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SUMMARY

Substance use disorders (SUDs) are debilitating disorders that affect millions of people worldwide. As yet, not enough is known about the aetiology of these disorders. Research has shown that there is a genetic component, however, due to the complexity of genetics, researchers have turned to examining biological mechanisms that may underlie SUDs, or endophenotypes. Physiological stress (re)activity is one of these potential endophenotypes. The two main mammalian physiological stress systems are the autonomic nervous system (ANS), and the hypothalamic-pituitary-adrenal (HPA) axis with its end product cortisol. Clinical research showed physiological dysregulation in patients with SUDs, however, from this research it cannot be discerned whether this dysregulation is the consequence of chronic and/or heavy substance use or whether it is an underlying mechanism. In order to shed more light on this matter, in this thesis, we examined physiological stress (re)activity during a psychosocial stress procedure in adolescents who are at heightened risk for developing SUDs. Specifically, we tested whether adolescents who engaged in risky substance use and adolescents whose parents were patients with SUDs showed physiological dysregulation. Furthermore, because physiological stress (re)activity has been increasingly examined as an endophenotype for (mental) health problems, we explored a wide range of determinants of stress reactivity, or background factors that may influence stress reactivity. The aims of this thesis were to examine:

Aims

1. Determinants of perceived and physiological stress reactivity;
2. The relation between perceived and physiological stress reactivity;
3. The relation between HPA axis activity and age of onset of alcohol use in adolescents;
4. The relation between ANS activity and frequency of alcohol and tobacco use in adolescents;
 - 4a. The relation between perceived stress reactivity and frequency of alcohol and tobacco use in adolescents;
5. The relation between familial risk for SUDs, ANS (re)activity and externalizing behaviors and substance use;

6. Whether cortisol levels during a psychosocial stress procedure differed between children of parents with a substance use disorder (CPSUDs) and controls;
 - 6a. Whether perceived stress during the psychosocial stress procedure differed between CPSUDs and controls;
7. Whether experiencing more adverse life events could account for differences in cortisol levels between CPSUDs and controls.

In our studies, we utilized two samples of participants. One was a general population sample ($N=711$), consisting of children and adolescents (aged 7-20 years), and was randomly drawn from municipal registers in South Holland, the Netherlands. We recruited a smaller sample of adolescents with familial risk for SUDs ($N=83$) mainly through their parents who were in treatment for a SUD at outpatient Bouman GGZ clinics throughout South Holland. All individuals participated in a psychosocial stress procedure, during which heart rate and respiration were measured constantly (from which we derived mean heart rate and respiratory-sinus-arrhythmia; RSA), and cortisol and perceived stress were measured at regular intervals. Furthermore, cortisol was measured at four time points on a normal day in order to assess the diurnal curve. During the psychosocial stress procedure, which was designed to elicit a stress response, participants completed a mental arithmetic task, a public speaking task, and a computer mathematics task. Questionnaires were completed by youth and their parents, yielding information on symptoms of psychopathology, substance use, parenting practices, life events and general health.

Findings

In **chapter two**, we examined determinants of stress reactivity, specifically, RSA, heart rate, cortisol and perceived stress reactivity in children and adolescents from the general population ($N=707$). In a stratified sample (children and adolescents were examined separately), we found individual, developmental, environmental and substance use-related factors that influenced each of the stress reactivity indices. Specifically, cortisol reactivity was related to sex and perceived parental emotional warmth in children, and emotionality, sociability, urbanicity and parental involvement in adolescents. Heart rate reactivity was related to urbanicity and socioeconomic

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status in both children and adolescents, and furthermore sex, sociability, parental involvement and tobacco use in adolescents. RSA reactivity was related to age and socioeconomic status in children, and activity level in adolescents. Perceived stress reactivity was related to shyness, age and perceived parental rejection in children, and perceived parental overprotection, parent-reported inconsistent discipline and tobacco use in adolescents. In chapter two, we also examined the relation between perceived and physiological stress reactivity, as these constructs are generally postulated to be closely related, but convincing evidence for this is minimal. In our study, perceived stress reactivity was significantly and positively related to cortisol reactivity in adolescents only. Perceived stress reactivity did not predict any other physiological reactivity measures in children or adolescents, although these relations were marginally significant (all $ps < .12$). As stress reactivity is frequently investigated as a vulnerability marker for (mental) health problems, we maintain that it is essential that future studies take into consideration factors that may account for such relations, and we provide an overview and indication of such variables when examining children and adolescents.

In **chapter three**, we examined the relation of age of onset of drinking alcohol with diurnal and stress-evoked cortisol levels in adolescents from the general population ($N=268$). The age at which the first alcoholic drink was consumed varied as a function of cortisol levels during the psychosocial stress procedure. Adolescents who began drinking at an earlier age showed lower cortisol levels at onset of the stressful tasks and during the stressful tasks, but not after the tasks (cortisol recovery). Effects were strongest for anticipatory cortisol levels at onset of the stress procedure. Diurnal cortisol levels did not differ in adolescents who began drinking at varying ages. We concluded that adolescents who exhibited risky substance use (i.e. drinking at an earlier age) showed blunted HPA activity in anticipation of and during a psychosocial stressor, which may signal inherent hypo-arousal in these adolescents.

In **chapter four**, we examined the relation between ANS activity during a psychosocial stress procedure and alcohol and tobacco use in adolescents from the general population ($N=275$). Adolescents who consumed a medium and high number of alcoholic drinks per week (more than two) exhibited lower mean heart rates during the entire stress procedure as compared to adolescents who drank less. Furthermore, adolescents who smoked tobacco everyday portrayed blunted heart rate reactivity to the stressful tasks as compared to adolescents who

smoked less frequently or not at all. Perceived stress was not related to alcohol or tobacco use. Similar to chapter three, we concluded that ANS hypo-arousal during a stressor is evident in adolescents who portray risky substance use.

In **chapter five**, we examined ANS activity during a psychosocial stress procedure in the adolescent children of parents with a SUD ($N=81$) and controls of the same age ($N=524$; 11-20 years). We examined the relations between familial risk for SUDs, resting RSA and heart rate, and RSA and heart rate reactivity and recovery, and the outcome variables externalizing symptoms and tobacco, alcohol and cannabis use. Using multiple outcome regression analyses, we tested additive, moderation and mediation models for each of the ANS variables. We found that externalizing symptoms were independently predicted by positive familial risk status, and blunted heart rate reactivity and recovery. Cannabis use was predicted by positive familial risk status only. Tobacco use was independently predicted by blunted heart rate reactivity and recovery. Furthermore, the relation between familial risk status and externalizing symptoms and tobacco use was partially mediated by heart rate recovery. Alcohol use was not related to familial risk status or ANS activity. This study provided evidence for blunted heart rate recovery as an endophenotype of tobacco use and externalizing symptoms.

In **chapter six**, we assessed diurnal and stress-evoked cortisol levels in children of parents with a SUD ($N=83$) and controls, matched on age, sex and socioeconomic status ($N=83$). Using multilevel piecewise growth curve modeling, we found that cortisol levels at onset of the stress procedure were explained by group status, such that children of parents with a SUD portrayed lower cortisol levels than controls. Diurnal cortisol levels did not differ between groups nor did cortisol reactivity or recovery during the psychosocial stress procedure. Because the experience of adverse life events has previously been related to HPA axis hypo-activity, and because children of parents with SUDs often report experiencing more adverse life events, we examined whether this was the case in our sample, and whether having experienced more adverse life events explained differences in cortisol levels. Children of parents with a SUD did report experiencing significantly more adverse life events, but this did not account for the finding of lower cortisol levels in anticipation of the stressor in these adolescents as compared to controls. We concluded that HPA axis dysregulation may be an endophenotype for SUDs as children of parents with SUDs show blunted activation in anticipation of stress. These blunted

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cortisol levels were not the result of having experienced more adverse life events, thus might reflect an inborn vulnerability to SUDs.

Conclusions

In **chapter 7**, the main findings of chapters two through six were discussed. Taken together, our findings indicated that adolescents at risk for developing SUDs later in life, that is, adolescents from the general population who showed risky substance use and the adolescent children of parents with a SUD, exhibited physiological hypo-arousal during a psychosocial stress procedure. Thus, during psychosocial stress, adolescents at risk for SUDs portrayed blunted physiological activation, either in anticipation of or during the stressor. This suggests that these individuals are inherently hypo-aroused, which increases their tendency to seek out stimulation actively, and therefore are more likely to engage in risky substance use or externalizing behavior. Furthermore, in chapter two, we examined determinants of physiological and perceived stress reactivity, and observed differential determinants for children and adolescents, as well as differential patterns in HPA axis and RSA responding during the psychosocial stress procedure. This underlines the necessity of further research on the nature of physiological responses to stress during the transitional period of childhood through adolescence. This thesis provides beginning evidence for physiological stress (re)activity as an endophenotype for substance use in adolescents and a keystone for future longitudinal studies that are needed to confirm our observations.