Neurobiological stress parameters in relation to disruptive behavior

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Chapter 1

Introduction

Juveniles who display disruptive behavior are at risk for a series of negative outcomes later in life, including criminal behavior, unemployment and psychiatric disorders (Kimonis & Frick, 2010; Loeber et al., 2009b; Maughan & Rutter, 2001). Specific subgroups such as delinquent adolescents are particularly at risk, due to the high prevalence of aggression, disruptive behavior disorders and other psychopathology within this group (Vermeiren et al., 2006). An extensive body of research has focused on factors that are related to the development and persistence of disruptive behavior. An important amount of psychosocial risk factors partly explaining disruptive behavior has been identified (Loeber et al., 2009b). In the last decades, interest in studying neurobiological parameters has increased substantially, aiming to find additional correlates and increase understanding of underlying mechanisms of disruptive behavior. Among the biological systems that have received attention in this respect are stress-related neurobiological systems, such as the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal-axis (HPA-axis, Beauchaine, 2001; Raine, 2002a; van Goozen et al., 2007). Beside relationships that were found at a cross-sectional level between ANS or HPA-axis parameters and disruptive behavior, a number of longitudinal studies have indicated a predictive value of neurobiological parameters for future and persistent disruptive behavior (El-Sheikh et al., 2011; Raine et al., 1995; Shoal et al., 2003). Furthermore, there are indications for complex interplays between neurobiological parameters and psychosocial risk factors in relation to disruptive behavior (Raine, 2002b; van Goozen et al., 2007). Current research and influential theories derived from these recent studies stress the need for continuing neurobiological research in order to reveal correlates of juvenile disruptive behavior (Popma & Raine, 2006; van Goozen & Fairchild, 2008). In order to improve the currently existing models, specific potentially important parameters and their relation to disruptive behavior will be discussed in detail in this thesis.

In the literature on correlates of juvenile disruptive behavior, several constructs have been used to study a wide range of deviant behaviors. In this thesis, *disruptive behavior* is used as an overarching term comprising a range of various types of behavioral problems. *Delinquency* is a judicial and criminological term, which refers to disruptive behavior that could lead to conviction. Delinquency can be studied by using either self-reports or by using officially registered offending. Because associations between both types of measurement were shown to be low (Maxfield et al., 2000; Wittebrood, 2000), it is important to study both when investigating potential correlates of such behavior. *Disruptive behavior disorder* (DBD) is a diagnostic category used in child and adolescent psychiatry, comprising both Oppositional Defiant

Disorder (ODD) and Conduct Disorder (CD). DBD can be diagnosed when disruptive behavior problems are severe and persistent, and affect several domains of a persons functioning (American Psychiatric Association, 1994). Studying disruptive behavior categorized in disorders like DBD is useful for clinical purposes. However, DBD diagnoses are heterogeneous, with different types of disruptive behavior combined in one category. Dimensional measures can focus on specific expressions of disruptive behavior (for example aggression) and can distinguish between levels of severity of disruptive behavior. *Aggression* has been defined as behavior that is deliberately aimed at inflicting physical or psychological harm to persons or property. In order to assess whether associations with neurobiological parameters are specific for DBD diagnoses or for disruptive behavior in general, in this thesis, both categorical and dimensional measures of disruptive behavior were applied. Furthermore, taking the heterogeneous nature of aggression into account as well, we studied two subtypes of aggression: proactive and reactive aggression, which will be discussed below.

A starting point when studying associations between stress regulation and disruptive behavior is the assumption that juveniles who display disruptive behavior show altered sensitivity to stress (van Goozen & Fairchild, 2008). When a person is confronted with a physical or psychological stressor, the body responds with activation of the main human stress regulation systems: the ANS and the HPA- axis. Activity of these systems is reflected in levels of peripheral parameters, which are accessible for research. Heart rate, as a general measure of ANS functioning, is an indicator of activity of both the sympathetic and the parasympathetic nervous system (respectively, SNS and PNS). The SNS prepares the organism for fight or flight in situations of threat or danger and involves increased heart rate and respiration. Several parameters reflect SNS activity, for example alpha-amylase, which can easily be obtained from saliva (Rohleder et al., 2004; Van Stegeren et al., 2006). The PNS is concerned with the conservation of energy and restoration to a calm state and is associated with lower overall emotional arousal (Berntson et al., 1991). The specific role of the PNS on cardiac activity can be illuminated by measuring heart rate variability (HRV), also studied as respiratory sinus arrhythmia (Berntson et al., 1993; Grossman & Taylor, 2007). HRV is the variation in the interval between consecutive heart beats in the respiration frequency range due to the influence of the vagus nerve on the sinoatrial node (Beauchaine, 2001; Berntson et al., 1997).

The activity of the HPA-axis has predominantly been studied by measuring its final product cortisol, the main human stress hormone. Adrenal cortisol secretion

represents the final step in a neuroendocrine cascade beginning with the release of corticotrophin releasing hormone (CRH) from the paraventricular nucleus (PVN) of the hypothalamus. CRH stimulates the release of ACTH from the anterior pituitary which, in turn, leads to activation of the adrenal glands, resulting in the synthesis and release of cortisol (Stratakis & Chrousos, 1995). Basal activity of the HPA-axis appears to support or permit acute fight/flight responses, while its response to stressors serves to suppress the impact of fight/flight reactions. The basal HPA axis activity is characterized by a robust circadian rhythm. A special component of this rhythm is the cortisol awakening response (CAR). Within 30 minutes after awakening, mean cortisol levels increase 50-100%. As such, the CAR comprises aspects of basal activity as well as flexibility of the HPA-axis during the first hour after awakening (Clow et al., 2004). The CAR is a widely used and reliable marker for investigating HPA-axis functioning (Pruessner et al., 1997), and is preferred over single cortisol measurements. Reactivity of the HPA-axis is usually studied by measuring cortisol levels during physical or psychosocial stressors.

Associations between the mentioned stress-regulation systems and disruptive behavior can be viewed from the perspective of various theories. In the *low arousal* theories, it is argued that individuals seek out stimulation, for example by displaying antisocial behavior, to optimize their low arousal which represents an unpleasant physiological state (sensation seeking theory, Zuckerman, 1979). In an alternative explanation, attenuated physiological responsivity to stress is regarded as a marker of low levels of fear and low punishment sensitivity. Hence, fearless juveniles are thought to be more likely to engage in disruptive behaviors because they do not fear the negative consequences of their actions (fearlessness theory, Raine, 1993; Raine, 2002a).

The specific association between parasympathetic activity and (disruptive) behavior is typically studied within the perspective of the *polyvagal* theory (Beauchaine, 2001; Porges, 1995; Porges, 2007). This theory specifies two distinct branches of the vagus nerve influencing the activity of the heart. The first branch, originating from the dorsal motor nucleus, functions to suppress metabolic demands under conditions of danger. The second, phylogenetically newer branch originates from the nucleus ambiguus. Deployment of this branch (increased HRV activity or decreased vagal withdrawal / HRV reactivity) suppresses the robust emotional reactions that characterize fight or flight responses by inhibiting acceleratory SNS input to the heart. When such vagally mediated social affiliative behaviors are ineffective in coping with a

stimulus, response shifts to the fight or flight response by withdrawal of the inhibitory vagal influence (increased vagal withdrawal / HRV reactivity). Functional deficiencies of this branch might place individuals at risk for emotional dysregulation, a hallmark for psychopathology (Beauchaine, 2001).

Previous cross-sectional studies on ANS and HPA-axis functioning in relation to juvenile disruptive behavior generally found low baseline activity and attenuated reactivity of heart rate and cortisol (for meta-analyses, see Ortiz & Raine, 2004; van Goozen et al., 2007), although findings are not entirely consistent (Alink et al., 2008; Lorber, 2004). Furthermore, low baseline HRV was consistently found in relation to disruptive behavior, whereas several studies did not find a relationship between HRV reactivity and disruptive behavior (Beauchaine et al., 2001; Beauchaine et al., 2008; Dietrich et al., 2007; Mezzacappa et al., 1997; Pine et al., 1998).

An important development in this field of research is the increasing use of longitudinal data. Longitudinal designs are needed, as they allow to study the predictive value of neurobiological parameters for future and persistent disruptive behavior. Previous studies showed that low resting heart rate and cortisol have a predictive value for future antisocial, delinquent or aggressive behavior throughout different age ranges (Raine et al., 1990; Raine et al., 1997; Shoal et al., 2003). In contrast to cross-sectional findings, a recent longitudinal study found that concurrent low resting HRV and attenuated HRV reactivity were associated with increasing delinquency symptoms during childhood (El-Sheikh et al., 2011). Some studies also showed a predictive value when baseline disruptive behavior was taken into account (Raine et al., 1995; Sondeijker et al., 2008), although other studies did not (Baker et al., 2009; van Bokhoven et al., 2005a). In longitudinal studies like these, it is important to incorporate the effect of baseline disruptive behavior, to examine the predictive value of neurobiological parameters over and above baseline disruptive behavior. Disruptive behavior has convincingly shown to predict future similar behavior (Burke et al., 2002; Loeber et al., 2009b), and (baseline) disruptive behaviors show cross-sectional associations with neurobiological parameters, as outlined above.

When using longitudinal designs with repeatedly measured neurobiological and behavioral parameters, the stability of these parameters over time can be studied. ANS parameters in resting conditions have shown moderate to strong correlations over consecutive assessments (El-Sheikh, 2005; Matthews et al., 1990; Matthews et al., 2002). However, findings on ANS reactivity to stress are less solid (El-Sheikh, 2005; Matthews et al., 1990). Studies on cortisol stability have mainly relied on cross-

sectional data examining multiple age groups at a single point in time and have not provided consistent results (Gunnar & Vazquez, 2006; Knutsson et al., 1997; Matchock et al., 2007; Netherton et al., 2004). Dimensional measures of disruptive behavior as well as DBD diagnoses have shown moderate to high stability during adolescence, in both general population and clinically referred samples (Barker et al., 2006; Feehan et al., 1993; Ferdinand & Verhulst, 1995; Loeber et al., 2009b; Van Bokhoven et al., 2006; Visser et al., 1999). However, stability has mainly been studied in general population and clinical samples, leaving unclear to what extend ANS / HPA-axis parameters and disruptive behavior are stable in delinquent samples.

Furthermore, longitudinal designs can enhance insight in the dynamics of the relationship between ANS / HPA-axis parameters and disruptive behavior over time. The stability of previously found cross-sectional relationships can be studied, as well as specific associations between the development of neurobiological parameters and the development of disruptive behavior. However, to date these aspects remain understudied. One study related repeatedly measured HRV to the development of externalizing behavior in children (El-Sheikh & Hinnant, 2011). Low initial HRV activity in childhood, but not development of HRV over time, was related to increasing externalizing symptoms. These findings need replication with additional neurobiological and behavioral parameters, as well as in other samples. In this thesis, the relationships between stability of ANS / HPA-axis parameters and continuity of disruptive behavior will be studied.

Whereas part of the previous studies examined single systems, investigating the pattern of activity in different systems involved in the stress-response is likely to shed further light on associations between stress-regulation and disruptive behavior. It has been suggested that disruptive children are characterized by a disturbance of the interplay between the different physiological systems involved in the regulation of stress (Bauer et al., 2002). This interplay is based within the underlying coordination network of both ANS and HPA-axis, involving limbic brain circuits including the amygdala and hippocampus, and the orbital/medial prefrontal cortex (Dolan, 2002; Gunnar & Quevedo, 2007). For example, it has generally been assumed that SNS and PNS display coupled, reciprocal actions on organ systems. However, non-reciprocal actions have been described as well (Autonomic space model, Berntson et al., 1991). This may result in concurrent increases or concurrent decreases in both branches, leading to ambiguous effects on physiological arousal (Berntson et al., 1993). Indeed, some studies found concurrent low levels of SNS and PNS to be related to juvenile

disruptive behavior (Beauchaine et al., 2007; Boyce et al., 2001; El-Sheikh et al., 2009). Another example of a disturbed interplay between systems that has been described, is the interplay between the SNS and the HPA-axis (Bauer et al., 2002). Generally, both systems show increased reactivity in response to stress. A study on the interaction between alpha-amylase and cortisol in relation to aggressive behavior showed that concurrent low reactivity in both parameters was associated with higher levels of aggression (Gordis et al., 2006). These results show the importance of concurrently assessing parameters from different stress-systems when studying neurobiological correlates of disruptive behavior.

Most previous studies investigated heterogeneous measures of disruptive behavior, whereas a small number of studies differentiated between specific subtypes of aggression, such as proactive and reactive aggression. It is proposed that these are two qualitative different forms of aggression, that likely show distinctive neurobiological profiles (Hubbard et al., 2002). Proactive aggression has been characterized as goal-oriented, planned and unprovoked. Proactive responses are fueled by reward contingencies that aim to achieve a goal such as possessions or the domination of others (i.e., cold-blooded, or instrumental; Dodge et al., 1997; Vitaro et al., 2006). In contrast, reactive aggression is a rather immediate and impulsive response to a source of provocation or threat, and is usually accompanied by the expression of anger (i.e., hot-blooded, or emotional; Dodge et al., 1997; Vitaro et al., 2006). Previous studies have indeed shown differences in neurobiological correlates of proactive and reactive aggression. Proactive aggression has been related to increased resting HRV, and attenuated heart rate and HRV responsivity, whereas reactive aggression has been associated with decreased HRV and increased cortisol (Lopez-Duran et al., 2009; Murray-Close & Rellini, 2011; Scarpa et al., 2009; van Bokhoven et al., 2005b). Because only a small amount of studies so far focused on the distinct neurobiological correlates of proactive and reactive aggression specifically, it is important to replicate and extend these findings, preferably in longitudinal designs.

Because there are indications for complex interplays between neurobiological parameters and other, psychological and social, risk factors in relation to disruptive behavior (Raine, 2002b; van Goozen et al., 2007), such risk factors should be incorporated when studying the longitudinal relationships between ANS / HPA-axis parameters and disruptive behavior. A potentially important factor in this respect is the presence of symptoms of posttraumatic stress disorder (PTSD). From theoretical models it has been proposed that (early) adverse or traumatic events may interact

with stress-related neurobiological systems like the ANS in relation to disruptive behavior (Raine, 2002b; Susman, 2006; van Goozen et al., 2007). A number of studies indeed found that ANS reactivity was only related to disruptive or aggressive behavior in the presence of a history of traumatic or adverse events (El-Sheikh et al., 2011; Gordis et al., 2010; Murray-Close & Rellini, 2011). However, only part of the juveniles who experience adverse or traumatic events develop symptoms of posttraumatic stress disorder (PTSD, Brosky & Lally, 2004). Furthermore, there are indications that the relation between experienced events and aggression is mediated by PTSD symptoms (Marsee, 2008; Ruchkin et al., 2007). Hence, studying PTSD symptoms is relevant in this context as well. PTSD symptoms have been related to altered stress (re)activity (Blechert et al., 2007; Kirsch et al., 2011; Pole, 2007) as well as to higher levels of aggression, particularly reactive aggression (Kivisto et al., 2009; Marsee, 2008). Because delinquent samples are characterized by high rates of PTSD symptoms, it is of particular importance to study PTSD symptoms in such a sample (Colins et al., 2010; Marsee, 2008; Ruchkin et al., 2002; Vermeiren et al., 2006).

AIMS AND STUDY DESIGN

The overall aim of this thesis was to investigate longitudinal relationships between ANS and HPA-axis activity and reactivity, and specific types of disruptive behavior in delinquent male adolescents. Specific aims were to study the predictive value of neurobiological parameters for future and persistent disruptive behavior. Furthermore, the stability of neurobiological parameters and disruptive behavior were investigated, as well as the longitudinal relationships between them. In addition, in one cross-sectional study the potential value of alpha-amylase as a correlate of disruptive behavior was studied.

In a prospective longitudinal design, delinquent male adolescents were assessed in early adolescence and after a follow-up period of five years. The baseline assessment was conducted in 2002 – 2004, results have been published previously (Popma et al., 2006; Popma et al., 2007b; Popma et al., 2007a; Popma & Raine, 2006). The follow-up assessment was conducted in 2006 – 2009.

At baseline, 112 participants were included after referral by the police to a delinquency diversion program (age at baseline assessment: 12-14 years). In the Netherlands, children between 12 and 18 years old who have committed a minor (first) offense can be sent to such a diversion program to prohibit court intervention.

Participants from the delinquent sample were divided in a subgroup with a disruptive behavior disorder (DP+) and a subgroup without such a disorder (DP-). As a control group, a normal adolescent sample was included (n = 38), this sample was matched group-wise to the delinquent sample on age, IQ, SES, and ethnicity. In the study presented in chapter 4, the normal control sample and the delinquent sample have been included.

Two aspects on the number of participants need to be mentioned. First, the number of participants in de delinquent sample varied per study. At baseline, 112 delinquents were included. Within this sample, 88 participants performed a valid CAR (see below) and a subsample of 71 participants was approached to perform the PST (see below). Similarly, 38 normal controls were included at baseline, of which 32 performed a valid CAR and 30 performed the PST. At follow-up, the total delinquent sample and the total normal control sample were approached, including the participants that did not perform a valid CAR or the PST at baseline. Second, as usual in this kind of studies, there was attrition between the two assessments. At follow-up, 86 delinquents (76.8%) and 27 normal controls (71.1%) re-participated, of which 59 (68.6%) delinquents and 22 (81.5%) normal controls completed the entire follow-up assessment. Re-assessment was refused by 18.0% of the participants (n=27), 4.0% did not live in the Netherlands at the time of approach (n = 6) and 2.7% was untraceable (n=4). Additional detailed information on the number of participants in each separate analysis is provided in the corresponding chapters of this thesis.

Both at baseline and at follow-up, participants and parents underwent behavioral, psychosocial and biological assessment. Behavioral assessment included a structured psychiatric interview; the Diagnostic Interview Schedule for Children (DISC), version IV (Shaffer et al., 2000). Furthermore, participants and their parents filled out various questionnaires: the Child Behavior Checklist (CBCL), the Youth Self Report (YSR) and the Reactive-Proactive aggression Questionnaire (RPQ). At follow-up, the official police registration was used to obtain data on reoffending.

Cortisol was measured from saliva using Salivettes. Participants were instructed to sample saliva at home, immediately after awakening, as well as 30 and 60 min after awakening. These three samples represent the cortisol awakening response (CAR). It needs to be mentioned that at baseline and at follow-up different laboratories and assay techniques were used for the cortisol analyses. Although we were able to assess correlations between cortisol at baseline and at follow-up, dissimilar assays lead to differences in mean values and ranges, therefore longitudinal analyses on mean values were not meaningful.

Heart rate, HRV, salivary cortisol and alpha-amylase were measured before, during and after a standardized psychosocial stress test procedure, consisting of a public speaking task (PST) in front of a one-way screen with video recording (Jansen et al., 2000). Participants were given 10 minutes to prepare a 5-minute speech on a topic of choice. It was suggested that-three psychologists were judging the participants' performance from behind the screen. The stressful situation was always ended by a positive judgment report. In healthy participants, similar psychosocial stress tests had elicited increases in heart rate, cortisol and alpha-amylase, and a decrease in HRV (Kudielka et al., 2004b; also referred to as vagal withdrawal, Kudielka et al., 2004a; Nater et al., 2005; Strahler et al., 2010).

OUTLINE OF THIS THESIS

The aim of the study presented in **chapter 2** was to examine the predictive value of ANS parameters (heart rate and HRV) for reoffending in the delinquent sample. Data from the baseline assessment on heart rate and HRV were used, measured at rest and in response to the PST. Data on reoffending were obtained from the official Dutch police registration system for criminal behavior (*Herkenningsdienstsysteem, HKS*). As an extension to the data on registered reoffending, in the study presented in **chapter 3**, neurobiological functioning was examined in relation to self-reported rule breaking behavior. Furthermore, self-reported overall aggression and proactive and reactive aggression were assessed in this study, as well as categorical DBD diagnoses. The aim of this study was to examine the predictive value of cortisol, heart rate and HRV for these different types of disruptive behavior. To investigate the exclusive value of neurobiological parameters over and above disruptive behavior, levels of disruptive behavior measured at baseline were incorporated as well.

In **chapter 4**, a cross-sectional study presented that aimed at examining the additional value of alpha-amylase to cortisol, heart rate and HRV as potential correlate of juvenile disruptive behavior in the delinquent and normal control samples. Furthermore, the combined activity of the biological parameters as well as interactions between the biological parameters in relation to disruptive behavior were investigated. Because alpha-amylase was only assessed at follow-up, this study has a cross-sectional design.

In **chapter 5**, a study on the stability of cortisol between baseline and follow-up assessment is presented. For the purpose of this study, a large sample of adolescents

from the general population was included (n=231). This sample was derived from the TRAILS study (Tracking Adolescents' Individual Lives Survey, Huisman et al., 2008). Cortisol stability in the delinquent sample was compared to stability in the TRAILS sample. The first aim of the study presented in **chapter 6** was to investigate stability of heart rate and HRV, as well as proactive and reactive aggression over five years in the delinquent sample. The second aim was to study longitudinal relationships between ANS parameters and proactive and reactive aggression, and, third, to investigate the moderating effect of PTSD symptoms on these relationships. Finally, **chapter 7** summarizes the main findings of this thesis and contains a general discussion and conclusion.