Psychosocial adversity and adolescents' mental health problems

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General introduction

While exposure to stressors is a well-established risk factor for externalizing and internalizing psychopathology in adolescence (for an overview, see Grant, Compas, Thurm, McMahon, & Gipson, 2004), there is substantial individual variation in outcome (Jenkins, 2008; Rutter, 2005). This PhD thesis aims to contribute to our understanding of that variation, by examining specific biological factors that may be associated with a favourable or unfavourable long-term mental health outcome after exposure to stressors. The research is focused on adolescence. Adolescence is an important developmental period for studying the stressors-psychopathology association, given associated major biological, psychological, and social changes (Hollenstein & Lougheed, 2013); as well as pronounced increases in prevalence rates of psychopathology (Newman et al., 1996) and number of stressors (Larson & Ham, 1993).

The stressors-psychopathology relationship

Factors that confer vulnerability or resilience by altering an association's direction or strength are referred to as moderators (Baron & Kenny, 1986). The substantial individual variation in mental health outcomes after exposure to stressors (Jenkins, 2008; Rutter, 2005) suggests the workings of such moderating factors. Potential moderators of the stressors-psychopathology association include relatively stable characteristics of the individual, group, or environment; that may be genetically or environmentally influenced; and that exist preceding stressor exposure (Grant et al., 2003). In a literature review of moderator effects on the stressors-psychopathology association in adolescence, Grant and colleagues (2006) demonstrated generally inconsistent findings and a lack of theory-based studies. The reported moderator studies addressed fixed individual characteristics (e.g., age, sex, ethnicity), more malleable psychological characteristics (e.g., cognitions, competence, coping) and environmental characteristics (e.g., social support, family or peer environment).

What stands out in this list is the absence of biological characteristics. Parallel in time to the review by Grant and colleagues, the resilience literature urged the need to consider biological factors, such as genetic markers, neurotransmitters, and hormones, as potential risk or protective factors in the face of adversity (Luthar, 2006). Meanwhile, literature reviews and meta-studies demonstrated great progress in the identification of specific biological risk factors (e.g., genetic variation, autonomic underarousal) of externalizing problems (oppositional defiant and conduct disorders, Burke, Loeber, & Birmaher, 2002; aggression, psychopathy, and conduct disorder, Lorber, 2004; antisocial behavior, Ortiz & Raine, 2004; antisocial and violent behavior, Raine, 2002a) and emerg-

ing interest in and evidence of interactions between biological and psychosocial risk factors to explain individual differences in externalizing problems (Raine, 2002b).

Thus, one decade ago, the literature called for more theory-driven research on biosocial interactions underlying individual differences in risk of psychopathology. Since, findings from the field of externalizing problems as well as the introduction of influential theories of sensitivity to the environment have drawn researchers' attention toward psychophysiology and genetic polymorphisms as potential mechanisms linking stressors to mental health problems. Biological factors central to this PhD thesis are basal cortisol level collected immediately upon waking, resting heart rate (HR), and the Dopamine D4 Receptor 7-repeat allele (*DRD4*-7R). We investigated if these biological variables aided in furthering our understanding of adolescents' externalizing (aggressive and rule-breaking) and internalizing (mood and anxiety) problems following exposure to stressors.

Individual differences in sensitivity to stressors

The heterogeneity in mental health outcomes following exposure to stressors suggests that some individuals are more "sensitive" than others. Individual differences in sensitivity to the environment have been addressed in several theoretical frameworks. According to the Diathesis-Stress model (Zuckerman, 1999), individuals with a certain vulnerability (diathesis) are more likely to be negatively affected by exposure to stressors than individuals without that vulnerability. Specifically, a vulnerability factor (e.g., psychological, physiological, genetic), or a combination of vulnerability factors from multiple domains, may interact with exposure to stressors to produce enhanced risk of mental health problems (Monroe & Simons, 1991), in line with the moderator definition provided above.

In the last decade, the Diathesis-Stress notion that some individuals are more sensitive to stressors than others has been extended by Biological Sensitivity to Context theory and the Differential Susceptibility hypothesis (Belsky, Bakermans-Kranenburg, & Van IJzendoorn, 2007; Boyce & Ellis, 2005; Ellis & Boyce, 2008; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & Van IJzendoorn, 2011). These models have proposed that that highly sensitive individuals, compared to those less sensitive, may not only be more affected by adverse environmental influences (e.g., parental hostility), but also by beneficial environmental influences (e.g., parental emotional warmth). High sensitivity, characterized by high attentiveness and responsiveness to environmental cues (e.g., social, emotional), may thus be advantageous or disadvantageous, depending on the environmental context. On the one hand, sustained exposure to stress-related cues may put sensitive

individuals at risk of stress overload and, consequently, externalizing and internalizing problems, impaired school or work performance, and other detrimental outcomes. On the other hand, in supportive, low-stress environments, the same sensitive individuals may optimally benefit from the care and education they receive (Shirtcliff & Essex, 2008), enabling them to thrive across multiple domains (e.g., mental and physical health, social functioning, school or work performance). In contrast, individuals with low sensitivity, characterized by low attentiveness and responsiveness to their surroundings, may be less affected by stressful situations as well as by positive experiences or efforts made by parents and teachers.[1]

In sum, whereas Biological Sensitivity to Context and Differential Susceptibility theories refer to sensitivity *for better and for worse*, Diathesis-Stress only covers the latter. Individual characteristics that may reflect individual differences in sensitivity to environmental influences (adverse, beneficial, or both), are thus of interest as potential moderators of the stressors-psychopathology association.

Potential biological markers of sensitivity

Whereas early Biological Sensitivity to Context work (e.g., Ellis, Essex, & Boyce, 2005) focused exclusively on psychobiological reactivity measures as indices of sensitivity, the Differential Susceptibility framework did not limit potential sensitivity indices to specific domains or types of measures. A recent integration of these complementary frameworks has pointed to individual differences in neurobiological sensitivity as the common denominator and has suggested that markers of sensitivity at the behavioral, neuroendocrine, neural, genetic, and epigenetic level may reflect a common sensitive endophenotype (Ellis et al., 2011). In this thesis, we investigate potential sensitivity markers at the neurobiologic and genetic level.

The neuroendocrine system strives for bodily homeostasis (i.e., equilibrium or balance) by regulating a wide range of physiological processes (e.g., reproduction, energy supply and usage). When homeostasis is disrupted (e.g., by injury, infection, or psychosocial stressors), a stress response is set into motion that enables the body to respond quickly and adequately in order for homeostasis to be restored. Neurobiological measures central to this thesis involve cortisol, the hormonal end product of the hypotha-

1 Somewhat hackneyed, yet illustrative, is the botanical analogy of high and low sensitivity with the orchid and the dandelion (Boyce & Ellis, 2005). In short, when growing in precisely the right circumstances, an orchid is a feast for the eyes, but any mild climate disturbance results in its downfall. The dandelion, in contrast, is not known for its aesthetic qualities, but will grow everywhere regardless of climate changes.

lamic–pituitary–adrenal (HPA) axis (Hawes, Brennan, & Dadds, 2009), also known as the stress axis (Dedovic, Duchesne, Andrews, Engert, & Pruessner, 2009); and HR, produced by the autonomic nervous system. At the genetic level, we have investigated a specific polymorphism that is related to dopamine, one of the brain's chemical messengers, as a potential marker of sensitivity.

Cortisol

In the absence of an acute stressor, cortisol levels follow a diurnal rhythm characterized by a typically steep increase approximately 30 minutes after waking (the cortisol awakening response, CAR), followed by smaller spikes and a gradual decline throughout the day until they start to rise again before dawn (Fries, Dettenborn, & Kirschbaum, 2009; Tsigos & Chrousos, 2002). A distinction is made between basal cortisol, reflecting unstimulated (resting) activity of the HPA axis, versus cortisol reactivity, that is, increases in cortisol level in the morning or in response to an acute stressor (Laceulle, Nederhof, Van Aken, & Ormel, 2015).

In line with Biological Sensitivity to Context theory's original focus on psychobiological reactivity, many studies set out addressing cortisol reactivity (or HR reactivity) in response to acute laboratory-induced stress, as a potential marker of sensitivity. Although laboratory paradigms have contributed significantly to our understanding of physiological stress systems, acute laboratory-based stressors may have less ecological validity when the goal is to enhance understanding of individuals' sensitivity to real-life stressors. In comparison to cortisol reactivity, studies on basal cortisol levels have been scarce.

The notion of basal cortisol level as a potential marker of sensitivity to the environment has been supported by findings, published nearly a decade ago, suggesting that individuals with high compared to low basal cortisol level are more sensitive to the negative effects of environmental instability (Shirtcliff & Essex, 2008). Nonetheless, basal cortisol level in relation to sensitivity has remained understudied, illustrated by the call for such studies (Marsman et al., 2012). Recent findings provide additional support for a link between basal cortisol level and sensitivity. Namely, high sensitivity to acute stressors (i.e., cortisol reactivity) in 9-10 year-old children was predicted by (morning but not evening) basal cortisol levels that had increased over the preceding 6 years, whereas low sensitivity was predicted by basal cortisol levels that had decreased over time (Laurent, Gilliam, Wright, & Fisher, 2015).

Basal cortisol level, as potential marker of sensitivity to the environment, may affect mental health problems in a favourable or unfavourable manner, depending on specific characteristics of the environment (e.g., supportive vs. hostile). This may explain in part

why prior findings of basal cortisol levels in relation to internalizing and externalizing problems have been mixed and typically weak (e.g., Adam, Sutton, Doane, & Mineka, 2008; Alink et al., 2008; Dietrich et al., 2013; Hartman, Hermanns, De Jong, & Ormel, 2013; Knorr, Vinberg, Kessing, & Wetterslev, 2010). Ideally, (suspected) sensitivity markers should not be investigated merely as a predictor, outside their explanatory context (i.e., the environmental characteristics that interact differentially with low vs. high sensitivity to produce favourable vs. unfavourable outcomes).

In order to be of interest as a potential marker of underlying stable trait characteristics such as sensitivity, biological measures should likewise be relatively stable over time and thus reproducible. According to recent estimates, around half of the variance in basal cortisol levels is stable across days (41-57%, Kertes & Van Dulmen, 2012; 39-57%, Van Hulle, Shirtcliff, Lemery-Chalfant, & Goldsmith, 2012), driven by stable individual characteristics (i.e., trait influence). In addition, basal cortisol levels have a substantial genetic component (e.g., 62%: Bartels, Van den Berg, Sluyter, Boomsma, & de Geus, 2003; 46-69% across morning cortisol levels: Riese, Rijsdijk, Rosmalen, Snieder, & Ormel, 2009). Moreover, recent findings illustrate a trait component in basal cortisol level by demonstrating an association with personality traits, including facets of neuroticism (Laceulle et al., 2015). In contrast, cortisol reactivity measures including the CAR were not associated with personality (Laceulle et al., 2015), suggesting that cortisol reactivity measures primarily reflect individual or environmental characteristics that vary across days or hours (i.e., state influence). In this thesis, we have focused specifically on basal cortisol levels collected directly upon waking, thus timed on the individual day curve.

Heart rate

The autonomic nervous system regulates brain and body arousal states, switching between activation and inhibition, that is, sympathetic and parasympathetic activity. The parasympathetic branch is thought to be dominant in non-threatening conditions, by inhibiting sympathetic activity (Thayer & Brosschot, 2005), thus functioning as a brake. In threatening conditions, the brake is released, allowing sympathetic activity full play. Resting HR, a measure of autonomic arousal (Ortiz & Raine, 2004), is thought to reflect the balance between these two branches.

Recent findings suggest that resting HR may reflect individual differences in sensitivity to beneficial environmental influences on disruptive behavior in youth. There appears to be a generally positive association between autonomic arousal level, including resting HR, and efficacy of cognitive behavioral therapy (CBT) in reducing antisocial behavior in youth (Cornet, De Kogel, Nijman, Raine, & Van der Laan, 2014). For example, in a sample of 7-12-year-olds who had been referred for disruptive behavior and treated with CBT,

those who showed significant improvement (i.e., decrease in disruptive symptoms) were characterized by high resting HR, whereas those who did not improve were characterized by low resting HR (Stadler et al., 2008). In addition, our research group has recently demonstrated that higher chronic stressor levels predicted greater severity of (externalizing and internalizing) mental health problems in preadolescents with high resting HR, but not in those with low resting HR (Oldehinkel, Verhulst, & Ormel, 2008). Together, these findings suggest that resting HR may be reflective of sensitivity to environmental influences, beneficial (such as CBT), as well as adverse (such as chronic stressors), in line with the Differential Susceptibility hypothesis. That is, youth with high resting HR may be likely to be positively affected by beneficial environmental influences but negatively by adverse influences. Conversely, preadolescents with low resting HR may not only be less sensitive to the positive effects of beneficial environments, but also to the detrimental effects of adverse environments.

However, there have also been findings that the combination of low resting HR and environmental risk factors such as violence exposure, poor parent-child relationship, or low socio-economic status, resulted in *increased risk* of externalizing problems (Raine, 2002b; Scarpa, Tanaka, & Haden, 2008). This is consistent with the well-established negative association between resting HR and externalizing problems, that is, low resting HR increases risk (Lorber, 2004; Ortiz & Raine, 2004; Portnoy & Farrington, 2015), whereas high resting HR is protective against externalizing problems (Portnoy, Chen, & Raine, 2013; Raine, 2002b). These conflicting findings illustrate the need for further research on resting HR as a moderator of the association between environmental influences, especially in the adverse range, and adolescents' externalizing problems.

Resting HR level measured in pre-adolescence appears to be sufficiently stable over time to be a potential marker of sensitivity, as evidenced by high reproducibility (i.e., high relative and absolute reliability; Intraclass Correlation Coefficient = .78, Coefficient of Variation = 6.8) across a 2-week period (Dietrich et al., 2010). Resting HR is substantially influenced by genetic factors (e.g., 29%, Baker et al., 2009; 51%, Zhang et al., 2014).

The Dopamine D4 Receptor 7-repeat allele

A polymorphism in the third exon of the *DRD4* gene encodes for a variable number of tandem repeats, ranging from 2 to 11 (Bakermans-Kranenburg & Van IJzendoorn, 2011; Dmitrieva, Chen, Greenberger, Ogunseitan, & Ding, 2011; Ptacek, Kuzelova, & Stefano, 2011). The 7-repeat (7R) variant results in lower affinity for dopamine (Ptacek et al., 2011), one of the brain's chemical messengers that is, through its role in reward mechanisms, motivation, and approach behavior (Dmitrieva et al., 2011), of interest in relation to externalizing problems.

DRD4-7R has been extensively examined as a moderator of environmental influences on externalizing problems, based on the notion that presence of one or two copies of *DRD4*-7R may reflect relatively high sensitivity to adverse as well as to beneficial environmental influences. This notion has received some, yet inconsistent, support from findings on toddlers and preschoolers (cf. Bakermans-Kranenburg & Van IJzendoorn, 2006; Bakermans-Kranenburg, Van IJzendoorn, Pijlman, Mesman, & Juffer, 2008; Propper, Willoughby, Halpern, Carbone, & Cox, 2007; Windhorst et al., 2015). Findings in (pre) adolescence especially have been mixed.

Specifically, one study has shown relatively high sensitivity in *DRD4*-7R carriers, for better and for worse, to the influence of early maternal stimulation and responsiveness, but not early family adversity, on CD/ODD and psychopathy in adolescence (Nikitopoulos et al., 2014). Another study showed relatively high sensitivity in *DRD4*-7R carriers, for better and for worse, to a broad range of intervention-targeted parenting behaviors in early adolescence, with respect to self-reported substance use, but not to parent-reported delinquency (Beach, Brody, Lei, & Philibert, 2010). Other findings showed no evidence that *DRD4*-7R moderated the influence of maternal expressed emotion (i.e., warmth, criticism) on conduct problems (Sonuga-Barke et al., 2009) or on prosocial and antisocial behavior (Richards et al., 2015).

Within our research group, one study showed that *DRD4*-7R moderated the association between parental separation and externalizing problems, although this effect pertained only to boys, not to girls, and only to the absence of parental separation, not to its presence (Nederhof, Belsky, Ormel, & Oldehinkel, 2012). That is, externalizing levels of *DRD4*-7R-carrying boys compared to noncarriers were relatively low if their families were intact but did not differ if their parents had separated, suggesting sensitivity for better but not for worse. Other studies from our research group showed no evidence that *DRD4*-7R carriers are relatively sensitive to the influence of social well-being and peer victimization on delinquency (Kretschmer, Dijkstra, Ormel, Verhulst, & Veenstra, 2013) or of perceived parental rejection, overprotection, and emotional warmth on delinquency and aggression (Marsman, Oldehinkel, Ormel, & Buitelaar, 2013) or substance use (Creemers et al., 2011).

What seems to stand out in these prior findings is the lack of evidence that *DRD4*-7R reflects sensitivity to the detrimental effects of adverse environmental influences. The few findings that did support high sensitivity not only for better but also for worse in *DRD4*-7R carriers (Beach et al., 2010; Nikitopoulos et al., 2014) were based on the absence of positive (beneficial) environmental influences. For example, whereas high levels of maternal stimulation and responsivity in the study by Nikitopoulos et al. (2014) were considered to be beneficial, low levels reflect an absence of beneficial influence, rather than presence of adverse influence (e.g., the presence of maternal hostility). In contrast,

of the prior findings in adolescence relating to actual adverse influence (i.e., early family adversity, perceived parental rejection or overprotection, maternal expressed criticism, peer victimization, parental divorce or separation), none suggested differences in externalizing levels between *DRD4*-7R carriers and noncarriers (Creemers et al., 2011; Kretschmer et al., 2013; Marsman et al., 2013; Nederhof et al., 2012; Nikitopoulos et al., 2014; Richards et al., 2015; Sonuga-Barke et al., 2009). Thus, the Differential Susceptibility hypothesis, extending the Diathesis-Stress theory (Zuckerman, 1999) that some individuals are more vulnerable to the detrimental effects of adverse influences, has not received much support from the data. Further research is needed in order to determine whether and how *DRD4*-7R moderates the influence of environmental factors, especially in the adverse range, on adolescents' externalizing problems.

Individual differences in general vulnerability: Parental psychiatric history

Effects of biological moderators on the stressors- psychopathology association may be more profound in the presence of high general vulnerability, as indexed by parental psychiatric history (PH). We focused on severity rather than presence versus absence, or on the domain (externalizing vs. internalizing) of PH, for the following reasons: First, PH is a strong predictor of increased genetic and environmentally-driven vulnerability for psychopathology in offspring (Burke et al., 2002; Kim-Cohen, Moffitt, Taylor, Pawlby, & Caspi, 2005). This vulnerability is not limited to a particular problem domain, given that externalizing and internalizing PH are each associated with both problem types in offspring (e.g., Kim-Cohen et al., 2005; Marmorstein, Malone, & Iacono, 2004). If familial transmission (partially) results in a non-specific vulnerability for psychopathology, the severity (i.e., complexity) of PH may be an important indicator of the degree of vulnerability. In line with this, prior research findings demonstrate increased risk of psychopathology in offspring when a parent is affected by both externalizing and internalizing psychopathology compared to only one type (Kim-Cohen et al., 2005), whereas offspring of two affected parents may be at even higher risk (Dierker, Merikangas, & Szatmari, 1999; Marmorstein et al., 2004).

Stressors

This PhD thesis covers two distinct types of psychosocial stressors. We have generally focused on chronic stressors, operationalized as number of long-term difficulties

encountered in the preceding years, assessed in early adolescence and again in mid-adolescence (average age 13.5 and 16 years, respectively). Stressors may become more potent in affecting mental health as they persist over time, taxing individuals' physical and psychological coping resources.

In addition, a focus on chronic stressors may capture subtle individual differences that would be missed when focusing solely on life events. To illustrate, the effect of parental divorce, a life event, on offspring is highly dependent on the degree of parental conflict surrounding the divorce as well as during the marriage. Namely, offspring's functioning is negatively affected by high peri-divorce conflict (Davidson, O'Hara, & Beck, 2014), but positively affected by a divorce if it ends long-lasting marital conflict (Amato, Loomis, & Booth, 1995). Conversely, long-lasting parental conflict that does not involve separation or divorce but rather endures has a more detrimental effect on offspring (Amato et al., 1995). Thus, in some instances, the distinction between life event and chronic difficulty may be artificial, which may cloud the stressors- psychopathology association. Even major life events with an evident direct and acute impact, such as death of a parent or a severe accident, are likely accompanied by chronic difficulties.

Furthermore, subtle individual differences in sensitivity may be missed when adverse environmental influences are rather narrowly operationalized, capturing only one aspect of individuals' lives (e.g., either family or peer group) while beneficial influences from other domains, if present, will compensate for their impact. Environmental influences that are chronic and reflect multiple adverse aspects across multiple environmental domains (e.g., family, peers, school, and neighborhood) may exceed sensitive individuals' ability to cope. Therefore, investigating chronic, multi-context, stressors may aid in capturing individual differences in sensitivity to the environment.

In addition to this general focus on chronic stressors, we have conducted one study investigating a single, normative, transitional event that may be an acute or enduring stressor for some, but may be positively challenging for others. Participant ratings of how enjoyable and how unpleasant the transition to middle school had been for them, enabled us to distinguish between positive and negative transition experiences and therewith to test for sensitivity for better and for worse.

Study design

We used data from the first three measurement waves (mean ages about 11, 13.5, and 16 years) of the Dutch "TRacking Adolescents' Individual Lives Survey" (TRAILS). TRAILS aims to contribute to the understanding of the etiology and course of mental health problems by following 10-12 year-old Dutch children biennially into adulthood. We

pooled data from the population-based birth cohort (n = 2230) and the parallel clinic-referred cohort (n = 543), to obtain a large sample with wide ranges of problem severity and chronic stress. The sampling procedures, descriptive statistics, and response rates of both cohorts are well-documented (e.g., De Winter et al., 2005; Huisman et al., 2008; Ormel et al., 2012).

Thesis outline

First, we investigated whether basal cortisol level collected immediately upon waking moderated the association between adolescents' experience of the transition to middle school and change in externalizing and internalizing mental health problems across the period in which the transition occurred (Chapter 2). Second, we examined whether the effect of basal cortisol level upon waking on the association between chronic stressors and externalizing and internalizing mental health problems would manifest to a greater degree in vulnerable individuals as indexed by parental psychiatric history (Chapter 3). Next, we investigated whether the effect of low resting HR on the association between chronic stressors and externalizing problems would manifest especially in vulnerable individuals, again as indexed by parental psychiatric history (Chapter 4). The last study investigated whether the *DRD4*-7R moderates the association between chronic stressors and externalizing problems (Chapter 5). Across these studies, our main expectations were that low basal cortisol level upon waking, low resting HR, and presence of *DRD4*-7R would be indicative of low sensitivity to the environment; and that high basal cortisol level upon waking, high resting HR, and absence of *DRD4*-7R would be indicative of high sensitivity to the environment. Finally, we discuss and integrate our main findings, concluding with methodological considerations and directions for future research (Chapter 6).

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