Psychosocial adversity and adolescents' mental health problems
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General discussion
The aim of this PhD thesis was to further our understanding of individual differences in the stressors-psychopathology association by longitudinally examining potential moderator effects of three biological factors: basal cortisol level upon waking, resting HR, and the $DRD4-7R$ allele; all assessed at baseline, when participants were on average 11 years old. In this final chapter, we summarize our results and discuss their relationship to previous findings, as well as their theoretical implications. Finally, we provide some important methodological considerations as well as directions for future research.

**Summary of the main results**

In Chapters 2 and 3, we investigated moderator effects of basal cortisol level upon waking in relation to internalizing and externalizing mental health problems, combined and separately, in the face of two distinct types of stressors: the transition to middle school (Chapter 2) and chronic stressors (Chapter 3). In Chapter 2, basal cortisol level upon waking moderated the association between adolescents’ experience of the transition to middle school and change in mental health problems. This effect was similar for both externalizing and internalizing problems. We showed that an ambivalent or negative transition experience predicted a rise in mental health problems, but only in adolescents with high basal cortisol level upon waking, not in adolescents with low basal cortisol level upon waking. A positive experience did not predict any change in mental health problems.

In Chapter 3, we examined whether the effect of basal cortisol level upon waking on the association between chronic stressors and mental health problems depended on individual differences in general vulnerability, as indexed by parental psychiatric history. We found a complex interaction between basal cortisol level upon waking and parental psychiatric history severity with chronic stressors in predicting mental health problems, with different results for externalizing and internalizing problems. Low basal cortisol level upon waking combined with the absence of a parental psychiatric history increased the risk of externalizing but not internalizing problems following chronic stressors. Conversely, low basal cortisol level upon waking combined with a parental psychiatric history increased the risk of internalizing but not externalizing problems following chronic stressors. High or average basal cortisol level upon waking combined with a parental psychiatric history increased the risk of parent-reported externalizing and internalizing problems but not self-reported problems, whereas, in the absence of a parental psychiatric history, higher levels of chronic stressors predicted higher parent-reported and self-reported internalizing but not externalizing problems. In contrast to our focus on both externalizing and internalizing problems in Chapters 2 and 3 on basal
cortisol level, our focus in Chapters 4 and 5, on resting HR and DRD4-7R, respectively, was only on externalizing problems, in line with the literature (see General introduction).

In Chapter 4, we investigated whether the effect of resting HR on the association between chronic stressors and externalizing problems depended on individual differences in vulnerability, again as indexed by parental psychiatric history. Results were in line with our hypotheses that the association between chronic stressors and externalizing problems would be strong in adolescents with high resting HR but weak in those with low resting HR, and that this moderating effect of resting HR would manifest to a greater degree in vulnerable individuals.

In Chapter 5, we investigated whether DRD4-7R moderated the association between chronic stressors and externalizing problems. We found that higher levels of chronic stressors were related to higher externalizing levels in DRD4-7R carriers but not in noncarriers.

**Previous findings**

At the outset of the four empirical studies described in this thesis, the main expectations had been that low basal cortisol level upon waking, low resting HR, and absence of DRD4-7R would be indicative of low sensitivity to the environment; and that high basal cortisol level upon waking, high resting HR, and presence of DRD4-7R would be indicative of high sensitivity to the environment.

With respect to basal cortisol, our expectation was primarily based on a prior study (Shirtcliff & Essex, 2008), which demonstrated that a rise in mental health problems (severity of internalizing and externalizing problems combined) across the transition to middle school was predicted by high but not low basal cortisol level, suggesting high and low sensitivity, respectively. However, it is difficult to interpret these findings as evidence of a moderating role of basal cortisol level on the stressor-psychopathology association because the researchers did not examine how the transition was experienced. Since the entire sample was exposed to the transition, it is unknown whether observed changes in mental health problems are actually related to the transition. Consequently, the Shirtcliff et al. design only allowed the researchers to study a main effect of basal cortisol level but not an interaction effect with the transition to middle school, and did not allow this transition to be interpreted as a stressor.

We extended the Shirtcliff et al. study by taking into account adolescents’ perception of the transition. We found an interaction effect, indicating that basal cortisol level was only relevant for participants reporting a negative (i.e., unpleasant, not enjoyable) or ambivalent transition experience. Among these adolescents, an increase in mental health
problems was predicted by high but not by low basal cortisol upon waking, suggesting high and low sensitivity, respectively, in line with our expectation. A positive transition experience, in contrast, did not predict any change in mental health problems, regardless of basal cortisol level upon waking. Thus, our study provides support for Shirtcliff et al.’s original hypothesis that basal cortisol level reflects sensitivity to the environment. Furthermore, our findings suggest that the perception of the transition rather than the transition itself affects mental health, and that effects are restricted to experiences that yield psychological stress. Potentially, Shirtcliff et al. could have found stronger associations, had they assessed individual differences in perceived impact or stressfulness of the transition to middle school.

However, in our discussion of basal cortisol level upon waking and chronic stressors in Chapter 3, we concluded that the premise that basal cortisol level indicates sensitivity to the environment may be premature or at least too simplistic. The findings in Chapter 3 are difficult to interpret, in general and with respect to theory and prior findings, but suggest that the role of basal cortisol level depends on individual differences in general vulnerability, as indexed by parental psychiatric history, and on the outcome of interest (i.e., different for internalizing and externalizing problems). In Chapter 3, we speculated that the association of high sensitivity with high cortisol described in the literature relates more to cortisol reactivity and less to basal cortisol levels, or that the present findings may be valid but appear unusual because of a publication bias in the basal cortisol literature. However, both explanations seem unlikely given that our findings relating to a negatively perceived transition to middle school, reported in Chapter 2, did provide support for basal cortisol level reflecting sensitivity.

A more likely explanation for our conflicting findings on basal cortisol upon waking level lies in the focus on a specific, normative, change in environment (Chapter 2) versus multi-context chronic stressors (Chapter 3). That is, the influence of basal cortisol level on the stressors-psychopathology association may depend on stressor quantity (e.g., single stressor, cumulative index), type (e.g., event, situation, transition), and / or duration (acute vs. chronic).

For example, the experience of stressors may initially cause increased activity of the stress system, but decreased activity over time (e.g., Ruttle et al., 2011). This downregulation is a protective measure of the body against the negative health effects of excessive cortisol production. We speculated in Chapter 3 that in individuals with low levels of mental health problems in the context of chronic stressors, low basal cortisol level may represent low sensitivity, while in other, more sensitive individuals, basal cortisol level may have been down-regulated following long-lasting stressor exposure and may have been high in the past, in the early phase of exposure to stressors. Although we lacked the data to test this specific post-hoc hypothesis, it is plausible that individual differences in
exposure to chronic stressors may complicate the interpretation of basal cortisol level as indicative of either high or low sensitivity.

Apart from the established down-regulating effect of ongoing stressor exposure on the HPA-axis and cortisol measures (e.g., Ruttle et al., 2011), chronicity of internalizing problems appears to have the same influence, given recent TRAILS findings that recent-onset depressive symptoms predicted increased cortisol reactivity to psychosocial stressors whereas chronic depressive symptoms predicted blunted cortisol reactivity (Booij, Bouma, De Jonge, Ormel, & Oldehinkel, 2013). Studies with long-term repeated measures of basal cortisol level are rare and have not yet resulted in a complete understanding of its normative developmental course. Most of these studies have focused on high-risk samples or environments, complicating the generalizability of findings to the general population. For example, in a sample of children (mean age 4 yrs at T1 and 10 yrs at T29) from low-income families, some in foster care, basal morning cortisol levels had decreased slightly over time (Laurent, Gilliam, Wright, & Fisher, 2015). One study on basal cortisol levels in abuse victims also reported on the developmental course in the control group (mean age 11 yrs at T1 and 24 yrs at T6); basal morning cortisol levels had steadily increased from middle childhood to early adolescence, followed by a leveling off (Trickett, Noll, Susman, Shenk, & Putnam, 2010). Given that the complete sample was female, the developmental course may or may not be different for males.

Taken together, as a moderator of the stressors-psychopathology association, basal cortisol level may depend on individual differences in general vulnerability; on stressor qualities, including duration of stressor exposure; and on type (e.g., internalizing vs. externalizing problems) and duration of mental health problems. In all, this is a tall order, and it is probably unrealistic to assume that we will soon understand how basal cortisol level relates to psychopathology.

Regarding resting HR, we had posited resting HR to be a potential marker of sensitivity based on findings that pre-adolescents with high resting HR were positively affected by beneficial environmental influences (Stadler et al., 2008) but negatively by adverse influences (Oldehinkel, Verhulst, & Ormel, 2008), whereas those with low resting HR were unaffected by both. Our findings (Chapter 4) show that higher levels of chronic stressors predicted higher parent-reported externalizing levels in vulnerable individuals with average or high HR but not in those with low resting HR, suggestive of high vs. low sensitivity, respectively. Our results contrast with prior findings that the combination of low resting HR and environmental risk factors resulted in increased risk of externalizing problems, which suggested that effects of risk factors on externalizing problems may accumulate (Raine, 2002; Scarpa, Tanaka, & Haden, 2008). Possibly, these prior findings pertained predominantly to samples with low general vulnerability. Our study additionally extended findings from a prior TRAILS study (Oldehinkel et al., 2008) that demonstrated
a stress-buffering effect of low resting HR, by showing that this effect continues into adolescence, is more pronounced in individuals with more severe parental psychiatric history, and is rather consistent across various operationalizations of mental health problems.

With respect to the latter, the original report of a stressor-buffering effect of low resting HR (Oldehinkel et al., 2008) focused on principal components of problem severity and direction (internalizing vs. externalizing), extracted from multi-informant (adolescent, parent, and teacher) data and separated from context and perspective components (also see Noordhof, Oldehinkel, Verhulst, & Ormel, 2008). An interaction effect of resting HR and chronic stressors predicted severity but not direction of mental health problems. In Chapter 4, despite our different methodological approach, we captured a similar stressor-buffering effect of low resting HR on parent-reported externalizing problems, whether or not adjusted for co-occurring internalizing problems.

On the genetic level, the notion that DRD4-7R reflects sensitivity for better and for worse has received inconsistent support in adolescence (cf. Beach, Brody, Lei, & Philibert, 2010; Creemers et al., 2011; Kretschmer, Dijkstra, Ormel, Verhulst, & Veenstra, 2013; Marsman, Oldehinkel, Ormel, & Buitelaar, 2013; Nederhof, Belsky, Ormel, & Oldenhinkel, 2012; Nikitopoulos et al., 2014; Richards et al., 2015; Sonuga-Barke et al., 2009). In particular, none of these prior studies have actually demonstrated individual differences in sensitivity to the detrimental effects of adverse environmental influences. We contributed to the literature by showing this sensitivity to adverse circumstances, at least to chronic stressors. By investigating chronic stressors that collectively capture all aspects of individuals’ lives (e.g., both family and peer contexts), which presumably have a major impact on sensitive individuals, taxing their ability to cope, but not on less sensitive individuals, we were able to capture individual differences in sensitivity to the environment reflected by DRD4-7R. Specifically, our finding that higher levels of chronic stressors predicted higher externalizing problem levels in DRD4-7R carriers but not in noncarriers suggests high vs. low sensitivity, respectively, to adverse environments.

Our results contrast with prior findings relating to adverse environmental influences (i.e., early family adversity, perceived parental rejection or overprotection, maternal expressed criticism, peer victimization, parental separation), showing no difference in externalizing problems 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).

One study that used a relatively broad measure of environmental influence, as was our measure of chronic stressors, found that DRD4-7R did not moderate the association between early family adversity and adolescents’ symptoms of CD/ODD and psychopathy in adolescence (Nikitopoulos et al., 2014). These findings were based on data from a
parent-interview, conducted when participants were 3 months old, assessing which of eleven family adversity factors (e.g., low educational level, marital discord) were present in the year prior to the child’s birth. One obvious explanation for the difference in findings would be the early age at which the environmental influence was assessed and, consequently, the large amount of time and contextual influences that passed between assessments of the environmental predictor and the behavioral outcome (i.e., 15 years); in contrast to our study, which assessed more recent environmental influences. However, given that the same study did show a moderating effect of \textit{DRD4}-7R on the influence of laboratory-observed early maternal stimulation and responsiveness, also assessed at 3 months, we cannot conclude that \textit{DRD4}-7R only moderates recent and not early environmental influences. Possibly, the focus on prenatal family adversity accounted for the null finding. Moreover, moderating effects of \textit{DRD4}-7R may be easier to detect when focusing on environmental influences that are chronic or ongoing, rather than influences that do not longer exist at the time of behavioral assessment.

Contrasting findings from our research group have shown that the influences of parental rejection and overprotection, as perceived by preadolescents at T1 (mean age 11 yrs) on delinquency and aggression at T2 (mean age 13.5 yrs, combined parent-report and self-report, Marsman et al., 2013) and on substance use at T3 (mean age 16 yrs, self-report, Creemers et al., 2011) were not moderated by \textit{DRD4}-7R (7R carriers vs. noncarriers). Furthermore, the influence of parental separation, assessed at T1 and T3, on self-reported externalizing levels at T3 did not differ between 7R carriers vs. noncarriers (Nederhof et al., 2012). Finally, teacher-reported peer victimization at T2 did not influence self-reported delinquency at T4 (mean age 19 yrs) in 7R carriers, in contrast to 4R carriers (Kretschmer et al., 2013). These findings have led our colleagues to suggest that moderating effects of \textit{DRD4}-7R on environmental influences on externalizing problems apply less to adolescence than to childhood (Kretschmer et al., 2013; Marsman et al., 2013), less to peer influence than to other environmental factors (Kretschmer et al., 2013), or may differ according to the operationalization of externalizing problems (Creemers et al., 2011). Given that samples, age range, and genetic and outcome measures used in these studies partially overlap with ours, our different findings likely lie in the way we have operationalized environmental adversity. Whereas some of the previously addressed adversities may be ongoing, as were the difficulties we have assessed, our study appears to stand alone in its measurement of chronic and multi-context difficulties. Thus, our findings suggest that moderating effects of \textit{DRD4}-7R on the association between adverse environmental influences and externalizing problems do extend to adolescence when focusing on chronic multi-context stressors. However, this novel finding will need to be replicated by future research.
Whereas the findings in Chapter 2 suggest that individual differences in sensitivity as reflected by basal cortisol upon waking may apply more to adverse than to beneficial environmental influences, Chapters 3-5 do not allow for an interpretation in terms of sensitivity for better and for worse. That is, rather than performing a formal test of Differential Susceptibility, which includes both beneficial and adverse aspects of the environment, we have only addressed the latter (i.e., chronic stressors), which constitutes a Diathesis-Stress model. Therefore, our findings do not show whether or not resting HR and DRD4-7R also reflect individual differences in sensitivity to the positive effects of beneficial environmental influences.

In sum, with regard to our main expectation that low basal cortisol level upon waking, low resting HR, and absence of DRD4-7R would be indicative of low sensitivity and that high basal cortisol level upon waking, high resting HR, and presence of DRD4-7R would be indicative of high sensitivity, we have provided mixed findings on basal cortisol level upon waking (Chapters 2 vs. 3) and supporting evidence regarding resting HR (Chapter 4) and DRD4-7R (Chapter 5). As suggested by the founders of Biological Sensitivity to Context and Differential Susceptibility theories, markers of sensitivity found on different levels (e.g. neuroendocrine, genetic) may reflect a common sensitive endophenotype (Ellis, Boyce, Belsky, Bakermans-Kranenburg, & Van Ijzendoorn, 2011). However, in our sample, absent or very weak correlations between resting HR and DRD4-7R (r = -.01, p = .75), basal cortisol level upon waking and DRD4-7R (r = .04, p = .13), and resting HR and basal cortisol level upon waking (r = .06, p = .013) suggest either that there is no common sensitive endophenotype or that resting HR, DRD4-7R, and / or basal cortisol level upon waking do not (or only minimally) mark this sensitivity. At present, it is too early to confirm or dismiss the existence of a common sensitive endophenotype. At the least, our findings suggest that a common sensitive endophenotype, if present, may be difficult to detect.

In addition, our findings may explain, at least in part, the difficulty in detecting consistent main effects of basal cortisol level on internalizing and externalizing problems (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), and of DRD4-7R on externalizing problems (Creemers et al., 2011; Kluger, Siegfried, & Ebstein, 2002; Luciano et al., 2004; Munafo, Yalcin, Willis-Owen, & Flint, 2008; Nederhof, Creemers, Huizink, Ormel, & Oldehinkel, 2011; Oak, Oldenhof, & Van Tol, 2000; Paterson, Sunohara, & Kennedy, 1999). While low resting HR is a well-established risk factor of externalizing problems, findings of high resting HR in relation to internalizing problems have been mixed (see Dietrich et al., 2009, for an overview), as well as findings of a bi-social interaction effect between resting HR and social risk factors (cf. Oldehinkel et al., 2008; Raine, 2002; Scarpa et al., 2008).
Limitations

It is important to discuss four limitations of our studies, as well as several strengths. First, both school transition ratings and chronic stressors levels were not derived from previously validated measures. The integration of prior stressors-psychopathology findings has been problematic due to great variability in both conceptualization and measurement of stressors (Grant et al. 2004). This PhD thesis may seem to make things worse by using yet another measure. However, at the time of the start of our study, a validated and developmentally sensitive measure of ongoing difficulties in adolescence was not available. We do not suggest generalizability of our findings to ‘stressors’ in general, nor to acute or specific stressful events. We collected parent-reports of long-term difficulties because we assume that parents are better and more stable judges of the difficulties that put chronic strain on family life. Still, rater bias may have led to underestimations of chronic stressors level (Chapters 3-5). With respect to the transition to middle school, our measure of transition experience was derived from just two items. In a multidisciplinary and longitudinal survey such as TRAILS, the range of predictor variables and outcome domains on which data is collected is broad, unfortunately sometimes at the expense of depth or detail. Collecting in-depth measures are not always possible due to financial and practical constraints, such as limited time and risk of increased dropout due to placing heavy demands on research participants. Still, our findings in Chapter 2 show that even with two items, we could differentiate positive from negative experiences.

Second, again due to financial constraints and risk of over-demanding research participants, basal cortisol level upon waking (Chapters 2 and 3) was assessed only once. Although recent evidence shows that single-day basal cortisol level is informative with respect to trait influences (Kertes & Van Dulmen, 2012), sampling of basal cortisol levels for a number of consecutive days would have enabled us to more reliably assess stable trait influence (Hellhammer et al., 2007). Note that an underestimation of trait influence on basal cortisol level upon waking likely resulted in an underestimation of effects, rather than an overestimation. On a related note, we lack longitudinal cortisol data to test our posthoc hypothesis that cortisol downregulation following prolonged chronic stressors exposure may account for our conflicting findings on basal cortisol level as a marker of sensitivity. Specifically, whether individuals with high chronic stressors levels and low basal cortisol levels may have had high basal cortisol levels in the past remains currently unknown. Future research that conducts multiple assessments of basal cortisol level over time may establish how individual basal cortisol levels are affected by recent-onset versus life-long chronic stressors. Although resting HR (Chapters 4 and 5) was also measured only once, prior research has demonstrated good test-retest reliability across a 2-week period (Dietrich et al., 2010), suggesting that resting HR, compared to basal
cortisol level, is less likely to fluctuate with (subtle) daily situational changes. However, long-term alterations like those referred to with regard to cortisol are unknown.

Third, the parental psychiatric history data (Chapters 3 and 4) do not reflect clinical diagnoses. Employing the gold standard, comprehensive diagnostic interviews with both parents, was likewise not possible due to financial constraints. We focused on lifetime disorders that had involved a professional, such as a psychiatrist, clinical psychologist, general practitioner, or law enforcement. Although this method enabled a reliable identification of parents with a history of psychopathology (i.e., less false positives), it may have led to underestimations in individuals with mild parental psychiatric problems. Furthermore, relying on one parent to describe the other parent’s psychiatric history may also have resulted in underestimations of participants’ parental history. Thus, potential bias in our parental history data may have led to underestimation of effects, rather than overestimation.

Finally, since both transition experience and chronic stressors were based on single-informant data, shared method variance may have inflated associations between transition experience and self-reported mental health problems (Chapter 2) and between chronic stressors and parent-reported mental health problems (Chapters 3-5). Results on mental health problem data provided by the other informant led to the same conclusion in Chapters 2, 3, and 5. In Chapter 4, we found a significant interaction effect between parental psychiatric history, resting HR, and chronic stressors in predicting parent-reported but not self-reported externalizing problems. However, shared method variance typically has less impact on interaction effects than on main effects.

Strengths of the study include the large sample of longitudinal, multi-informant mental health problems data from preadolescence well into adolescence and large interindividual differences in externalizing and internalizing problem levels, school transition experience, and chronic stressors exposure.

Future research

The often expressed wish to understand the substantial individual variation in mental health problems following exposure to stressors (Jenkins, 2008; Rutter, 2005) has resulted in an abundance of studies on factors that potentially influence or explain adolescents’ mental health problems following specific, cumulative and / or chronic stressors. A set of four articles, in which this literature has been comprehensively reviewed (Grant et al., 2003; McMahon, Grant, Compas, Thurm, & Ey, 2003; Grant, Compas, Thurm, McMahon, & Gipson, 2004; Grant et al., 2006), demonstrated large variance in the stressors-psychopathology association strength across studies and generally inconsistent findings.
of moderator effects. The majority of studies reviewed were not based on previously validated stressor measures (Grant et al., 2004). Therefore, part of the inconsistencies and cross-study variance may be due to between-study differences in conceptualization (e.g., objective versus subjective stressors; definition of populations of events and difficulties to be included), reliability, and validity of the stressor measures.

Subjective ratings may be especially important in studying normative but potentially stressful events or transitions. In studies aimed at identifying mechanisms of risk or resilience in normative events that are only stressful for a subgroup of individuals, neglecting individuals’ perception may result in failure to detect important associations. We recommend studies on long-term effects of other transitions and how they are perceived—for example, school entry in preschoolers or labor market entry in young adults—in relation to mental health problems and basal cortisol. However, subjective measures have a disadvantage, in that they may be confounded by potential moderators, such as coping skills or personality, and by the outcome, the so-called effort after meaning effect (e.g., Brown, 2002). To some extent, the latter phenomenon may be ameliorated by, beforehand, measuring an individual’s anticipation of how stressful the transition or event will be. Note that this is only feasible with regard to normative events and not to stressors that are not “planned.” Also for non-normative life events it holds that the subjective experience may diverge widely.

In the case that the degree of stressfulness (i.e., objective threat) of events or situations is dependent on specific circumstances, failing to assess those circumstances may cloud the stressors- psychopathology association. For example, focusing on offspring mental health problems in relation to parental divorce, without considering the degree of marital and peri-divorce conflict, important moderators (Amato, Loomis, & Booth, 1995; Davidson, O’Hara, & Beck, 2014; Goeke-Morey, Cummings, & Papp, 2007) will introduce an unknown portion of variance that reflects characteristics of the divorce or the parents, rather than vulnerability or resilience characteristics of the child, thus obscuring the stressors- psychopathology association. It is therefore important to take into account the specific circumstances that influence the degree of stressfulness (Grant et al., 2003). An alternative approach is to focus directly on these circumstances, rather than on the events that they surround. In the general introduction of this thesis, we have suggested that a focus on the effects of chronic, multi-context, stressors may capture individual differences in outcome that would be missed when focusing solely on life events. In Chapters 3, 4, and 5, the association between chronic stressors and mental health problems over time was evident, in line with the literature (Grant et al. 2004).

Effect sizes of the biological measures investigated in this thesis were small. It seems unlikely that basal cortisol level, even when measured across multiple days, will ever be useable in the reliable identification of at-risk or sensitive individuals. Namely, even
when the numerous within-the-day and day-to-day influences are taken into account, cortisol levels may reflect either recent-onset or chronic stressor exposure (e.g., Ruttle et al., 2011), recent-onset or chronic internalizing problems (Booij et al., 2013), and, possibly, other influential factors that have not yet been identified. This suggests that cortisol levels, stressor levels, and mental health problems would have to be repeatedly assessed over a significant time period before any meaningful interpretation is possible. If only for the major costs and complexity of such work, it is unlikely that basal cortisol level will prove to have advantages, in terms of clinical relevance or practical use, over current methods of identifying at-risk individuals through questionnaires and individual interviews. We conclude that the relative instability of individuals’ basal cortisol level over time and our currently limited knowledge and understanding of its dependency upon other factors disqualifies basal cortisol level as potentially useful to clinical practice as a marker of risk or resilience.

Despite small effect sizes, we encourage additional research on resting HR and DRD4-7R as moderators of the stressors-psychopathology association and as potential markers of sensitivity to environmental influences. Given the well-established finding that individuals with low resting HR are at increased risk of externalizing problems, the possibility that the same individuals are not or hardly affected by stressors is intriguing and consistent with the modern view of risk as one side of a coin, as in the Differential Susceptibility framework. The two studies that have demonstrated a stress-buffering effect of low resting HR (Chapter 4 and Oldehinkel et al., 2008) were based on partially overlapping samples and measures. Hence, to rule out the possibility that this effect is specific to TRAILS data, we encourage replication studies. Few studies have tested for interaction effects of resting HR with environmental factors, even though interaction effects may explain additional variance in externalizing problems aside from the rather consistent main effect of low resting HR, and may perhaps explain some of the inconsistencies in prior findings of high resting HR in relation to internalizing problems (see Dietrich et al., 2009, for an overview).

Future research may demonstrate whether our findings on resting HR and DRD4-7R extend to a broader range of adverse environmental influences or are rather specific to chronic psychosocial stressors, and whether our findings extend to beneficial influences.

**Conclusion**

With the studies presented here, we have answered to calls for theory-based research of biological factors as potential moderators of the stressors-psychopathology association over time. We have demonstrated that resting HR, DRD4-7R, and basal cortisol level
upon waking, potentially reflective of sensitivity to the environment, all significantly moderated the association between stressors and mental health problems, although findings on basal cortisol were mixed. We also demonstrated that moderating effects of basal cortisol level upon waking and resting HR were dependent on parental psychiatric history, a presumed proxy for general vulnerability in offspring. However, effects were small and not always consistent with the sensitivity hypothesis. Therefore, it is difficult to imagine that single measures such as basal cortisol level, resting HR, or genetic polymorphisms will someday be useful to clinical practice in terms of risk assessment or in determining treatment course. The stressors-psychopathology association is likely influenced by a large network of interacting factors. Investigating combinations of previously established effects of risk and resilience may increase the amount of explained variance and may thus further enhance our understanding of the stressors-psychopathology association.
References


