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CHAPTER 1

General introduction
Central to this study is the search for mechanisms that predict the risk for aggressive behavior in early human development. Aggressive behavior is part of typical development of young children (Tremblay, 2000), and is seen as a natural way to express negative emotions such as anger and frustration. Physical aggression typically peaks around age two and three, and then declines from the fourth year onwards (Alink et al., 2006). However, studies investigating trajectories of aggressive behavior over time, have found that a high level of aggressive behavior in early childhood is a strong predictor of delinquency and antisocial behavior later in life (Côté, Vaillancourt, LeBlanc, Nagin, & Tremblay, 2006; Nagin & Tremblay, 1999; NICHD Early Child Care Research Network, 2004). Young children with persistent high levels of aggressive behavior may face negative long-term outcomes including low academic achievement, poor interpersonal relationships, alcohol and drug abuse, accidents, violent crimes, depression, suicide attempts, spouse abuse, and neglectful and abusive parenting (Campbell et al., 2006; Farrington, 1994; Fergusson & Horwood, 1998; Kokko & Pulkkinnen, 2000; Nagin & Tremblay, 1999; Serbin et al., 1998; Stattin & Magnusson, 1989). Chronic aggressive behavior is difficult to treat, and current successful psychosocial intervention programs only achieve a moderate effect size at best (Fossum, Handegard, Martinussen, & Morch, 2008; Smeets et al., 2015). Severe aggressive behavior during childhood and adolescence may come at high costs for individuals, their family and society. In 2015, the Dutch government stated in a report that the consequences of criminal behavior cost our society more than €20 billion euros per year (Moolenaar, Vlemmings, Van Tulder, & De Winter, 2016). Research on factors that help to identify early mechanisms that predict the risk for aggression at a very early age may eventually help to diminish the impact of early aggression on later development.

Longitudinal studies have identified a number of maternal prenatal risk factors associated with high levels of aggressive behavior during (early) childhood, such as low socioeconomic status, low educational attainment, early entry into parenthood (Côté et al., 2006; NICHD Early Child Care Research Network, 2004; Tremblay et al., 2004), smoking during pregnancy (Huijbregts, Seguin, Zoccolillo, Boivin, & Tremblay, 2008; Tremblay et al., 2004), mothers’ own history of antisocial behavior (Hay, Pawlby, Waters, Perra, & Sharp, 2010; Tremblay et al., 2004), and high levels of stress, anxiety or depression during pregnancy (Hay et al., 2011; O’Connor, Heron, Golding, Beveridge, & Glover, 2002). Others have established the role of stressful, adverse home environments and negative parenting practices during the first years of life in the development of aggressive behavior (Tremblay et al., 2004). However, current theoretical models stress that the influence of these risk factors on the development of aggressive behavior is influenced in part by the child’s ability for
self-regulation (Boyce & Ellis, 2005; Calkins & Keane, 2009; El-Sheikh & Erath, 2011), which in turn might be sensitive to the negative influences of the aforementioned risk factors itself (Dawson, Ashman, & Carver, 2000).

Self-regulation can be defined as the capacity to control physiological, emotional, cognitive, and behavioral responses (Baumeister & Vohs, 2004), and is directly and interactively linked with the development of aggressive behavior (Calkins & Keane, 2009). The development of self-regulation is relatively protracted due to its dependence on the maturation of prefrontal and limbic brain systems (Beauregard, Lévesque, & Paquette, 2004), and emerges in the form of basic and automatic regulation of physiological processes in infancy and gradually develops into more self-conscious and intentional regulation of emotion, cognition and behavior from the second year onwards that requires, and is supported by physiological processes (Ochsner & Gross, 2004). Although early self-regulatory processes may moderate the effects of environmental risk on aggressive behavior, other, complementary developmental models emphasize that individual physiological vulnerabilities that are associated to aggressive behavior are fostered by environmental stressors during prenatal and early postnatal development (Dawson et al., 2000; Van Goozen, Fairchild, Snoek, & Harold, 2007).

Infancy is a period of increased sensitivity to the effects of environmental stressors on the biological systems involved in self-regulation (Dawson et al., 2000). Further, brain structures underlying cognitive self-regulation show immense development during early childhood. Research on early predictors and processes that lead to early forms of aggression is critical to enable identification of children at risk at an early age and to intervene timely, before developmental trajectories leading to aggression begin to set. However, most research has focused on childhood and adolescence and much less is known about these factors in infancy and early childhood. The aim of this dissertation is to provide insight into: 1) processes by which early forms of self-regulation and prenatal risk increase vulnerability for aggressive behavior in early childhood and in turn, 2) how prenatal risk predicts early self-regulation at a physiological level (see Figure 1). The studies that comprise the current dissertation focus on self-regulation in very young children measured at a parent-reported emotional and cognitive level (Chapter 5), and an individual experienced physiological level (Chapter 4.1, 4.2, and 5).
Figure 1. This model illustrates the different associations examined in this dissertation between prenatal risk, self-regulation and aggressive behavior. The numbers refer to the chapters in which these associations are described. This model is derived in part from the self-regulatory framework for understanding early childhood behavior problems (Calkins & Keane, 2009), the neurobiological model of childhood antisocial behavior (Van Goozen et al., 2007), Biological Sensitivity to Context framework (Boyce & Ellis, 2005), and the biopsychosocial model of describing Familial risk x ANS functioning interactions predicting psychopathology (El-Sheikh & Erath, 2011).
Emotional and cognitive self-regulation: Negative emotionality and inhibitory control

Vulnerability for aggressive behavior during childhood is associated with a temperament that is characterized by high levels of negative emotionality (NE) (Calkins & Fox, 2002; Eisenberg et al., 2009). NE is generally defined as the child’s tendency to react to stressors with high degrees of emotionality, including anger, irritability, fear or sadness (Rothbart & Bates, 2006). High levels of NE make children prone to develop aggressive behavior, but theoretical models suggest that the negative impact of high NE can be buffered by effortful control (Muris & Ollendick, 2005).

Effortful control refers to self-regulative processes that pertain to controlling or regulating one’s emotions and behavior. Effortful control has strongly been associated with activity in the anterior cingulate gyrus and regions of the prefrontal cortex (Posner & Rothbart, 2007), and encompasses both inhibitory control (IC), defined as the ability to inhibit a dominant response to perform a subdominant response, and attentional control, which can be defined as the ability to focus and shift attention as needed (Rothbart & Bates, 2006). Previous studies have provided evidence for the specific link between IC and aggressive behavior (Raaijmakers et al., 2008; Sterzer & Stadler, 2009).

Although there is evidence that NE and IC each play a unique role in the development of aggressive behavior, according to Muris and Meesters’ interactive model (2005), studying NE in the context of cognitive regulatory capacities allows for a more specific prediction of (the development of) aggressive behavior. However, NE and (components of) effortful control are mostly studied independently and the few studies that have been conducted in young children that included both factors have shown inconsistent results (Belsky, Friedman, & Hsieh, 2001; Gartstein, Putnam, & Rothbart, 2012; Lawson & Ruff, 2004; Olson, Sameroff, Kerr, Lopez, & Wellman, 2005). Longitudinal and cross-sectional studies have demonstrated initial development of effortful control between 27 and 30 months of age (Kochanska, Murray, & Harlan, 2000; Rothbart, Ellis, Rueda, & Posner, 2003). However, effortful control demonstrates vast improvement from infancy through the end of early childhood (Eisenberg, Spinrad, & Eggum, 2010), with further protracted development of executive function components into early adulthood (Diamond, 2002). Hence, the question is whether effortful control abilities have developed sufficiently to buffer the negative effects of NE on aggressive behavior in younger children, or that this can only be expected at a later stage in early childhood.
Physiological self-regulation: Autonomic nervous system (ANS)

The autonomic nervous system (ANS) is part of the peripheral nervous system and provides a physiological window on self-regulatory skills, and maturation of the ANS during the prenatal period and the first year after birth provides the foundation for more complex self-regulation observed later in development (Porges & Furman, 2011). The ANS functions as a complex system of afferent (up) and efferent (down) feedback pathways, that are integrated with other neurophysiological and neuroanatomical processes, and reciprocally link the ANS with central nervous system processes (brain and spinal cord) (Chambers & Allen, 2007). Feedback pathways between the central- and peripheral nervous systems are functional relatively early in development (Porges, 2007); however, individual differences in these systems depend on both genetics and environmental influences. The ANS is comprised of the sympathetic (SNS) and parasympathetic (PNS) nervous system, which perform opposing actions. The SNS initiates the ‘fight/flight’ response by increasing heart rate and respiration. Sympathetic activation frees and directs metabolic resources in order to support active defense behaviors. In contrast, the PNS has an inhibitory effect on the SNS and its role is to maintain homeostasis and to regulate recovery following challenge by decreasing heart rate and respiration.

PNS activity is often assessed by respiratory sinus arrhythmia (RSA), the heart rate variability at the frequency of respiration (Cacioppo, Uchino, & Berntson, 1994), which is thought to index the neural control of the heart via the vagus nerve (Porges, 2007). In response to emotional challenge, RSA levels are assumed to decline, indicating withdrawal of the ‘brake’ on the SNS allowing for flexible responding to environmental events, active engagement with the environment, and coping with mild to moderate environmental stressors (see Porges & Furman, 2011 for a review). If withdrawal of the PNS is not sufficient to manage a challenging situation, SNS activity is expected to increase in order to prepare the body for more active stress responses. Research suggests that higher levels of baseline RSA and greater withdrawal of the PNS during challenging conditions reflect more effective emotion regulation in infancy (Bazhenova, Plonskaia, & Porges, 2001; Moore & Calkins, 2004).

The vast majority of studies examining ANS functioning in young children have focused on RSA or global measures of autonomic functioning like heart rate without assessments of the SNS (Propper & Holochwost, 2013). However, adaptive autonomic responses to emotionally challenging situations requires a delicate balance in the operation of both the PNS and SNS (see next paragraph), and in order to fully understand the link between ANS functioning and behavior, both branches need to be considered (El-Sheikh & Erath, 2011; Quas et al., 2014). SNS functioning can be measured by the pre-ejection period (PEP), which represents the time between the
onset of the heartbeat and ejection of blood into the aorta (Cacioppo et al., 1994). Although assessment of SNS activity by skin conductance level (SCL) is more common, PEP is considered to be a more pure and direct indicator of cardiac SNS activity and can be reliably measured in infants (Alkon et al., 2006; Quigley & Stifter, 2006).

Most studies focus on baseline ANS levels and ANS reactivity to stress or challenge. Baseline measures are thought to be indicative of response potential (Beauchaine, 2001), and reactivity measures of the ANS represent an individual’s physiological response to a discrete environmental challenge compared to a resting state (Alkon, Boyce, Davis, & Eskenazi, 2011). Although recognized as an important parameter of ANS functioning (Porges, 2007), measures indexing autonomic recovery from stress or challenge (i.e. return to baseline) are underrepresented in the current literature (El-Sheikh & Erath, 2011). A study in late preschool children reported that lower PNS recovery was linked to maladaptive emotion regulation responses to frustration (Santucci et al., 2008). Less effective physiological recovery following challenge may result in high ANS activation, even after the stressor has passed, contributing to allostatic load. In sum, measuring the ability to self-regulate at a physiological level should take into account baseline, response, and recovery measures in order to provide a more complete picture of physiological reactivity and regulation (Fox, 1998).

Interaction between prenatal risk and the ANS

Deficits in ANS functioning have been linked to aggression and externalizing behavior in children, adolescents and adults (Beauchaine, Gatzke-Kopp, & Mead, 2007; Van Goozen et al., 2007). However, the pattern of findings between measures of ANS functioning and aggressive behavior is complex and inconsistent. This is likely due to several factors. For example, findings appear to differ in children from non-clinical versus clinical samples (Beauchaine, 2009). In non-clinical samples, increased PNS withdrawal is associated with reduced externalizing behaviors, whereas increased PNS withdrawal is also documented in children with clinically significant externalizing behaviors. Moreover, as mentioned earlier, several theories posit that the influence of individual differences in ANS functioning on behavior occur not directly but in interaction with early adversity (Boyce & Ellis, 2005; El-Sheikh & Erath, 2011). So far, there have been only a handful of studies that investigated the interaction between early adversity and ANS functioning in predicting aggressive or externalizing behavior in early childhood. These studies have exclusively focused on the moderating role of PNS activity (Conradt et al., 2016; Conradt, Measelle, & Ablow, 2013; Eisenberg et al., 2012), with the exception of one study (Waters, Boyce, Eskenazi, & Alkon, 2016) that...
reported that less RSA withdrawal and greater PEP reactivity in infancy each predicted more externalizing problems in childhood in the context of maternal depression.

Furthermore, more recent studies suggest that the coordination of the PNS and SNS is predictive of maladjustment (El-Sheikh & Erath, 2011). According to the autonomic space model (see Table 1), there are different modes of autonomic activation and the synergistic action of both the PNS and SNS determines the effectiveness of self-regulation (Berntson, Cacioppo, & Quigley, 1991). Reciprocal autonomic activation, in which the PNS and SNS are oppositely activated, with increased activation of one system and decreased activation of the other, reflects a coordinated response in which both systems either increase or decrease physiological arousal to support responses to environmental demands. Reciprocal ANS activation in response to stress, is presumed to be normative (Alkon et al., 2011; Salomon, Matthews, & Allen, 2000), and linked to better emotion regulation in young children (Stifter, Dollar, & Cipriano, 2011). However, decreased or increased activation of both the PNS and SNS at the same time, is possible (Berntson et al., 1991). Decreased PNS and SNS activation (i.e. coinhibition) or increased activation of the PNS and SNS (i.e. coactivation) may indicate a breakdown in stress regulation, in which either the PNS or SNS fails to perform its adaptive function in response to stress (Porges, 2007). Indeed, recent studies in middle childhood (El-Sheikh et al., 2009; Gordis, Feres, Olezeski, Rabkin, & Trickett, 2010) have shown that coinhibition and coactivation are associated with increased risk for aggressive and externalizing behavior problems in the context of adversity, as opposed to reciprocal activation between the two systems (i.e. reciprocal PNS activation and reciprocal SNS activation).

Relations between ANS functioning and behavioral outcome may differ in infancy and middle childhood (Beauchaine et al., 2007), as patterns of PNS and SNS responding evolve across early childhood (Alkon et al., 2011; Alkon et al., 2003). This underlines the need to study interactions between the PNS and SNS in infancy and to determine which patterns of PNS and SNS regulation are indicative of increased biological sensitivity to prenatal adversity.
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Table 1. Autonomic nervous system profiles.

<table>
<thead>
<tr>
<th>Profile</th>
<th>PNS</th>
<th>SNS</th>
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<tbody>
<tr>
<td>Reciprocal PNS activation</td>
<td>Activation (high RSA baseline or RSA increase)</td>
<td>Inhibition (high PEP baseline or PEP increase)</td>
</tr>
<tr>
<td>Reciprocal SNS activation</td>
<td>Inhibition (low RSA baseline or RSA decrease)</td>
<td>Activation (low PEP baseline or PEP decrease)</td>
</tr>
<tr>
<td>Coactivation</td>
<td>Activation (high RSA baseline or RSA increase)</td>
<td>Activation (low PEP baseline or PEP decrease)</td>
</tr>
<tr>
<td>Coinhibition</td>
<td>Inhibition (low RSA baseline or RSA decrease)</td>
<td>Inhibition (high PEP baseline or PEP increase)</td>
</tr>
</tbody>
</table>

Note: PNS = parasympathetic nervous system, SNS = sympathetic nervous system, RSA = respiratory sinus arrhythmia, PEP = pre-ejection period (source: El-Sheikh & Erath, 2011).
Effects of prenatal risk on the developing ANS

Physiological systems underlying self-regulation are especially vulnerable to the effects of environmental stressors during the perinatal period (Dawson et al., 2000). Exposure to the risk factors during sensitive periods of fetal development can alter neurological development through fetal programming (i.e. fetal adjustments to cues from the intrauterine environment), thereby affecting the developing ANS (Barker, 1998). Although, as described in the previous paragraph, moderation of the effects of prenatal risk on aggressive behavior by the ANS is presumed, it is therefore also important to consider the possibility that the ANS is already influenced (to some extent) by risk factors during the prenatal (and early postnatal) period.

In a recent review, Propper and Holochwost (2013) concluded that exposure to risk factors during the prenatal period (i.e. maternal stress and substance use) and early postnatal period (i.e. poor quality parent-child interactions, and disruptions in parenting behavior through maternal depression and marital conflict) was consistently related to an altered pattern of ANS functioning in infancy and early childhood, marked by higher baseline heart rate and reduced baseline PNS activity, and increased heart rate but reduced or absent PNS withdrawal in response to challenge (irrespective of type of risk factor and exposure to risk during the prenatal or postnatal period). Although limited, there is some evidence indicating that exposure to adversity during the early postpartum year(s) is associated with heightened SNS activity in early childhood (Hill-Soderlund et al., 2008; Oosterman, de Schipper, Fisher, Dozier, & Schuengel, 2010). However, the effects of prenatal risk on the SNS in infancy has only been scarcely studied. One longitudinal study reported that exposure to maternal prenatal adverse experience, in the form of low social support, was associated with attenuated trajectories of heart rate and SNS responsivity to challenge from six months to five years of age (Alkon et al., 2014). The results so far are contradictory and it is possible that somewhere during early childhood a switch might take place from SNS hyperreactivity to SNS hyporeactivity (Miller, Chen, & Zhou, 2007). The current study aims to investigate the effects of prenatal risk on PNS and SNS response and recovery in infancy.
Outline of this dissertation

The studies that comprise the current dissertation aim to provide insight into the processes by which early self-regulation (measured at different levels, i.e. physiological, emotional and cognitive) and prenatal risk increase vulnerability for aggressive behavior, and how prenatal risk predicts early self-regulation at a physiological level (see Figure 1). To investigate these aims, we used data from two different empirical studies.

In the first study (Chapter 2), we examined how self-regulation at the emotional and cognitive level (respectively NE and IC) predicted aggressive behavior across the preschool years. We specifically tested whether aggressive behavior could be predicted from the interaction between NE and IC. For this study, we recruited a general population sample of 855 preschool children (aged 2-5 years) at child day care centers, preschools and elementary schools throughout The Netherlands. NE, IC and aggressive behavior were assessed through parental reports.

In the second study (Chapters 4.1, 4.2, and 5), we examined how self-regulation at the physiological level (i.e. PNS and SNS functioning) in infancy, in interaction with prenatal risk, predicted aggressive behavior (specifically physical aggression) in toddlerhood (Chapter 4.1 and 4.2), and next, we addressed the question to what extent this self-regulation at a physiological level is already influenced by prenatal risk (Chapter 5). The analyses for the studies described in these chapters, were based on data from a subsample of the Mother-Infant NeuroDevelopment Study (MINDS) – Leiden (The Netherlands). This is a longitudinal study into neurobiological and neurocognitive predictors of early behavior problems, consisting of six assessment waves starting during pregnancy until 42 months post-partum. A total of 275 women with their first-born child participated in this study. Based on the presence of one or more risk factors for poor parenting practices and child emotional and behavioral problems (e.g. presence of maternal psychopathology, substance use, and social adversity; World Health Organization, 2005, 2016), women were assigned to either the low-risk or the high-risk group. Women in the high-risk group were randomly assigned to the intervention or high-risk control group (data from the intervention group is not included in the studies described in this dissertation). The background, design, and study population of the MINDS-Leiden study are described in Chapter 3.

In the studies described in Chapter 4.1, 4.2 and 5, we used data from four of the six assessment waves: third trimester of pregnancy (wave 1; home-visit), six months post-partum (wave 2; home-visit), 20 months post-partum (wave 4; home-visit) and 30 months post-partum (wave 5; lab-visit). The number of participating mothers and children differed somewhat between the studies described in Chapter 4.1,
4.2 and 5, depending on the data available at that point. During the pregnancy assessment, we screened for the presence of risk factors (e.g. maternal psychiatric disorders, substance (ab)use, and social adversity). At six months post-partum, mothers and infants participated in two emotionally challenging tasks: a social stress task (Still Face Paradigm; Mesman, Van IJzendoorn, & Bakermans-Kranenburg, 2009; Tronick, Als, Adamson, Wise, & Brazelton, 1978), and a frustration task (Car seat; Goldsmith & Rothbart, 1999). Infant PNS (i.e. RSA) and SNS (i.e. PEP) activity was measured during baseline, throughout the emotional challenge tasks and during recovery from challenge. At 20 and 30 months post-partum, mothers reported on their child’s externalizing behavior problems; physical aggression at 20 and 30 months and oppositional behavior problems at 30 months only.

In Chapter 4.1, we examined the interactive effects between cumulative prenatal risk and PNS and SNS response to and recovery from stress at six months as predictors of physical aggression at 20 months. In Chapter 4.2, we extended the study in Chapter 4.1 by measuring physical aggression at a later age (30 months) and by investigating interactions within dimensions (e.g. PNS baseline x SNS baseline etc.) and between dimensions (e.g. PNS baseline x SNS response, and PNS response x SNS recovery etc.). Further, we examined whether the interactive effects between early adversity and ANS regulation were specific for physical aggression versus non-aggressive externalizing behavior problems (i.e. oppositional behavior problems) (Burt, 2012).

In Chapter 5, we examined the extent to which prenatal risk was associated with infant PNS and SNS response to and recovery from a social stressor (Still Face Paradigm). Different from the studies described in Chapter 4.1 and 4.2, we examined differences in ANS functioning between the low-risk and high-risk group and, in additional analyses, we examined the effects of separate risk factors and the full range of risk by looking at the association between ANS functioning and cumulative prenatal risk. A secondary aim of this study was to investigate the relation between ANS regulation and emotional regulation (e.g. Negative affect and Gaze towards the mother; this reflects the extent to which infants successfully regulated distress and used other-directed emotion regulation strategies) measured during the social stress task.

In Chapter 6, the results of the studies are summarized and discussed in the context of previous literature.