & Wilson (2018) applied the polygenic score identified by Keers and colleagues (2016) as a moderator to study internalizing symptoms in 10-year-olds and the effects of intervention. These results also supported DST.

In another study the researchers created a polygenic risk score derived from GWAS results and investigated the effect of Stressful life events on developing depression (Arnau-Soler et al., 2019). The findings revealed evidence of differential susceptibility in women, and diathesis-stress effects in men: A higher polygenic risk score proved protective for women, but not men, in the absence of stressful life events. This finding suggests a possibility of sex dependent effects, and further demonstrates the importance of controlling for possible moderating factors, e.g. sex.

***Genome wide environment interaction studies*.** In addition to GWAS, the very newly developed *genome wide environment interaction studies* (GWEIS) are considered important when studying how individual SNPs moderate the relationship between environment and outcome (Assary et al., 2018). GWEIS allows researchers to study interaction effects rather than just main effects captured by GWAS (Lemery-Chalfant et al., 2018). GWEIS are still in a preliminary state and to my knowledge no GWEIS have tested DST. However, GWEIS yields promising possibilities for studying interactions between millions of genetic variations and environmental factors and might become important in investigating DST.

Polygenic studies based on hypothesized susceptible genes. In addition to the polygenic studies derived from the GWAS mentioned above, other researchers have conducted studies with polygenic scores formed from known potential markers of susceptibility. Belsky and Beaver (2011) conducted a study several years ago where they tested whether a plasticity index of 5 hypothesized plasticity alleles would moderate the relationship between parenting and adolescence self-regulation. They found evidence of DST in males, but not females. The index consisted of the 10-repeat allele of *DAT1,* the A1 allele of *DRD2*, the 7-repeat allele of *DRD4*, the S allele of *5-HTTLPR*, and the 2-repeat/3-repeat alleles of *MAOA*. The authors recommended more polygenic studies in addition to candidate gene studies, and more researchers have followed in their footsteps. Even so, the number of studies on polygenic effects are still relatively scarce. Examples of polygenic studies investigating DST will be presented in the following.

Polygenic research on DST. In 2014, Masarik and colleagues created a polygenic score, summing together potential susceptibility alleles from *5-HTTLPR, DRD2, DRD4, DAT1* and *COMT*. They found that the polygenic score moderated the effect of hostile or positively engaged parenting on hostile or healthy romantic relationships in their adult children, supporting DST. Another study showed that the presence of both the *DRD4* 7-repeat allele and the *DAT1* 10-repeat allele moderated the relationship between low birth weight and negative emotionality in infancy in a DST manner (Tung et al., 2017). A high polygenic score has also been shown to contribute to highest or lowest BMI in the presence or absence of cumulative stress (Sun et al, 2018). One study examined the intervention effect from the behavioral parent training program *the incredible years* (IY) on externalizing behavior (Chhangur et al., 2017). Findings used a polygenic score consisting of variants of 5 different dopaminergic genes, namely *DRD4, DRD2, DAT1*, *MAOA* and *COMT*. The results indicated a larger decrease in externalizing problems following the intervention for children with a high polygenic susceptibility score. However, this effect was only evident in boys (Chhangur et al.,

2017). Thibodeau, Cicchetti and Rogosch (2015) used a polygenic score from variations of *DRD4*, *DRD2*, *DAT1* and *COMT* as a hypothesized moderator for impulsivity and antisocial behavior after child maltreatment. They found that a high polygenic score moderated the relationship between impulsivity and antisocial behavior. However, all participants came from disadvantaged socioeconomic backgrounds, both in the control group and individuals who had experienced maltreatment. The authors argue that this study only tested the negative end of the spectrum, as disadvantaged socioeconomic backgrounds may be regarded as negative environments. Nonetheless, their findings were indicative of DST in the lower spectrum of impulsivity, where a high polygenic score yielded the least impulsivity in the absence of maltreatment.

GxGxE studies. In addition to studying how the mere summation of many genes creates higher susceptibility as presented above, some researchers have sought to study interaction effects in genetic variations, making some genes moderators of the effect of other genes on environmental susceptibility. This is referred to as Gene X Gene interactions, or Gene x Gene x Environment interactions (Wang, Li, Deater-Deckard, & Zhang, 2018). If strong GxGxE interaction effects are present, a susceptibility gene will only contribute to plasticity, or contribute a smaller or greater amount, depending on whether another genetic variant is present. This effect could be hard to separate from just additive effects, especially since single gene effects can be small or seemingly not present without other susceptibility genes. Knowledge of GxG effects may still yield important insights to GxE research. One research group investigated GxGxE interaction effects between *MAOA*-uVNTR, *BDNF* Val66Met and *5-HTTLPR* and found support for DST (Nilsson, Comasco, Hodgins, Oreland, & Aslund, 2015). However, to my knowledge, very few studies have directly tested GxGxE effects in DST. There exist GxGxE studies of proposed susceptibility genes not directly testing DST. For instance, there is some evidence that individuals carrying the Val allele of the *COMT* gene, as well as the long (L) allele of *5-HTTLPR,* are less prone to stress in difficult environments (Conway et al., 2010). Another GxGxE study investigated two genetic polymorphisms; *MAOA* T941G and *COMT* Ala22/72Ser (Wang et al., 2018). They found that male carriers of at least one *COMT* T allele and MAOA T allele were significantly more affected by SLE than other genotypes. The outcome was aggressive behavior. Although none of these studies directly tested for better and for worse effects, they found evidence of possible moderating GxG effects, which is valuable knowledge in further DST research. Contrasting findings of DST research may be partly due to such effects.

Temperament. Several studies have found evidence for temperament traits being markers of differential susceptibility, and some examples will be presented in the following. One study demonstrated that attentional focusing, similar to attention span (Rothbart et al., 2001), moderates the relationship between socioeconomic backgrounds and inhibitory control in 4-year olds (Mills, Day, Van Lieshout, & Schmidt, 2019). Another study showed that temperamental reactivity moderates the effects of maternal structuring on cognitive functioning in children (Gueron-Sela, Atzaba-Poria, Meiri, & Marks, 2016). Yet another study demonstrated that infant temperamental reactivity moderates the effects of maternal and grandmaternal sensitivity on infant general anxiety (Xing, Zhou, Archer, Yue, & Wang, 2016).

In a large meta-analysis, Slagt, Dubas, Dekovic, and van Aken (2016) investigated temperament as a marker of DST. This meta-analysis reviewed parenting as the environmental influence. The results supported DST: Children with relatively more difficult temperament were more susceptible to positive and negative parenting. However, the effect applied to negative emotionality only, not other temperamental dimensions such as surgency or effortful control. Moreover, negative emotionality was only evident as a marker of DST when measured in infancy. A review by Rioux, Castellanos-Ryan, Parent and Seguin (2016) found evidence for DST when temperament was measured in childhood, and evidence of diathesis-stress when temperament was measured in adolescence. Of note, reactive temperament was measured in childhood, whereas self-regulatory dimensions of temperament were measured in adolescence only. The above noted research provides evidence for the possibility that differential susceptibility is restricted to, or at least more strongly present, in some periods of life, and demonstrates that measuring subdimensions of temperament is essential to reveal specific effects.

Contradicting evidence. Similar to genetic studies, there are discrepant findings in the temperament x E literature as well. For instance, a longitudinal study by Tung, Norona, Lee, Langley and Waterman (2018) studied adopted children who had previously lived in foster care, and risk for externalizing behaviors in adolescence. They investigated whether reactive children would benefit more from adoptive family cohesion as well as demonstrate more externalizing behavior as a result of early maltreatment. They failed to find support for temperament as a marker of DST. The study demonstrated a main effect between early negative temperament and later externalizing behavior, not that temperament moderated the interaction effect between foster care and externalizing behaviors in a for better and for worse

manner. The environmental variable most related to externalizing behavior was age of adoption, although sexual abuse and violence were also identified as risk factors.

In a study of 15-year old adolescents, Rioux, Castellanos-Ryan, Parent, Vitaro and Seguin (2019) investigated whether the relationship between parental knowledge and adolescent substance abuse was moderated by the temperamental factors impulsivity and sensation seeking, in a DST manner. Low sensation seeking emerged as a DST marker. However, the findings regarding impulsivity were in line with diathesis-stress reasoning. In a novel article, Cruz and colleagues (2018) investigated how child temperament moderated the relationship between mother–child interactions on later child persistence in school, comparing DST with diathesis-stress. Findings revealed evidence of diathesis-stress, not DST. Another longitudinal study investigated parenting and negative affect (Stoltz, Beijers, Smeekens, & Dekovic, 2017). Initially, the results seemed to support DST. However, after more stringent tests, the evidence showed that children characterized by negative affectivity seemed to be more vulnerable to later problem behavior, regardless of parenting quality, supporting diathesis-stress theory. The researchers noted the possibility that differential susceptibility is only present in certain periods of life (Stoltz et al., 2017). Clearly, the evidence of temperament as a marker of DST is inconclusive.

Physiological reactivity.

Cortisol. Cortisol, both resting cortisol and cortisol reactivity, are proposed markers of DST. A few recent examples of studies are presented here. Kalomiris and colleagues (2019) found that high cortisol reactivity moderated the effect of maternal behavior on anxiety, in a DST manner. Cortisol reactivity and maternal behavior was measured between 12 and 18 months, and anxiety was measured one year later. The results showed that maternal protection led to increased anxiety, whereas maternal encouraging of novelty led to decreased anxiety in highly reactive children. No effect of maternal behavior was found for children low in cortisol reactivity. Steeger, Cook, and Connell (2018) also found evidence for cortisol reactivity as a moderator of stressful family life events on both externalizing and internalizing problems in adolescents, supporting DST. Moreover, Wagner and colleagues (2019) found evidence for both diathesis-stress effects and vantage sensitivity, not DST; infants with high resting cortisol and high cortisol reactivity showed more callous-unemotional behavior in middle childhood when faced with maternal harsh intrusion in infancy (diathesis-stress), and infants with elevated cortisol reactivity benefited more from supportive parenting by showing less conduct problems in middle childhood. This effect was especially evident if parents were

supportive in stressful environments. The authors did not find support for DST in the lower spectrum of maternal sensitivity, and the results did therefore not directly support DST.

Heart rate reactivity. Some studies have found evidence of HR reactivity being a potential susceptibility marker. One study demonstrated that the relationship between child maltreatment and later depression in young adults was moderated by higher mean HR reactivity in a manner consistent with DST (Somers et al, 2017). Another study measured stress reactivity in adolescence, using both cortisol and heart rate as indicators (Cook, Wilkinson, & Stroud, 2018). Individuals that were grouped as highly reactive demonstrated both high cortisol reactivity and high HR reactivity. The results showed that high reactivity led to an increase and decrease in externalizing and internalizing problems, depending on whether parents facilitated a low or high degree of autonomy, in line with DST. However, a third study of adolescence failed to find evidence of HR reactivity as a marker of DST (Sijtsema et al., 2013). The authors suggest that the lack of evidence for differential susceptibility may be due to age differences, and that differential susceptibility is more pronounced in childhood.

Respiratory sinus arrhythmia. As mentioned earlier, respiratory sinus arrhythmia is a measure of heart rate variability and is considered a measure of parasympathetic activity. *Low* RSA is associated with higher HPA activity (Somers et al., 2019), and consequently is a plausible marker of DST because it increases reactivity to stressors. Obradovic, Bush, Stamperdahl, Adler and Boyce (2010) demonstrated that low RSA moderated the effect of adversity on several outcomes, including externalizing symptoms, prosocial behavior, school engagement and academic performance, in a DST manner: Individuals with low RSA showed maladaptive development in the presence of adversity, but better adaptation than those with high RSA in the presence of low adversity. On the other hand, some studies have found support for high RSA being more strongly linked to heightened susceptibility (Conradt, Measelle, & Ablow, 2013; Somers et al., 2019). Whether high or low RSA indicates a heightened susceptibility is in other words not clear.

Findings from another study demonstrated low RSA to be a better marker of diathesis-stress than DST. The link between sensitive parenting during toddlerhood (ages 24 and 36 months) and children's later effortful control (EF) was moderated by children's RSA and cortisol. The relationship was evident only among children who had low levels of baseline RSA (Gueron-Sela et al., 2017). However, supportive parenting protected against negative outcomes for children with low RSA, but children with low RSA did not demonstrate fewer negative outcomes than individuals with high RSA. Another study found no support for DST

or diathesis-stress with either low or high RSA, but rather seemed to support vantage sensitivity: Infants with high RSA were more attentive to positive stimuli, but less attentive to negative stimuli (Wass, 2018). Notably, the sample size in this study was very small (n=12).

Beyond single markers. As noted, markers of DST are not necessarily independent of each other. To a certain degree they could, and most likely do, *exist together and represent the same underlying process* (Ellis et al., 2011). For instance, inhibited temperament, similar to difficult temperament and characterized by shyness and carefulness (Clauss et al., 2015; Belsky et al., 1998), has been linked to a number of hypothesized susceptibility genes (Clauss et al., 2015). Also, temperament is hypothesized to have a biological basis in heightened stress reactivity (Clauss et al., 2015). However, research indicate that these markers do not merely represent the same underlying process. For instance, several studies have demonstrated that susceptibility genes may influence how temperamental dimensions develop in response to experience (e.g. Tung et al., 2017; Bouvette-Turcot et al., 2015). Allegrini and colleagues (2019) investigated DST using polygenic scores to see whether genetics moderated the relationship between life adversity and HR and heart rate variability (HRV); a measure of parasympathetic nervous system functioning (Allegrini et al., 2019). They found evidence for DST when looking at HRV, but not HR. More life adversity led to either very high or very low HRV score when susceptibility genes were present. Esposito and colleagues (2017) demonstrated how HR increases in response to stress is shaped depending on genetic predispositions, showing that HR increase in response to prolonged stress is dependent on genetic variations. Differential susceptibility was evident in carriers of the short A allele of the region rs2254298 *OXTR* gene. More specifically, carriers of the A allele showed lower HR in response to social distress when early paternal care was good, and higher HR in response to distress in the presence of overprotective parenting, thus supporting the DST hypothesis. There are at least two implications of these findings. First, genetics may influence how phenotypes like temperament and physiological reactivity develop. Second, both high and low reactivity was found in initially susceptible individuals, indicating that both high and low reactivity could be markers of susceptibility. It may therefore not be sufficient to look for high physiological reactivity exclusively, or a difficult temperament, when investigating DST. Perhaps it is necessary to measure both genetics and life experiences along with temperament or physiological reactivity, as it seems like temperament and physiological reactivity may be outcomes as well as markers.

Limitations of the included literature on markers.

Gene x Environment studies. As noted, most of the research on genetics in reference to DST has been through cGxE studies. However useful this has been in generating hypotheses and providing early knowledge about genetic influences, cGxE studies yield conflicting results, and significant effect sizes have proved difficult to replicate (Dick et al., 2015). One central, plausible reason for differing results and a lack of replication is that most complex phenotypes are a result of multiple genetic variations (Donnelly, 2008). Hence, one single gene would likely explain only a very small portion of the phenotypic variance. Therefore, failures to replicate effects from cGxE studies, or just finding very weak effect sizes, does not necessarily imply that a gene is not a marker of DST.

Another possible reason for a lack of replication is that replication studies differ from the original studies in important manners. For instance, environmental factors can be measured slightly or very differently, e.g. stressful/serious life events, ranging from including homework overload (Wang et al., 2018) and daily life stressful experiences (Chen et al., 2015) to using elements from the *List of Threatening Experience* (Arnau-Soler et al., 2019).

CGxE studies have frequently been criticized for being prone to false positives; finding an effect when there is none (Del Giudice, 2017). This is also known as type 1 errors. Del Giudice (2017) also found that methods and criteria used to detect differential susceptibility (i.e. Roisman et al., 2012) are particularly likely to generate false positives. One central limitation in studies to date, according to Del Giudice (2017), is a small sample size. A much larger sample size might be necessary to uncover reliable effects and protect against false positives.

Although not unique to cGxE studies, cGxE studies have been especially criticized of publication bias (Dick et al., 2015); publishing results when they support the hypothesis and omit publishing when the results show no relationship. In addition to a high amount of potential false positives, publication bias will further enhance a potentially false impression of valid GxE effects.

***Differences in conceptualizations*.** Important considerations in research on temperament is the use of different tools applied to measure temperament and differences in how temperament is defined. As noted, temperament is conceptualized and tested in several ways. One finding may therefore not be generalizable to other definitions of temperament. For instance, Cruz and colleagues (2018) used Child Personality Scale to measure temperament, which might not be generalizable to other definitions of temperament, such as temperament conceptualized with three subdimensions (Rothbart et al., 2001). Different conceptualizations of temperament measure slightly different subdimensions of temperament, and different

subdimensions of temperament might not predict differential susceptibility to the same degree. For instance, in the study by Rioux and colleagues (2019), findings demonstrated that low sensation seeking could be a DST marker. Impulsivity on the other hand was not supported as a DST marker. Thus, making an index of temperament based on subscale scores could potentially affect the results, hiding effects in some subdimensions of temperament. Hence, it is important to be aware of the fact that different conceptualizations of temperament could explain some of the contrasting evidence of DST. A thorough evaluation of all similar but different conceptualizations of factors, e.g. environmental factors, markers or outcome, will further strengthen the evidence of DST.

Research designs. Research on DST still lacks empirical evidence from longitudinal studies (Boyce, 2016). Longitudinal studies could perhaps clarify if susceptibility changes over time in the same individuals. Some longitudinal studies have been carried out with varying support for DST, some showing support for DST in early childhood (Keers & Pluess, 2017), some finding no support for DST (Pitzer et al., 2017) and some finding support for DST throughout adolescence (Deane et al., 2019).

Few DST studies applying a RCT design have been conducted. Many studies of DST have been carried out by merely measuring stable environmental variables, not exposing individuals to a new condition. Because of this, it is difficult to demonstrate that the same individuals are susceptible for better *and* for worse, and not merely demonstrating diathesis-stress and vantage sensitivity. RCT studies would be fitting to separate these from one another, because its experimental design enables researchers to place individuals in an environment that differs from what they grew up in. However, it would obviously not be ethically acceptable to move children permanently to other caretakers to investigate this effect or impose any kind of severe adversity on individuals. Treatment studies with an experimental design might shed light on how much adolescents and adults benefit from positive input, even though they have been reared in a harsh environment. Such studies exist, as shown, although more treatment studies are needed.

Of note, a recent review found that methods of GxE research have significantly improved in recent years, including more longitudinal studies and RCT studies (Leighton, Botto, Silva, Jimenez, & Luyten, 2017).

Summary of markers. Evidence of markers in DST is still increasing, both regarding genetics, temperament and physiological markers. In addition, researchers investigate how markers may interact with each other or represent similar underlying mechanisms. New research designs are being developed, allowing researchers to investigate more complex

interactions of DST markers. Nonetheless, recent research on markers also fail to find support for DST. The reasons for diverging findings are unclear.

What are Current Hypotheses of mechanisms in DST?

The second research question is aimed at investigating what is known about mechanisms of DST. After searching for empirical testing of proposed mechanisms of differential susceptibility, only a few studies were identified, including some studies investigating sensory processing sensitivity (e.g. Gard, Shaw, Forbes, & Hyde, 2018; Jagiellowicz et al., 2011; Acevedo et al., 2014). Indeed, researchers highlight that theoretical explanations of mechanisms underlying GxE is lacking (Weeland et al., 2015), and consequently very few have had the chance to empirically test theoretical claims of mechanisms. As DST is dependent on GxE studies, DST has also been lacking theoretical explanations of mechanisms, at least until recently. However, several researchers have recently described possible theoretical mechanisms of DST. These theoretical mechanisms include both neurobiological mechanisms as well as adaptive mechanisms. The following section focuses on the proposed theoretical mechanisms of DST.

Neurobiological mechanisms. One way of examining mechanisms of DST is by investigating which neurobiological processes are at play when someone responds more strongly to environmental experience (Boyce, 2016; Moore & Depue, 2016). At the core of DST is the statement that individuals vary in their neurobiological sensitivity to environmental stimuli (Ellis et al., 2011). The variation in phenotype is mirrored in variations in neurological activation (Belsky & Pluess, 2013). As previously mentioned, proposed neurobiological mechanisms in DST are similar to physiological reactivity in that they describe individual differences in susceptibility on a biological level (Boyce, 2016). However, what is referred to as hypotheses of mechanisms in DST arguably have a broader focus than investigating single physiological processes such as cortisol activation or heart rate.

Differences in perception. We constantly deal with information coming from both external and internal cues. How this is perceived by the brain may vary from individual to individual. Thus, *differences in perception*, and in particular how much stimuli are perceived, could be a mechanism underlying DST. Weeland, Van den Akker, Slagt and Putnam (2017) have studied *perceptual sensitivity*, a subdimension of the temperament trait effortful control, as a potential mechanism of DST. The degree of perceptual sensitivity reflects how much stimuli each individual detects. In other words, it does not propose that individuals react differently to the same, perceived information, nor does it exclude this possibility. Boyce (2016) proposes a similar mechanism, named *sensory gating*. A deficit in sensory gating, the

sorting out of some stimuli in favour of others, could result in an increased amount of sensory information. Sensory processing Sensitivity theory, which shares the notion that some individuals are more susceptible for better and for worse, also states that highly sensitive individuals might have a heightened sensitivity to stimuli, and thus process more subtle stimuli (Grimen & Diseth, 2016; Aron, Aron, & Jagiellowicz, 2012). In conclusion, if some individuals detect more information than others, they might also be more susceptible to the influence of their environment, thereby enhancing susceptibility.

Differences in responses to stimuli. Another concept that may impact susceptibility is how individuals respond to perceived stimuli. Several researchers have proposed that different thresholds for activation and arousal may play a part in DST, as described in the following. Boyce (2016) points to hypotheses of differences in threshold for induced *Long Term potential* (LTP) and *kindling* as possible mechanisms of DST. LTP refers to a lasting and/or strong stimulation which alters the synaptic strength, while kindling refers to a process where continuous exposure to a stimulus might induce sensitization, both of which may lead to a heightened sensitization over time.

Moore and Depue (2016) published a review where they addressed hypothesized neurobiological mechanisms of DST. With this, they sought to create a comprehensive neurobehavioral framework explaining what they referred to as *environmental sensitivity*, i.e. another term for the concept of differential susceptibility, which will contribute to understanding mechanisms of DST. The authors argued that a lowered threshold of arousal is at the core of differential susceptibility. In short, a lesser external stimulus will be required to elicit a response in more reactive individuals, while a strong stimulus will elicit a response in less reactive individuals.

Differences in response to stimuli can also be investigated at the synaptic level. A heightened sensitivity might be characterized by a deeper information processing (Belsky & Pluess, 2013). The enhanced duration and increased strength of neuronal firing is what is thought to mediate this deeper processing. One theory that focuses on this mechanism is sensory processing sensitivity (Greven et al., 2019; Homberg, Schubert, Asan, & Aron, 2016), stating that highly reactive individuals show greater activation in specific brain areas in response to environmental cues.

Brain circuitry and connectivity. Research has moved from studying functions of specific brain structures to also looking at how different areas of the brain communicate with each other (Boyce, 2016). These pathways may be referred to as neural pathways or neural circuits (Boyce, 2016). Especially important are areas that are known to regulate the

processing of other brain areas. For instance, the filtering capacities of the prefrontal cortex could be a potential mechanism moderating the strength of processing, ultimately affecting sensitivity to the environment (Boyce, 2016). Research on sensory processing sensitivity also highlight brain circuits as a possible mechanism of sensitivity (Acevedo, Aron, Pospos, & Jessen, 2018). In addition, prenatal stress might affect various brain structures (Hartman & Belsky, 2018), and thereby affect the connectivity between brain structures, shaping susceptibility before, as well as after, birth.

Epigenetic mechanisms. Epigenetic processes are, simply put, alterations in gene expression in response to environmental influence (Conradt et al., 2018). Genes are not deterministic of phenotype (Conradt et al., 2018), but are expressed as a response to environmental experience. In other words, being a carrier of a gene does not automatically indicate that this gene is expressed. For instance, susceptibility genes might be expressed if an individual grows up in a stressful environment, but not otherwise, in line with the claim that susceptibility seems to be shaped by environmental factors if a genetic disposition is present (Ellis et al., 2011). Thus, epigenetic processes, i.e. processes where environmental experiences shape the phenotypic outcome depending on genotype, are highly probable mechanisms in DST (Boyce, 2016). A few studies investigating DNA methylation, an epigenetic process, have found evidence of DST, specifically that carriers of susceptibility genes have the most or least DNA methylation of genes related to psychopathology depending on whether they experienced stressful or safe environments in childhood, respectively (Klengel et al., 2013; Beach et al., 2014). Still, more studies aimed at testing epigenetic mechanisms in DST are needed.

Adaptive mechanisms of DST. In addition to neurobiological mechanisms, researchers have also investigated and developed hypotheses of how and why differential susceptibility develops. Three central contributions to investigating adaptational mechanisms will be addressed here.

Aiming to diminish the gap between purely neurobiological mechanisms and psychological mechanisms, Moore and Depue (2016) addressed hypothesized biological markers and mechanisms while relating them to motivational systems. According to Moore and Depue (2016), reactivity is hypothesized to be specific to behavior and underlying neuromodulators. For instance, dopaminergic reactivity is hypothesized to be connected to behavior related to motivational systems and reward cues. Consequently, individuals with a reactive dopaminergic system will be more easily enthusiastic, optimistic and experience a stronger feeling of desire. This might also include a stronger activation in specific brain areas,

and consequently a strengthening of these synaptic connections (Moore & Depue, 2016). Hence, the authors link various potential markers to regulating systems and emotional-motivational systems. This theory makes an important contribution to the understanding of DST in that it also connects susceptibility markers to specific environmental contexts and outcomes, arguing for a domain specificity in DST where each marker might increase susceptibility to a certain type of environment.

Michael Pluess, a central researcher in the field of DST, published an article with the aim of integrating various research lines of differential susceptibility, naming the concept *environmental sensitivity* (2015). Particularly interesting is the proposed hypothesis that sensitivity is more evident in early childhood than later in life. Pluess (2015) proposes that individuals are sensitized by the experience of their early years, and thereby becomes sensitized to a certain type of environment, which may help them respond to the environments they encounter later in life. According to his model, people who early in life are exposed to an overweight of experiences with negative value will later be more susceptible to negative experiences than positive experiences, even though they initially had an equally heightened susceptibility for both positive and negative experiences. The same logic applies to highly susceptible individuals subjected to mainly positive and supportive environments. These individuals would be more resilient to adversity in adulthood than other less susceptible individuals, and more susceptible to positive experience, demonstrating vantage sensitivity.

Another recent theoretical explanation of possible mechanisms behind differential susceptibility is that of Ellis and Giudice (2019). They address the adaptational mechanisms of differential susceptibility with Life History Theory as a backdrop (Ellis et al., 2009; Ellis & Giudice, 2019). Life History Theory emphasizes that even though a strategy is adaptive, meaning that it makes passing on genes possible, these strategies often come with a cost. From this theory, Del Giudice et al. (2011) developed a model to describe differences in stress responsivity, namely Adaptive Calibration Model (ACM). ACM holds that individuals adapt to the environment through conditional adaptation, i.e. that experiences condition an individual to adapt in a way suitable to a given environment. Much like early research by Boyce and Ellis, ACM hypothesizes that individuals gather information about the demands of life through early environmental experience, conditioning them to develop adaptive stress responses. Interestingly, ACM also proposes that individuals respond to stressors with two separate adaptive patterns, named vigilant and unemotional. The vigilant pattern is characterized by a highly reactive SNS, while the unemotional pattern is characterized by the opposite; a lowering in reactivity. Both hyper- and hypo-reactivity are common reactions to

extreme stress, possibly with different adaptive advantages. In ACM, the authors hypothesize that one group of children initially react with hyper-reactivity when exposed to stressors, but later goes on to develop hypo-reactivity in later childhood or adolescence. This initially susceptible group become more specialized to certain environments as they grow older (Ellis & Del Giudice, 2019). This resembles the hypothesis by Pluess (2015), claiming that individuals are specialized to fit their environment early on. With this framework, Ellis and Del Giudice (2019) offers a perspective on possible mechanisms of differential susceptibility. Although they refer to the concept differential susceptibility and not solely DST, the hypothesis may contribute to a refinement of DST, as DST has integrated elements from other research traditions before.

Summary of mechanisms. Several theoretical mechanisms of the differential susceptibility concept, i.e. for better and for worse patterns, have been proposed in recent years, including both neurobiological mechanisms and adaptive mechanisms. These proposed mechanisms may contribute to a theoretical refinement of DST. The proposed theoretical mechanisms have many overlapping elements. Studies aimed at testing whether these mechanisms underlie differential susceptibility still needs to be conducted.

What are Current Evidence and Hypotheses of the Possible Age Difference in DST?

The third research question is aimed at investigating whether there exists an age difference in DST. As mentioned, whether differential susceptibility varies with age or is life long is still uncertain. Evidence supporting both views will be presented in the following.

Evidence of DST primarily in the early years. Several studies indicate that differential susceptibility is more evident in early childhood compared to later ages, and that proposed DST markers function as risk factors, not DST markers, later on (Tung et al., 2018; Belsky & Pluess, 2012; Slagt et al., 2016; Rioux et al., 2016). Many hypothesized mechanisms of DST are also compatible with this view. As mentioned, Pluess (2015) suggested that individuals might be shaped by their early environment to develop a specialized type of sensitivity as they grew older. This is in line with research indicating a stronger effect of DST markers when measured in early years, like negative emotionality (Slagt et al., 2016). A large, longitudinal study by Keers and Pluess (2017) investigated a British cohort, starting in 1958 (n=13927). Participants were tested for 8 SNPs, from which the researchers generated a polygenic score of susceptibility. The results showed that children who had a childhood characterized by a high-quality material environment, i.e. social class, employment of parents and financial status, and a high polygenic score were *less* vulnerable to a poor material environment when they grew older compared to their less “susceptible”

counterparts. Children with a high polygenic score who experienced a low-quality material environment as children were more vulnerable to adversity as adults. This is in line with the hypothesis by Pluess (2015) that environmental experience may shape susceptibility to fit the environment the individual grows up in and could imply that individuals develop either a pattern of diathesis-stress or vantage sensitivity (Keers & Pluess, 2017). The findings outlined above demonstrate that susceptibility "for better and for worse" might not be equally distributed across the lifespan but may be stronger in childhood.

Evidence supporting lifelong differential susceptibility. Even though some research shows evidence of differential susceptibility being strongest in infancy and toddlerhood (Slagt et al., 2016; Rioux et al., 2016), other findings show otherwise. Some studies of intervention and treatment effects have found evidence of DST in older children (e.g. Lemery-Chalfant et al., 2018), adolescents (e.g. Beach, Brody, Lei, & Philibert, 2010; Belsky & Beaver, 2011), as well as in adults (e.g. Cicchetti et al., 2015), supporting DST in all age groups. Studies of the moderating effect of polygenic scores on treatment effects support DST in older children (Lemery-Chalfant et al., 2018; Keers et al., 2016; Overbeek, 2017), as do one study of children with a history of difficult temperament (Pluess & Belsky, 2010). Researchers using Sensory Processing Sensitivity as theoretical framework have demonstrated differential susceptibility in adults (Acevedo, Jagiellowicz, Aron, Marhenke, & Aron, 2017). One study also showed that adults homozygous of the SS allele of the *5-HTTLPR* gene demonstrated a heightened susceptibility to stressful life events: SS carriers had the highest and lowest scores on neuroticism compared with L carriers, depending on the number of Stressful life events they had experienced recently (Pluess et al., 2010). To be noted, other studies on treatment effect found no moderation of temperament or genetic variants (Weeland et al., 2017). Several studies on adolescents also support DST (e.g. Steeger et al., 2018; Belsky & Beaver, 2011; Cook et al., 2018), although the overall evidence of DST in this age group is somewhat inconsistent. Lastly, one review that critically evaluated research methods of differential susceptibility and GxE found no differences in research findings depending on what genetic markers were investigated. However, the findings showed an age difference, namely that findings of differential susceptibility were stronger if measured in *young adults* rather than old adults (Leighton et al., 2017). This review supports the notion that age might influence differential susceptibility. Interestingly, it shows that differential susceptibility was more present in early adulthood as opposed to older adulthood, implying that differential susceptibility could exist in adulthood as well as early childhood. Age might moderate

differential susceptibility continuously as individuals grow older, as opposed to being present in infancy or early childhood exclusively.

Summary of age in DST. Findings supporting DST find evidence for both an age dependent differential susceptibility and differential susceptibility throughout the life span. The latter includes experimental designs like treatment and intervention studies. However, to my knowledge, none of these studies test age differences in DST as their primary aim. Studies designed to investigate age differences more thoroughly, for instance reviews, would grant new important insights to the question of age in DST.

Discussion

The aim of this thesis was to review evidence of central aspects in DST, as well as shed light on recent advancements and contributions to the theory. This was done by answering the three research questions *"to what degree does current evidence support proposed markers of DST?", "What are current hypotheses of mechanisms in DST?" and "What are current evidence and hypotheses of the relative importance of age in DST?".* Recent and central studies testing DST demonstrate that research supporting DST is increasing. A lot of proposed markers of DST are supported by research, although GxE studies have received criticism. Still, the theory lacks knowledge about several aspects, e.g. evidence of mechanisms and whether other factors like age moderate how markers predict differential susceptibility.

Increasing but Conflicting Evidence of DST Markers

The findings of this semi-structured literature study demonstrate that evidence supporting markers of DST is increasing, although a lot of contradictory findings do exist. As outlined above, studies of single markers often fail to find support for DST. An increasing amount of studies have begun to search for a more complex interplay of several markers, various environments and other possible moderating factors. Indeed, if DST turns out to be valid, the phenotype of a heightened susceptibility is likely characterized by a complex interplay of factors, genetic and environmental ones. The contribution of a single marker may be limited, and possibly not consistently linked to an outcome of heightened susceptibility.

Mechanisms of DST seem to be complex and multifaceted

Research on mechanisms of DST is still scarce, and the contributions to DST regarding mechanisms is mostly theoretical and hypothetical to date. A few empirical studies aiming to test mechanisms of DST exist, and there are reasons to assume that such studies will increase in near future. Interestingly, the proposed theoretical mechanisms from various researchers have many overlapping elements, e.g., a lowered threshold for neural excitation or

differences in how much information is processed. Similar proposed mechanisms may indicate that these mechanisms are indeed mediating differential susceptibility. However, various research traditions might also influence and borrow elements from each other, which could explain the overlapping evidence. Mechanisms might also function together to form differential susceptibility, or different mechanisms could be in play in different individuals. Studies which aim to test these theories of mechanisms will hopefully emerge in few years, as the body of research today is scarce.

DST may be more evident in childhood, but evidence is conflicting and scarce

Theoretical models of mechanisms, and some larger reviews, argue that differential susceptibility seems to be more evident in childhood. Nevertheless, some single studies show effects in line with DST in adolescents and adults. The brain is changing throughout life, and some individuals may be more malleable than others throughout life as well. There might also be a difference in degree of differential susceptibility in early years compared to older age, and not a question of either-or.

Implications

There are some important implications of the findings in the present thesis. The question of age in DST could have implications for early intervention in childhood; if children in stressful environments are especially susceptible for positive support - but mainly for a short period - this time window should be used as well as possible. However, the practical use of this implication remains uncertain, as individual differences in susceptibility may not be possible to measure accurately on an individual level. There are also ethical considerations to such knowledge. If some children are hypothesized to be less susceptible and malleable, one might speculate if they should be prioritized in treatment groups. Knowledge of DST could inform but also complicate the decisions of how resources should be allocated. It is therefore essential to investigate to what degree it is possible to foresee the effects of an intervention based on a hypothesized susceptibility. As shown, some research also indicate that treatment effects may depend on both degree of susceptibility and type of treatment (Keers et al., 2016). Less susceptible individuals may not be unaffected by all forms of intervention but may benefit more from one treatment form than another.

Possible explanations for contrasting findings

Throughout this thesis, evidence supporting and opposing DST has been presented. The seemingly contrasting findings could have different explanations. Some limitations and common critique of the included literature has already been addressed. Additional possible explanations for the results will be discussed in the following.

One possibility for diverging results is related to the third research question; that differential susceptibility is *only or mostly present in early childhood* and is then substituted for a more specialized adaptation to the environment. If differential susceptibility is more pronounced in early childhood, evidence of diathesis-stress and vantage sensitivity in adolescence and adulthood could hypothetically be an example of a specialized adaptation to environmental demands, as hypothesized by Pluess (2015). Much research on DST measures stable environmental variables that do not necessarily change over time, e.g. the quality of parental care, and researchers often do not include an intervention or change of environment (Kalomiris et al., 2019). Hence, the same individuals are not tested for both positive and negative rearing environments, as their environment does not change. Children who possess markers of DST, e.g. reactive children, often show the most and least problems, which is commonly interpreted as evidence that susceptible individuals are susceptible *for better and for worse.* However, it is possible that the individuals who demonstrate positive outcomes are especially susceptible to positive environments, while individuals who demonstrate negative outcomes are especially susceptible to negative environments, demonstrating vantage sensitivity and diathesis-stress, respectively. For instance, early research by Boyce and Ellis (2005; 2008) showed that both abnormally stressful and abnormally supportive environments yielded more sensitive individuals, characterized by heightened physiological reactivity. The reactive individuals reared in supportive environments showed less health problems (Ellis & Boyce, 2008). However, how these children might be affected by stressful life events, early on or later, was not measured. Similarly, children who grew up in stressful environments showed the most health problems, but it was not assessed how they reacted to positive experiences, and if they would benefit from them (Ellis & Boyce, 2008). Thus, the early works of Ellis & Boyce exemplifies that reactivity can imply susceptibility to both positive and negative environments, but not necessarily in the same individuals, or at the same time in the same individuals. Instead, there could exist an adaptive programming, where the individual is prepared to be especially receptive to the environment they grew up in, respectively supportive or dangerous environments. One could argue that they demonstrated vantage sensitivity and diathesis-stress, respectively, instead of differential susceptibility. Consequently, evidence of diathesis-stress or vantage sensitivity in adolescence does not necessarily oppose DST but could imply that DST might be more strongly present in early childhood.

Another highly interesting and related question is whether different markers could be predictive of differential susceptibility depending on specific periods of development.

Temperament is a trait that is partly shaped by environmental experiences. As mentioned, Tung and colleagues (2018) found that the temperament trait negative emotionality predicted externalizing behavior, consistent with diathesis-stress, not DST. However, temperament was measured after age three, and the children had already been in foster care until adoption. It is plausible that their temperament had already been affected by their environments in foster care. Physiological reactivity has also been shown to be affected by experience and genetics, and markers of physiological reactivity may vary depending on age. Ellis and Del Giudice (2019) give possible explanations for seemingly contradictory findings of physiological markers. Both hypo- and hyper-reactivity are common reactions to extreme stress (van Bodegom, Homberg, & Henckens, 2017), and whether an individual demonstrates hypo- or hyper-reactivity to stressors might vary with age or other factors. Consequently, it seems questionable to regard high physiological reactivity as a stable marker of heightened susceptibility, and both hypo- and hyper-reactivity could be patterns of reactivity in present or formerly highly susceptible individuals. In conclusion, findings presented in this thesis support the possibility that some markers may predict susceptibility in some age periods but not others, which could result in seemingly contrasting findings.

In addition to age, *other factors may moderate the predictive value of markers*. Sex differences could potentially moderate the relationship between a marker and the environment (Sulik et al., 2015; Arnau-Soler et al., 2019). Males are generally assumed to be more affected by stressors than females (Del Giudice et al., 2018). Controlling for sex differences could be an important contribution to finding more specific effect sizes in research on DST. Lastly, genetic variants could possibly indicate susceptibility in some ethnic groups, but not in others (van IJzendoorn et al., 2012). One review found that 90% of all GxE studies of DST use samples from North America and Europe (Leighton et al., 2017).

As mentioned, DST might be domain specific, and *the interaction of age and context might influence how susceptibility plays out*. It is reasonable to assume that susceptibility related to adolescent developmental tasks, e.g. social responsiveness and autonomy, is more pronounced in adolescence than in childhood. (Cook et al., 2018; Schriber & Guyer, 2016). It is also possible that differential susceptibility to e.g. social peer situations, is more evident in adolescence compared to e.g. susceptibility to parenting. An example of a marker with a possible interaction between age and context is the *MAOA* gene, which is mainly studied in relationship to aggressive and antisocial behavior, behavior that is mostly related to adolescence and adulthood. Therefore, the moderating effect of *MAOA* might be both domain specific and age dependent. As mentioned above, it will be important to consider how

environments and outcomes are conceptualized and defined if the aim is to measure domain specificity.

If DST proves to be domain specific, this could also contribute to explaining differing results in polygenic research. Polygenic research sums up various genetic variants to form a polygenic score, thus the contribution of each single genetic variant is not investigated. A polygenic effect does not necessarily mean that each gene contributes significantly to an outcome. On the contrary, it is possible that some genes heighten susceptibility for some environments, but not others. For instance, dopaminergic susceptibility genes could yield susceptibility mainly to awarding cues, while serotonergic susceptibility genes could yield susceptibility to emotional cues, as suggested by Moore and Depue (2016). Polygenic scores could arguably give the impression that all included genetic variations play an equal part in shaping susceptibility, which would be false if DST is domain specific. If DST is domain specific, susceptibility genes would contribute to heightened susceptibility to some environments but not others. Consequently, if the same polygenic score is used for different environments, the results may differ because of domain specificity.

Another possible reason for diverging results is obviously that differential susceptibility does not exist, and studies supporting the theory are mostly false positives. As mentioned, GxE studies have been criticized for being prone to false positives. Publication bias may also influence the impression of the current research body. However, researchers continue to find support for DST even though research methods are improving (Leighton et al., 2017).

Strengths and limitations

The main strength of this thesis is the broad covering of DST, assessing both markers and mechanisms. To my knowledge, no former study has captured such breadth, as earlier reviews focused on narrower areas, e.g. mechanisms exclusively or only a selected number of markers (Boyce, 2016; Pluess, 2015), or a more in-depth discussion of neurobiological or adaptive processes (Moore & Depue, 2016; Ellis & Del Giudice, 2019). The present thesis thus adds to existing work by giving an overview of the current state of DST, as markers and mechanisms are core elements of the theory. Former DST reviews have also not reviewed and discussed the possible importance of age, although the possibility of age differences has been noted in previous work (e.g. Ellis et al., 2011; Assary et al., 2018).

On the other hand, the above noted strengths may also be seen as downsides of the present work. Because of the broad scope of this thesis, a very carefully and thorough evaluation and review of all relevant papers was not possible. In addition, only one research

base was used for selecting articles. It is highly likely that additional relevant articles have been left out.

Although this thesis seeks to give an overview of evidence supporting each DST marker, the thesis does not evaluate and control for moderating factors other than age. Not thoroughly assessing the importance of factors like specific environment and outcome, ethnicity and sex might hide possible explanations for the results and give the false impression of a relationship or no relationship. All these factors deserve to be more thoroughly investigated and reviewed in future DST research. As noted, domain specificity or sex could be such factors, and could possibly explain some of the contrasting results if controlled for. As demonstrated in this thesis, differences in age may play a large role in whether a marker predicts differential susceptibility. It is possible that other markers than age also contribute significantly to research findings.

Conclusion

The aim of this thesis was to cover a broad area of research on DST, assessing central markers and mechanisms as well as investigate studies that might shed light on the importance of age in DST. Many studies support DST theory, including reviews and recent studies. However, a lot of studies also fail to support DST. This might be due to bias and limitations of the included studies. Studies also indicate that each marker may contribute a very small amount and perhaps under certain circumstances. This might imply that the complexity of DST makes it hard to prove and replicate through small studies of single markers. Theoretical contributions regarding mechanisms in DST seem to overlap to a great extent for both neurobiological mechanisms and adaptive mechanisms. Still, more empirical evidence of mechanisms is necessary, as evidence of mechanisms is still scarce. More empirical evidence regarding the relative importance of age in DST is also called-for, preferably from longitudinal studies or RCT studies. Suggested implications of DST research are perhaps only hypothetical at the time being, partly due to some limitations: Even if there exist small differences on a group level in susceptibility, it could be questionable to characterize a single individual as highly susceptible. Factors may not consistently contribute to susceptibility for all and might be dependent on other variables as well. It therefore seems unethical to label some individuals as highly susceptible at this point, and problematic to suggest consequences for treatment, upbringing and intervention on an individual level. However, if for instance a growing body of evidence suggests that differential susceptibility is formed prenatally, highly present in early childhood and then declines, one could perhaps argue on a general level that early intervention seems even more important than before.

Overall, DST has advanced our understanding of child development and developmental psychopathology. Future theorizing and research should aim to advance our understanding even further.

References

Acevedo, B., Aron, E., Pospos, S., & Jessen, D. (2018). The functional highly sensitive brain: a review of the brain circuits underlying sensory processing sensitivity and seemingly related disorders. *Philosophical Transactions of the Royal Society B-Biological Sciences, 373*(1744). doi:10.1098/rstb.2017.0161

Acevedo, B. P., Aron, E. N., Aron, A., Sangster, M. D., Collins, N., & Brown, L. L. (2014). The highly sensitive brain: an fMRI study of sensory processing sensitivity and response to others' emotions. *Brain and Behavior, 4*(4), 580-594. doi:10.1002/brb3.242

Acevedo, B. P., Jagiellowicz, J., Aron, E., Marhenke, R., & Aron, A. (2017). SENSORY PROCESSING SENSITIVITY AND CHILDHOOD QUALITY'S EFFECTS ON NEURAL RESPONSES TO EMOTIONAL STIMULI. *Clinical Neuropsychiatry, 14*(6), 359-373. doi:10.1098/rstb.2017.0161

Allegrini, A. G., Evans, B. E., de Rooij, S., Greaves-Lord, K., & Huizink, A. C. (2019). Gene x Environment contributions to autonomic stress reactivity in youth. *Development and Psychopathology, 31*(1), 293-307. doi:10.1017/s095457941700181x

Arnau-Soler, A., Adams, M. J., Clarke, T. K., MacIntyre, D. J., Milburn, K., Navrady, L., . . . Generation Scotland, M. (2019). A validation of the diathesis-stress model for depression in Generation Scotland. *Translational Psychiatry, 9*, 1-10. doi:10.1038/s41398-018-0356-7

Aron, E. N., & Aron, A. (1997). Sensory-processing sensitivity and its relation to introversion and emotionality. *Journal of Personality and Social Psychology, 73*(2), 345-368. doi:10.1037/0022-3514.73.2.345

Aron, E. N., Aron, A., & Jagiellowicz, J. (2012). Sensory Processing Sensitivity: A Review in the Light of the Evolution of Biological Responsivity. *Personality and Social Psychology Review, 16*(3), 262-282. doi:10.1177/1088868311434213

Aslund, C., & Nilsson, K. W. (2018). Individual biological sensitivity to environmental influences: testing the differential susceptibility properties of the 5HTTLPR polymorphism in relation to depressive symptoms and delinquency in two adolescent general samples. *Journal of Neural Transmission, 125*(6), 977-993. doi:10.1007/s00702-018-1854-8

Assary, E., Vincent, J. P., Keers, R., & Pluess, M. (2018). Gene-environment interaction and psychiatric disorders: Review and future directions. *Seminars in Cell & Developmental Biology, 77*, 133-143. doi:10.1016/j.semcdb.2017.10.016

Bajgarova, Z., & Stuchlikova, I. (2019). Infant difficult temperament. *Ceskoslovenska Psychologie, 63*(1), 104-115.

Bakermans-Kranenburg, M. J., & van Ijzendoorn, M. H. (2006). Gene-environment interaction of the dopamine D4 receptor (DRD4) and observed maternal insensitivity predicting externalizing behavior in preschoolers. *Developmental Psychobiology, 48*(5), 406-409. doi:10.1002/dev.20152

Bakermans-Kranenburg, M. J., & van Ijzendoorn, M. H. (2011). Differential susceptibility to rearing environment depending on dopamine-related genes: New evidence and a meta-analysis. *Development and Psychopathology, 23*(1), 39-52. doi:10.1017/s0954579410000635

Bakermans-Kranenburg, M. J., & van Ijzendoorn, M. H. (2015). The Hidden Efficacy of Interventions: Gene x Environment Experiments from a Differential Susceptibility Perspective. In S. T. Fiske (Ed.), *Annual Review of Psychology, Vol 66* (Vol. 66, pp. 381-409). doi:10.1146/annurev-psych-010814-015407

Baptista, J., Belsky, J., Mesquita, A., & Soares, I. (2017). Serotonin transporter polymorphism moderates the effects of caregiver intrusiveness on ADHD symptoms among institutionalized preschoolers. *European Child & Adolescent Psychiatry, 26*(3), 303-313. doi:10.1007/s00787-016-0890-x

Barone, L., Ozturk, Y., & Lionetti, F. (2019). The key role of positive parenting and children's temperament in post-institutionalized children's socio-emotional adjustment after adoption placement. A RCT study. *Social Development, 28*(1), 136-151. doi:10.1111/sode.12329

Beach, S. R. H., Brody, G. H., Lei, M. K., & Philibert, R. A. (2010). Differential Susceptibility to Parenting Among African American Youths: Testing the DRD4 Hypothesis. *Journal of Family Psychology, 24*(5), 513-521. doi:10.1037/a0020835

Beach, S. R. H., Brody, G. H., Lei, M. K., Kim, S., Cui, J., & Philibert, R. A. (2014). Is serotonin transporter genotype associated with epigenetic susceptibility or vulnerability? Examination of the impact of socioeconomic status risk on African American youth. *Development and Psychopathology, 26*(2), 289-304. doi:10.1017/s0954579413000990

Belsky, J. (1997). Theory testing, effect-size evaluation, and differential susceptibility to rearing influence: The case of mothering and attachment. *Child Development, 68*(4), 598-600. doi:10.1111/j.1467-8624.1997.tb04221.x

Belsky, J. (2015). Beyond Vulnerability: Attachment, Adversity, Gene-Environment Interaction, and Implications for Intervention. *Journal of Developmental and Behavioral Pediatrics, 36*(6), 464-466. doi:10.1097/dbp.0000000000000184

Belsky, J., Bakermans-Kranenburg, M. J., & van Ijzendoorn, M. H. (2007). For better and for worse: Differential susceptibility to environmental influences. *Current Directions in Psychological Science, 16*(6), 300-304. doi:10.1111/j.1467-8721.2007.00525.x

Belsky, J., & Beaver, K. M. (2011). Cumulative-genetic plasticity, parenting and adolescent self-regulation. *Journal of Child Psychology and Psychiatry, 52*(5), 619-626. doi:10.1111/j.1469-7610.2010.02327.x

Belsky, J., Hsieh, K. H., & Crnic, K. (1998). Mothering, fathering, and infant negativity as antecedents of boys' externalizing problems and inhibition at age 3 years: Differential susceptibility to rearing experience? *Development and Psychopathology, 10*(2), 301-319. doi:10.1017/s095457949800162x

Belsky, J., Jonassaint, C., Pluess, M., Stanton, M., Brummett, B., & Williams, R. (2009). Vulnerability genes or plasticity genes? *Molecular Psychiatry, 14*(8), 746-754. doi:10.1038/mp.2009.44

Belsky, J., & Pluess, M. (2009). The Nature (and Nurture?) of Plasticity in Early Human Development. *Perspectives on Psychological Science, 4*(4), 345-351. doi:10.1111/j.1745-6924.2009.01136.x

Belsky, J., & Pluess, M. (2012). Differential susceptibility to long-term effects of quality of child care on externalizing behavior in adolescence? *International Journal of Behavioral Development, 36*(1), 2-10. doi:10.1177/0165025411406855

Belsky, J., & Pluess, M. (2013). Beyond risk, resilience, and dysregulation: Phenotypic plasticity and human development. *Development and Psychopathology, 25*(4), 1243-1261. doi:10.1017/s095457941300059x

Belsky, J., & van Ijzendoorn, M. H. (2017). Genetic differential susceptibility to the effects of parenting. *Current Opinion in Psychology, 15*, 125-130. doi:10.1016/j.copsyc.2017.02.021

Bouvette-Turcot, A. A., Pluess, M., Bernier, A., Pennestri, M. H., Levitan, R., Sokolowski, M. B., . . . Team, M. R. (2015). Effects of Genotype and Sleep on Temperament. *Pediatrics, 136*(4), E914-E921. doi:10.1542/peds.2015-0080

Boyce, W. T. (2016). Differential Susceptibility of the Developing Brain to Contextual Adversity and Stress. *Neuropsychopharmacology, 41*(1), 142-162. doi:10.1038/npp.2015.294

Boyce, W. T., & Ellis, B. J. (2005). Biological sensitivity to context: I. An evolutionary-developmental theory of the origins and functions of stress reactivity. *Development and Psychopathology, 17*(2), 271-301. doi:10.1017/s0954579405050145

Burns, S. B., Szyszkowicz, J. K., Luheshi, G. N., Lutz, P. E., & Turecki, G. (2018). Plasticity of the epigenome during early-life stress. *Seminars in Cell & Developmental Biology, 77*, 115-132. doi:10.1016/j.semcdb.2017.09.033

Cao, C., Cao, L., & Chen, J. (2019). Differences in Sensitivity to Environment Depending on Catechol-O-Methyltransferase (COMT) Gene? A Meta-analysis of Child and Adolescent Gene-by-Environment Studies. *Journal of Youth and Adolescence, 48*(4), 655-667. doi:10.1007/s10964-019-01004-3

Cao, C., Rijlaarsdam, J., van der Voort, A., Ji, L. Q., Zhang, W. X., & Bakermans-Kranenburg, M. J. (2018). Associations Between Dopamine D2 Receptor (DRD2) Gene, Maternal Positive Parenting and Trajectories of Depressive Symptoms from Early to Mid-Adolescence. *Journal of Abnormal Child Psychology, 46*(2), 365-379. doi:10.1007/s10802-017-0294-5

Caspi, A., McClay, J., Moffitt, T. E., Mill, J., Martin, J., Craig, I. W.,... Poulton, R. (2002). Role of genotype in the cycle of violence in maltreated children. *Science, 297*(5582), 851–854. doi:10.1126/science.1072290

Chen, J., Yu, J., Liu, Y. J., Zhang, L. L., & Zhang, J. X. (2015). BDNF Val66Met, stress, and positive mothering: Differential susceptibility model of adolescent trait anxiety. *Journal of Anxiety Disorders, 34*, 68-75. doi:10.1016/j.janxdis.2015.06.001

Chhangur, R. R., Weeland, J., Overbeek, G., Matthys, W., de Castro, B. O., van der Giessen, D., & Belsky, J. (2017). Genetic Moderation of Intervention Efficacy: Dopaminergic Genes, The Incredible Years, and Externalizing Behavior in Children. *Child Development, 88*(3), 796-811. doi:10.1111/cdev.12612

Cho, J. H., Kogan, S. M., & Brody, G. H. (2016). Genetic Moderation of Transactional Relations Between Parenting Practices and Child Self-Regulation. *Journal of Family Psychology, 30*(7), 780-790. doi:10.1037/fam0000228

Cicchetti, D., Toth, S. L., & Handley, E. D. (2015). Genetic moderation of interpersonal psychotherapy efficacy for low-income mothers with major depressive disorder: implications for differential susceptibility. *Development and Psychopathology, 27*(1), 19-35. doi:10.1017/s0954579414001278

Clauss, J. A., Avery, S. N., & Blackford, J. U. (2015). The nature of individual differences in and risk for psychiatric disease: A review and meta-analysis. *Progress in Neurobiology, 127*, 23-45. doi:10.1016/j.pneurobio.2015.03.001

Conradt, E., Adkins, D. E., Crowell, S. E., Raby, K. L., Diamond, L. M., & Ellis, B. (2018). Incorporating epigenetic mechanisms to advance fetal programming theories. *Development and Psychopathology, 30*(3), 807-824. doi:10.1017/s0954579418000469

Conradt, E., Measelle, J., & Ablow, J. C. (2013). Poverty, Problem Behavior, and Promise: Differential Susceptibility Among Infants Reared in Poverty. *Psychological Science, 24*(3), 235-242. doi:10.1177/0956797612457381

Conway, C. C., Hammen, C., Brennan, P. A., Lind, P. A., & Najman, J. M. (2010). Interaction of chronic stress with serotonin transporter and catechol-O-methyltransferase polymorphisms in predicting youth depression. *Depress Anxiety*, *27*, 737–745

Cook, E. C., Wilkinson, K., & Stroud, L. R. (2018). The role of stress response in the association between autonomy and adjustment in adolescents. *Physiology & Behavior, 189*, 40-49. doi:10.1016/j.physbeh.2018.02.049

Cruz, O., Abreu-Lima, I., Canario, C., & Burchinal, M. (2018). Does Temperament Moderate the Relation between Preschool Parenting and School-Age Self-Regulation? Contrasting Diathesis-Stress and Differential Susceptibility Models. *Parenting-Science and Practice, 18*(2), 126-140. doi:10.1080/15295192.2018.1444133

Culverhouse, R. C., Saccone, N. L., Horton, A. C., Ma, Y., Anstey, K. J., Banaschewski, T., . . . Bierut, L. J. (2018). Collaborative meta-analysis finds no evidence of a strong interaction between stress and 5-HTTLPR genotype contributing to the development of depression. *Molecular Psychology, 23*, 133-142. doi:10.1038/mp.2017.44

Davies, P., Cicchetti, D., & Hentges, R. F. (2015). Maternal Unresponsiveness and Child Disruptive Problems: The Interplay of Uninhibited Temperament and Dopamine Transporter Genes. *Child Development, 86*(1), 63-79. doi:10.1111/cdev.12281

Deane, C., Vijayakumar, N., Allen, N. B., Schwartz, O., Simmons, J. G., Bousman, C. A., . . . Whittle, S. (2019). Parenting × Brain Development interactions as predictors of adolescent depressive symptoms and well-being: Differential susceptibility or diathesis-stress? *Development and Psychopathology*, 1-12. doi:10.1017/S0954579418001475

Del Giudice, M. (2017). Statistical tests of differential susceptibility: Performance, limitations, and improvements. *Development and Psychopathology, 29*(4), 1267-1278. doi:10.1017/s0954579416001292

Del Giudice, M., Barrett, E. S., Belsky, J., Hartman, S., Martel, M. M., Sangenstedt, S., & Kuzawa, C. W. (2018). Individual differences in developmental plasticity: A role for early androgens? *Psychoneuroendocrinology, 90*, 165-173. doi:10.1016/j.psyneuen.2018.02.025

Del Giudice, M., Ellis, B. J., & Shirtcliff, E. A. (2011). The Adaptive Calibration Model of stress responsivity. *Neuroscience and Biobehavioral Reviews, 35*(7), 1562-1592. doi:10.1016/j.neubiorev.2010.11.007

DeMaster, D., Bick, J., Johnson, U., Montroy, J. J., Landry, S., & Duncan, A. F. (2019). Nurturing the preterm infant brain: leveraging neuroplasticity to improve neurobehavioral outcomes. *Pediatric Research, 85*(2), 166-175. doi:10.1038/s41390-018-0203-9

Dibble, E., & Cohen, D. J. (1974). Companion instruments for measuring children's competence and parental style. *Archives of General Psychiatry, 30*, 805–815. doi:10.1001/archpsyc.1974.01760120061010

Dick, D. M., Agrawal, A., Keller, M. C., Adkins, A., Aliev, F., Monroe, S., . . . Sher, K. J. (2015). Candidate Gene-Environment Interaction Research: Reflections and Recommendations. *Perspectives on Psychological Science, 10*(1), 37-59. doi:10.1177/1745691614556682

Donnelly, P. (2008) Progress and challenges in genome-wide association studies in humans. *Nature, 456*, 728–731. https://doi.org/10.1038/nature07631

Ellis, B. J., & Boyce, W. T. (2008). Biological sensitivity to context. *Current Directions in Psychological Science, 17*(3), 183-187. doi:10.1111/j.1467-8721.2008.00571.x

Ellis, B. J., Boyce, W. T., Belsky, J., Bakermans-Kranenburg, M. J., & van Ijzendoorn, M. H. (2011). Differential susceptibility to the environment: An evolutionary-neurodevelopmental theory. *Development and Psychopathology, 23*(1), 7-28. doi:10.1017/s0954579410000611

Ellis, B. J., & Del Giudice, M. (2019). Developmental Adaptation to Stress: An Evolutionary Perspective. In S. T. Fiske (Ed.), *Annual Review of Psychology, Vol 70* (Vol. 70, pp. 111-139). 10.1146/annurev-psych-122216-011732

Esposito, G., Truzzi, A., Setoh, P., Putnick, D. L., Shinohara, K., & Bornstein, M. H. (2017). Genetic predispositions and parental bonding interact to shape adults' physiological

responses to social distress. *Behavioural Brain Research, 325*, 156-162. doi:10.1016/j.bbr.2016.06.042

Fine, A., Mahler, A., Simmons, C., Chen, C. S., Moyzis, R., & Cauffman, E. (2016). Relations Between Three Dopaminergic System Genes, School Attachment, and Adolescent Delinquency. *Developmental Psychology, 52*(11), 1893-1903. doi:10.1037/dev0000166

Flasbeck, V., Moser, D., Kumsta, R., & Brune, M. (2018). The OXTR Single-Nucleotide Polymorphism rs53576 Moderates the Impact of Childhood Maltreatment on Empathy for Social Pain in Female Participants: Evidence for Differential Susceptibility. *Frontiers in Psychiatry, 9*, 1-9. doi:10.3389/fpsyt.2018.00359

Gard, A. M., Shaw, D. S., Forbes, E. E., & Hyde, L. W. (2018). Amygdala Reactivity as a Marker of Differential Susceptibility to Socioeconomic Resources During Early Adulthood. *Developmental Psychology, 54*(12), 2341-2355. doi:10.1037/dev0000600

Greven, C. U., Lionetti, F., Booth, C., Aron, E. N., Fox, E., Schendan, H. E., . . . Homberg, J. (2019). Sensory Processing Sensitivity in the context of Environmental Sensitivity: A critical review and development of research agenda. *Neuroscience and Biobehavioral Reviews, 98*, 287-305. doi:10.1016/j.neubiorev.2019.01.009

Grimen, H. L., & Diseth, A. (2016). Sensory Processing Sensitivity: Factors of the Highly Sensitive Person Scale and Their relationships to Personality and Subjective Health Complaints. *Perceptual and Motor Skills, 123*(3), 637-653. doi:10.1177/0031512516666114

Gueron-Sela, N., Atzaba-Poria, N., Meiri, G., & Marks, K. (2016). Temperamental Susceptibility to Parenting among Preterm and Full-Term Infants in Early Cognitive Development. *Infancy, 21*(3), 312-331. doi:10.1111/infa.12120

Gueron-Sela, N., Wagner, N. J., Propper, C. B., Mills-Koonce, W. R., Moore, G. A., & Cox, M. J. (2017). The Interaction Between Child Respiratory Sinus Arrhythmia and Early Sensitive Parenting in the Prediction of Children's Executive Functions. *Infancy, 22*(2), 171-189. doi:10.1111/infa.12152

Gunnar, M. R., & Quevedo, K. (2007). The neurobiology of stress and development. Annual Review of Psychology, 58, 145–173.

Hammen, C., Bower, J. E., & Cole, S. W. (2015). OXYTOCIN RECEPTOR GENE VARIATION AND DIFFERENTIAL SUSCEPTIBILITY TO FAMILY ENVIRONMENT IN PREDICTING YOUTH BORDERLINE SYMPTOMS. *Journal of Personality Disorders*, *29*(2), 177-192. doi:10.1521/pedi_2014_28_152

Hartl, D. L. (2011). *Essential Genetics. A Genomics Perspective.* (5th ed.). Boston: Jones and Bartlett Publishers.

Hartman, S., & Belsky, J. (2016). An Evolutionary Perspective on Family Studies: Differential Susceptibility to Environmental Influences. *Family Process, 55*(4), 700-712. doi:10.1111/famp.12161

Hartman, S., & Belsky, J. (2018). Prenatal programming of postnatal plasticity revisited-And extended. *Development and Psychopathology, 30*(3), 825-842. doi:10.1017/s0954579418000548

Homberg, J. R., Schubert, D., Asan, E., & Aron, E. N. (2016). Sensory, processing sensitivity and serotonin gene variance: Insights into mechanisms shaping environmental sensitivity. *Neuroscience and Biobehavioral Reviews, 71*, 472-483. doi:10.1016/j.neubiorev.2016.09.029

Hygen, B. W., Belsky, J., Li, Z., Stenseng, F., Guzey, I. C., & Wichstrom, L. (2017). Change in Parenting, Change in Student-Teacher Relationships, and Oxytocin Receptor Gene (OXTR): Testing a Gene-X-Environment (G X E) Hypothesis in Two Samples. *Developmental Psychology, 53*(7), 1300-1315. doi:10.1037/dev0000333

Hygen, B. W., Belsky, J., Stenseng, F., Lydersen, S., Guzey, I. C., & Wichstrom, L. (2015). Child Exposure to Serious Life Events, COMT, and Aggression: Testing Differential Susceptibility Theory. *Developmental Psychology, 51*(8), 1098-1104. doi:10.1037/dev0000020

Jagiellowicz, J., Xu, X. M., Aron, A., Aron, E., Cao, G. K., Feng, T. Y., & Weng, X. C. (2011). The trait of sensory processing sensitivity and neural responses to changes in visual scenes. *Social Cognitive and Affective Neuroscience, 6*(1), 38-47. doi:10.1093/scan/nsq001

Jiang, Y. S., Chew, S. H., & Ebstein, R. P. (2013). The role of D4 receptor gene exon III polymorphisms in shaping human altruism and prosocial behavior. *Frontiers in Human Neuroscience, 7,* 1-7. doi:10.3389/fnhum.2013.00195

Kalomiris, A. E., Phelps, R. A., & Kiel, E. J. (2019). The Relation between Specific Parenting Behaviors and Toddlers' Early Anxious Behaviors is Moderated by Toddler Cortisol Reactivity. *Journal of Abnormal Child Psychology*. doi:10.1007/s10802-019-00522-9

Keers, R., Coleman, J. R. I., Lester, K. J., Roberts, S., Breen, G., Thastum, M., . . . Eley, T. C. (2016). A Genome-Wide Test of the Differential Susceptibility Hypothesis Reveals a Genetic Predictor of Differential Response to Psychological Treatments for Child

Anxiety Disorders. *Psychotherapy and Psychosomatics, 85*(3), 146-158. doi:10.1159/000444023

Keers, R., & Pluess, M. (2017). Childhood quality influences genetic sensitivity to environmental influences across adulthood: A life-course Gene x Environment interaction study. *Development and Psychopathology, 29*(5), 1921-1933. doi:10.1017/s0954579417001493

King, A. P., Muzik, M., Hamilton, L., Taylor, A. B., Rosenblum, K. L., & Liberzon, I. (2016). Dopamine Receptor Gene DRD4 7-Repeat Allele X Maternal Sensitivity Interaction on Child Externalizing Behavior Problems: Independent Replication of Effects at 18 Months. *Plos One, 11*(8). doi:10.1371/journal.pone.0160473

Klengel, T., Mehta, D., Anacker, C., Rex-Haffner, M., Pruessner, J. C., Pariante, C. M., . . . Binder, E. B. (2012). Allele-specific FKBP5 DNA demethylation mediates gene–childhood trauma interactions. *Nat Neurosci, 16*(1), 33-41. doi:10.1038/nn.3275

Kok, R., Bakermans-Kranenburg, M. J., van Ijzendoorn, M. H., Velders, F. P., Linting, M., Jaddoe, V. W. V., . . . Tiemeier, H. (2013). The role of maternal stress during pregnancy, maternal discipline, and child COMT Val158Met genotype in the development of compliance. *Developmental Psychobiology, 55*(5), 451-464. doi:10.1002/dev.21049

Kushner, S. C., Herzhoff, K., Vrshek-Schallhorn, S., & Tackett, J. L. (2018). Depression in early adolescence: Contributions from relational aggression and variation in the oxytocin receptor gene. *Aggressive Behavior, 44*(1), 60-68. doi:10.1002/ab.21724

Laucht, M., Blomeyer, D., Buchmann, A. F., Treutlein, J., Schmidt, M. H., Esser, G., . . . Banaschewski, T. (2012). Catechol-O-methyltransferase Val158Met genotype, parenting practices and adolescent alcohol use: testing the differential susceptibility hypothesis. *Journal of Child Psychology and Psychiatry, 53*(4), 351-359. doi:10.1111/j.1469-7610.2011.02408.x

Lee, D., Brooks-Gunn, J., McLanahan, S. S., Notterman, D., & Garfinkel, I. (2013). The Great Recession, genetic sensitivity, and maternal harsh parenting. *Proceedings of the National Academy of Sciences of the United States of America, 110*(34), 13780-13784. doi:10.1073/pnas.1312398110

Leighton, C., Botto, A., Silva, J. R., Jimenez, J. P., & Luyten, P. (2017). Vulnerability or Sensitivity to the Environment? Methodological Issues Trends, and Recommendations in Gene-Environment Interactions Research in Human Behavior. *Frontiers in Psychiatry, 8,* 1-14. doi:10.3389/fpsyt.2017.00106

Lemery-Chalfant, K., Clifford, S., Dishion, T. J., Shaw, D. S., & Wilson, M. N. (2018). Genetic moderation of the effects of the Family Check-Up intervention on children's internalizing symptoms: A longitudinal study with a racially/ethnically diverse sample. *Development and Psychopathology, 30*(5), 1729-1747. doi:10.1017/s095457941800127x

Levitan, R. D., Jansen, P., Wendland, B., Tiemeier, H., Jaddoe, V. W., Silveira, P. P., . . . Meaney, M. (2017). A DRD4 gene by maternal sensitivity interaction predicts risk for overweight or obesity in two independent cohorts of preschool children. *Journal of Child Psychology and Psychiatry, 58*(2), 180-188. doi:10.1111/jcpp.12646

Liu, Y. P., Chen, X. Y., Zhao, S. M., Way, N. B., Yoshikawa, H., Zhang, G. Z., . . . Deng, H. H. (2017). Interactions between MAOA gene polymorphism and maternal parenting in predicting externalizing and internalizing problems and social competence among Chinese children: Testing the genetic vulnerability and differential susceptibility models. *Infant and Child Development, 26*(6), 1-17. doi:10.1002/icd.2024

Marshall, E. (1997). Snipping away at genome patenting. *Science, 277*(5333), 1752-1753. doi: 10.1126/science.277.5333.1752

Masarik, A. S., Conger, R. D., Donnellan, M. B., Stallings, M. C., Martin, M. J., Schofield, T. J., . . . Widaman, K. F. (2014). For Better and for Worse: Genes and Parenting Interact to Predict Future Behavior in Romantic Relationships. *Journal of Family Psychology, 28*(3), 357-367. doi:10.1037/a0036818

Mesquita, A. R., Belsky, J., Li, Z., Baptista, J., Carvalho-Correia, E., Maciel, P., & Soares, I. (2015). Institutionalization and indiscriminate social behavior: Differential-susceptibility versus diathesis-stress models for the 5-HTTLPR and BDNF genotypes. *Physiology & Behavior, 152,* 85-91. doi:10.1016/j.physbeh.2015.09.015

Meyer, A., Hajcak, G., Hayden, E., Sheikh, H. I., Singh, S., & Klein, D. N. (2018). A genetic variant brain-derived neurotrophic factor (BDNF) polymorphism interacts with hostile parenting to predict error-related brain activity and thereby risk for internalizing disorders in children. *Development and Psychopathology, 30*(1), 125-141. doi:10.1017/s0954579417000517

Mills, A., Day, K., Van Lieshout, R., & Schmidt, L. (2019). Relations among Temperament, Familial Socioeconomic Status, and Inhibitory Control in Typically Developing Four-Year-Old Children. *Journal of Child and Family Studies, 28,* 1-9. doi:10.1007/s10826-019-01329-4

Miu, A. C., Carnuta, M., Vulturar, R., Szekely-Copindean, R. D., Bilc, M. I., Chis, A., . . . Gross, J. J. (2017). BDNF Val66Met polymorphism moderates the link between child maltreatment and reappraisal ability. *Genes Brain and Behavior, 16*(4), 419-426. doi:10.1111/gbb.12366

Monroe, S. M., & Simons, A. D. (1991). DIATHESIS STRESS THEORIES IN THE CONTEXT OF LIFE STRESS RESEARCH - IMPLICATIONS FOR THE DEPRESSIVE-DISORDERS. *Psychological Bulletin, 110*(3), 406-425. doi:10.1037/0033-2909.110.3.406

Moore, S. R., & Depue, R. A. (2016). Neurobehavioral Foundation of Environmental Reactivity. *Psychological Bulletin, 142*(2), 107-164. doi:10.1037/bul0000028

Morgan, B., Kumsta, R., Fearon, P., Moser, D., Skeen, S., Cooper, P., . . . Tomlinson, M. (2017). Serotonin transporter gene (SLC6A4) polymorphism and susceptibility to a home-visiting maternal-infant attachment intervention delivered by community health workers in South Africa: Reanalysis of a randomized controlled trial. *Plos Medicine, 14*(2). doi:10.1371/journal.pmed.1002237

Nilsson, K. W., Aslund, C., Comasco, E., & Oreland, L. (2018). Gene-environment interaction of monoamine oxidase A in relation to antisocial behaviour: current and future directions. *Journal of Neural Transmission, 125*(11), 1601-1626. doi:10.1007/s00702-018-1892-2

Nilsson K.W., Comasco, E., Hodgins, S., Oreland, L., & Aslund, C. (2015). Genotypes do not confer risk for delinquency but rather alter susceptibility to positive and negative environmental factors: gene–environment interactions of BDNF Val66Met, 5-HTTLPR, and MAOA-uVNTR. *Int J Neuropsychopharmacol, 18*(5), 1-10. doi.org/10.1093/ijnp/pyu107

Obradovic, J. (2012). How can the study of physiological reactivity contribute to our understanding of adversity and resilience processes in development? *Development and Psychopathology, 24*(2), 371-387. doi:10.1017/s0954579412000053

Obradovic, J., Bush, N. R., Stamperdahl, J., Adler, N. E., & Boyce, W. T. (2010). Biological Sensitivity to Context: The Interactive Effects of Stress Reactivity and Family Adversity on Socioemotional Behavior and School Readiness. *Child Development, 81*(1), 270-289. doi:10.1111/j.1467-8624.2009.01394.x

Olofsdotter, S., Aslund, C., Furmark, T., Comasco, E., & Nilsson, K. W. (2018). Differential susceptibility effects of oxytocin gene (OXT) polymorphisms and perceived parenting

on social anxiety among adolescents. *Development and Psychopathology, 30*(2), 449-459. doi:10.1017/s0954579417000967

Overbeek, G. (2017). Parenting intervention effects on children's externalizing behavior: the moderating role of genotype and temperament. *Current Opinion in Psychology, 15*, 143-148. doi:10.1016/j.copsyc.2017.02.025

Perez-Perez, B., Cristobal-Narvaez, P., Sheinbaum, T., Kwapil, T. R., Ballesp, S., Pena, E., . . . Barrantes-Vidal, N. (2018). Interaction between FKBP5 variability and recent life events in the anxiety spectrum: Evidence for the differential susceptibility model. *Plos One, 13*(2). doi:10.1371/journal.pone.0193044

Pitzer, M., Esser, G., Schmidt, M. H., Hohm, E., Banaschewski, T., & Laucht, M. (2017). Child regulative temperament as a mediator of parenting in the development of depressive symptoms: a longitudinal study from early childhood to preadolescence. *Journal of Neural Transmission, 124*(5), 631-641. doi:10.1007/s00702-017-1682-2

Pluess, M. (2015). Individual Differences in Environmental Sensitivity. *Child Development Perspectives, 9*(3), 138-143. doi:10.1111/cdep.12120

Pluess, M., & Belsky, J. (2010). Differential Susceptibility to Parenting and Quality Child Care. *Developmental Psychology, 46*(2), 379-390. doi:10.1037/a0015203

Pluess, M., & Belsky, J. (2011). Prenatal programming of postnatal plasticity? *Development and Psychopathology, 23*(1), 29-38. doi:10.1017/s0954579410000623

Pluess, M., Belsky, J., Way, B. M., & Taylor, S. E. (2010). 5-HTTLPR moderates effects of current life events on neuroticism: Differential susceptibility to environmental influences. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 34*(6), 1070-1074. doi:10.1016/j.pnpbp.2010.05.028

Rioux, C., Castellanos-Ryan, N., Parent, S., & Seguin, J. R. (2016). The interaction between temperament and the family environment in adolescent substance use and externalizing behaviors: Support for diathesis-stress or differential susceptibility? *Developmental Review, 40*, 117-150. doi:10.1016/j.dr.2016.03.003

Rioux, C., Castellanos-Ryan, N., Parent, S., Vitaro, F., & Seguin, J. R. (2019). The Interactive Effects of Parental Knowledge with Impulsivity and Sensation Seeking in Adolescent Substance Use. *Child Psychiatry & Human Development, 50*(1), 95-107. doi:10.1007/s10578-018-0825-5

Roisman, G. I., Newman, D. A., Fraley, R. C., Haltigan, J. D., Groh, A. M., & Haydon, K. C. (2012). Distinguishing differential susceptibility from diathesis-stress:

Recommendations for evaluating interaction effects. *Development and Psychopathology, 24*(2), 389-409. doi:10.1017/s0954579412000065

Rothbart, M. K., Ahadi, S. A., Hershey, K. L., & Fisher, P. (2001). Investigations of temperament at three to seven years: The Children's Behavior Questionnaire. *Child Development, 72*, 1394-1408. doi:10.1111/14678624.00355.

Rutter, M. (2012). Resilience as a dynamic concept. *Development and Psychopathology, 24*(2), 335-344. doi:10.1017/s0954579412000028

Schriber, R. A., & Guyer, A. E. (2016). Adolescent neurobiological susceptibility to social context. *Developmental Cognitive Neuroscience, 19*, 1-18. doi:10.1016/j.dcn.2015.12.009

Sijtsema, J. J., Nederhof, E., Veenstra, R., Ormel, J., Oldehinkel, A. J., & Ellis, B. J. (2013). Effects of family cohesion and heart rate reactivity on aggressive/rule-breaking behavior and prosocial behavior in adolescence: The Tracking Adolescents' Individual Lives Survey study. *Development and Psychopathology, 25*(3), 699-712. doi:10.1017/s0954579413000114

Silveira, P. P., Gaudreau, H., Atkinson, L., Fleming, A. S., Sokolowski, M. B., Steiner, M., . . . Dube, L. (2016). Genetic Differential Susceptibility to Socioeconomic Status and Childhood Obesogenic Behavior Why Targeted Prevention May Be the Best Societal Investment. *Jama Pediatrics, 170*(4), 359-364. doi:10.1001/jamapediatrics.2015.4253

Slagt, M., Dubas, J. S., Dekovic, M., & van Aken, M. A. G. (2016). Differences in Sensitivity to Parenting Depending on Child Temperament: A Meta-Analysis. *Psychological Bulletin, 142*(10), 1068-1110. doi:10.1037/bul0000061

Somers, J. A., Ibrahim, M. H., & Luecken, L. J. (2017). Biological Sensitivity to the Effects of Childhood Family Adversity on Psychological Well-Being in Young Adulthood. *Child Maltreatment, 22*(3), 236-244. doi:10.1177/1077559517711041

Somers, J. A., Jewell, S. L., Ibrahim, M. H., & Luecken, L. J. (2019). Infants' Biological Sensitivity to the Effects of Maternal Social Support: Evidence Among Mexican American Families. *Infancy, 24*(2), 275-296. doi:10.1111/infa.12266

Steeger, C. M., Cook, E. C., & Connell, C. M. (2017). The Interactive Effects of Stressful Family Life Events and Cortisol Reactivity on Adolescent Externalizing and Internalizing Behaviors. *Child Psychiatry & Human Development, 48*(2), 225-234. doi:10.1007/s10578-016-0635-6

Stogner, J. M. (2015). DAT1 and alcohol use: differential responses to life stress during adolescence. *Criminal Justice Studies, 28*(1), 18-38. doi:10.1080/1478601x.2014.1000003

Stoltz, S., Beijers, R., Smeekens, S., & Dekovic, M. (2017). Diathesis stress or differential susceptibility? testing longitudinal associations between parenting, temperament, and children's problem behavior. *Social Development, 26*(4), 783-796. doi:10.1111/sode.12237

Sulik, M. J., Eisenberg, N., Spinrad, T. L., Lemery-Chalfant, K., Swann, G., Silva, K. M., . . . Verrelli, B. C. (2015). Interactions among catechol-O-methyltransferase genotype, parenting, and sex predict children's internalizing symptoms and inhibitory control: Evidence for differential susceptibility. *Development and Psychopathology, 27*(3), 709-723. doi:10.1017/s0954579414000807

Sun, Y., Fang, J., Wan, Y. H., Hu, J. J., Xu, Y. Y., & Tao, F. B. (2018). Polygenic differential susceptibility to cumulative stress exposure and childhood obesity. *International Journal of Obesity, 42*(6), 1177-1184. doi:10.1038/s41366-018-0116-z

Thibodeau, E. L., Cicchetti, D., & Rogosch, F. A. (2015). Child maltreatment, impulsivity, and antisocial behavior in African American children: Moderation effects from a cumulative dopaminergic gene index. *Development and Psychopathology, 27*(4), 1621-1636. doi:10.1017/s095457941500098x

Tung, I., Morgan, J. E., Norona, A. N., & Lee, S. S. (2017). Prenatal programming of postnatal plasticity for externalizing behavior: Testing an integrated developmental model of genetic and temperamental sensitivity to the environment. *Developmental Psychobiology, 59*(8), 984-996. doi:10.1002/dev.21549

Tung, I., Norona, A. N., Lee, S. S., Langley, A. K., & Waterman, J. M. (2018). Temperamental sensitivity to early maltreatment and later family cohesion for externalizing behaviors in youth adopted from foster care. *Child Abuse & Neglect, 76*, 149-159. doi:10.1016/j.chiabu.2017.10.018

Tuvblad, C., Narusyte, J., Comasco, E., Andershed, H., Andershed, A. K., Colins, O. F., . . . Nilsson, K. W. (2016). Physical and Verbal Aggressive Behavior and COMT Genotype: Sensitivity to the Environment. *American Journal of Medical Genetics Part B-Neuropsychiatric Genetics, 171*(5), 708-718. doi:10.1002/ajmg.b.32430

van Bodegom, M., Homberg, J. R., & Henckens, M. (2017). Modulation of the Hypothalamic-Pituitary-Adrenal Axis by Early Life Stress Exposure. *Frontiers in Cellular Neuroscience, 11*, 1-33. doi:10.3389/fncel.2017.00087

van Ijzendoorn, M. H., & Bakermans-Kranenburg, M. J. (2015). Genetic differential susceptibility on trial: Meta-analytic support from randomized controlled experiments. *Development and Psychopathology, 27*(1), 151-162. doi:10.1017/s0954579414001369

van Ijzendoorn, M. H., Belsky, J., & Bakermans-Kranenburg, M. J. (2012). Serotonin transporter genotype 5HTTLPR as a marker of differential susceptibility? A meta-analysis of child and adolescent gene-by-environment studies. *Translational Psychiatry, 2*. doi:10.1038/tp.2012.73

VanZomeren-Dohm, A. A., Pitula, C. E., Koss, K. J., Thomas, K., & Gunnar, M. R. (2015). FKBP5 moderation of depressive symptoms in peer victimized, post-institutionalized children. *Psychoneuroendocrinology, 51*, 426-430. doi:10.1016/j.psyneuen.2014.10.003

Viddal, K. R., Berg-Nielsen, T. S., Belsky, J., & Wichstrom, L. (2017). Change in Attachment Predicts Change in Emotion Regulation Particularly Among 5-HTTLPR Short-Allele Homozygotes. *Developmental Psychology, 53*(7), 1316-1329. doi:10.1037/dev0000321

Villani, V., Ludmer, J., Gonzalez, A., Levitan, R., Kennedy, J., Masellis, M., . . . Atkinson, L. (2018). Dopamine receptor D2 (DRD2), dopamine transporter solute carrier family C6, member 4 (SLC6A3), and catechol-O-methyltransferase (COMT) genes as moderators of the relation between maternal history of maltreatment and infant emotion regulation. *Development and Psychopathology, 30*(2), 581-592. doi:10.1017/s0954579417001122

Wagner, N. J., Mills-Koonce, W. R., Willoughby, M. T., Cox, M. J., Vernon-Feagans, L., Blair, C., . . . Family Life Project, K. (2019). Parenting and Cortisol in Infancy Interactively Predict Conduct Problems and Callous-Unemotional Behaviors in Childhood. *Child Development, 90*(1), 279-297. doi:10.1111/cdev.12900

Wang, M. P., Li, H. L., Deater-Deckard, K., & Zhang, W. X. (2018). Interacting Effect of Catechol-O-Methyltransferase (COMT) and Monoamine Oxidase A (MAOA) Gene Polymorphisms, and Stressful Life Events on Aggressive Behavior in Chinese Male Adolescents. *Frontiers in Psychology, 9,* 1-9. doi:10.3389/fpsyg.2018.01079

Wass, S. V. (2018). How orchids concentrate? The relationship between physiological stress reactivity and cognitive performance during infancy and early childhood. *Neuroscience and Biobehavioral Reviews, 90,* 34-49. doi:10.1016/j.neubiorev.2018.03.029

Weeland, J., Overbeek, G., de Castro, B. O., & Matthys, W. (2015). Underlying Mechanisms of Gene-Environment Interactions in Externalizing Behavior: A Systematic Review and Search for Theoretical Mechanisms. *Clinical Child and Family Psychology Review, 18*(4), 413-442. doi:10.1007/s10567-015-0196-4

Weeland, J., Van den Akker, A., Slagt, M., & Putnam, S. (2017). Perception is key? Does perceptual sensitivity and parenting behavior predict children's reactivity to others' emotions? *Journal of Experimental Child Psychology, 163*, 53-68. doi:10.1016/j.jecp.2017.06.012

Windhorst, D. A., Mileva-Seitz, V. R., Linting, M., Hofman, A., Jaddoe, V. W. V., Verhulst, F. C., . . . Bakermans-Kranenburg, M. J. (2015). Differential Susceptibility in a Developmental Perspective: DRD4 and Maternal Sensitivity Predicting Externalizing Behavior. *Developmental Psychobiology, 57*(1), 35-49. doi:10.1002/dev.21257

Xing, S. F., Zhou, Q., Archer, M., Yue, J. H., & Wang, Z. Y. (2016). Infant temperamental reactivity, maternal and grandparental sensitivity: Differential susceptibility for behavior problems in China. *Early Human Development, 101*, 99-105. doi:10.1016/j.earlhumdev.2016.08.014

Zandstra, A. R. E., Ormel, J., Dietrich, A., van den Heuvel, E. R., Hoekstra, P. J., & Hartman, C. A. (2018). Sensitivity to psychosocial chronic stressors and adolescents' externalizing problems: Combined moderator effects of resting heart rate and parental psychiatric history. *Biological Psychology, 134*, 20-29. doi:10.1016/j.biopsycho.2018.02.009

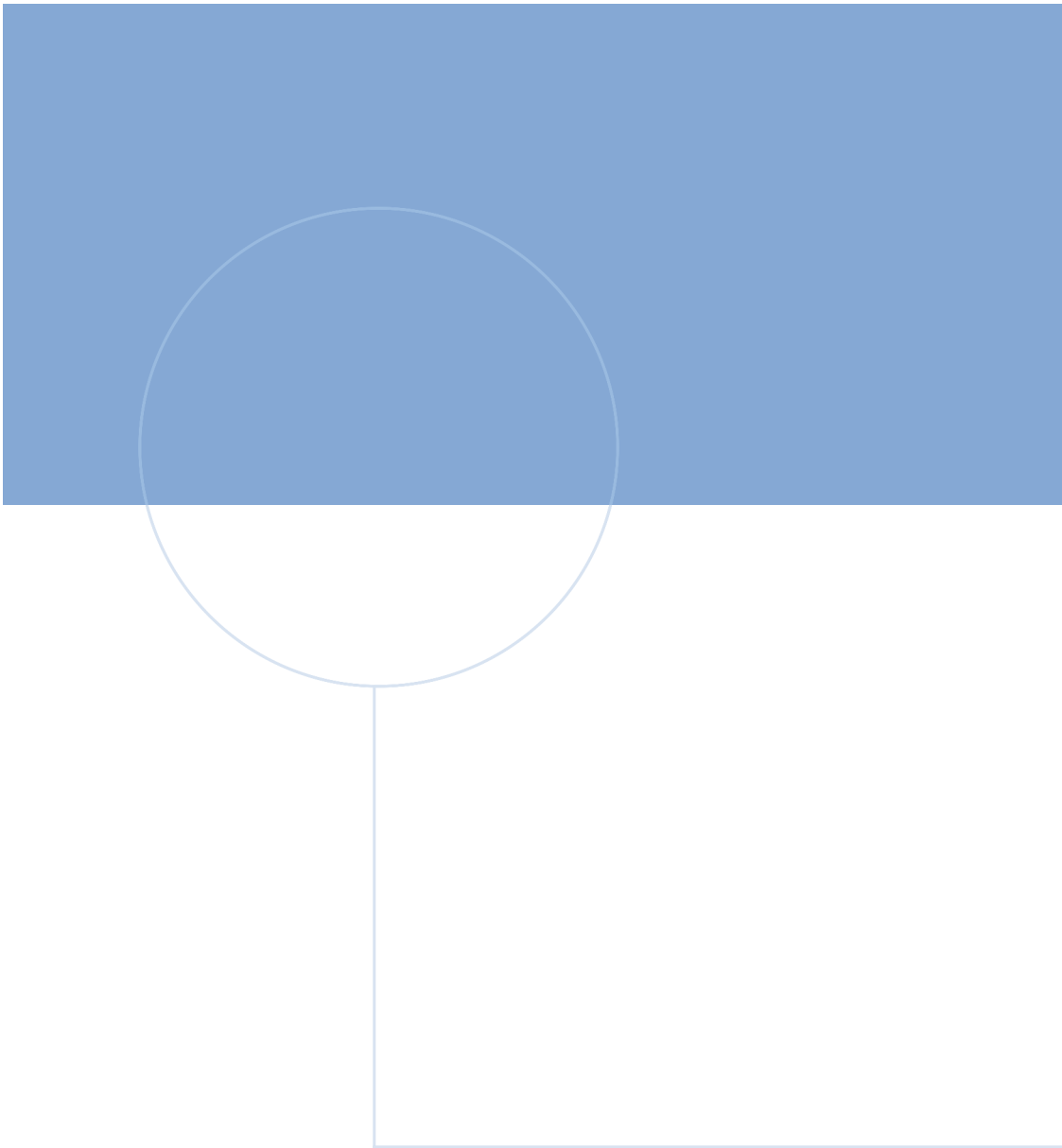
Zhang, L. L., Li, Z., Chen, J., Li, X. Y., Zhang, J. X., & Belsky, J. (2016). The BDNF Val66Met Polymorphism Interacts with Maternal Parenting Influencing Adolescent Depressive Symptoms: Evidence of Differential Susceptibility Model. *Journal of Youth and Adolescence, 45*(3), 471-483. doi:10.1007/s10964-015-0378-x

Zhang, W. X., Cao, C., Wang, M. P., Ji, L. Q., & Cao, Y. M. (2016). Monoamine Oxidase A (MAOA) and Catechol-O-Methyltransferase (COMT) Gene Polymorphisms Interact with Maternal Parenting in Association with Adolescent Reactive Aggression but not Proactive Aggression: Evidence of Differential Susceptibility. *Journal of Youth and Adolescence, 45*(4), 812-829. doi:10.1007/s10964-016-0442-1

Zhang, W. X., Cao, Y. M., Wang, M. P., Ji, L. Q., Chen, L., & Deater-Deckard, K. (2015). The Dopamine D2 Receptor Polymorphism (DRD2 TaqIA) Interacts with Maternal Parenting in Predicting Early Adolescent Depressive Symptoms: Evidence of

Differential Susceptibility and Age Differences. *Journal of Youth and Adolescence, 44*(7), 1428-1440. doi:10.1007/s10964-015-0297-x

Zuckerman, M. (1999). *Vulnerability to psychopathology: A biosocial model.* Washington, DC: American Psychological Association.



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