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Motivation Science

ISSN: 2333-8113

2022, Vol. 8, No. 2, 133–149
https://doi.org/10.1037/mot0000259

Understanding Aggression in Adolescence by Studying the Neurobiological Stress System: A Systematic Review

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Aggression in adolescence is an important antecedent of an antisocial developmental pathway. Research on the stress responsivity system, specifically, the hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous system (ANS), has been instrumental in understanding the development of aggression, yet a recent overview of research on these bio-behavioral associations is currently lacking. We synthesized and analyzed literature since 2011 on HPA-axis (i.e., cortisol) and ANS (i.e., heart rate and skin conductance) measures during rest and stress, with aggression in adolescence (11–19 years). We considered general aggression as well as its subclassifications (e.g., proactive, reactive aggression), and included both self-/other-reports, and laboratory aggression. A literature search (PubMed, Embase, APA PsycINFO) was performed up to March 19, 2021. Sixteen-hundred-fourteen records were screened for eligibility, 28 articles were included in the final synthesis. Although base measures (lower basal cortisol and resting heart rate) related to higher levels of aggression fairly consistently, studies assessing HPA-axis and ANS reactivity yield mixed findings, possibly due to variations in tasks used to evoke reactivity. Furthermore, tentative evidence suggests that lowered arousal relates to proactive forms of aggression, while higher arousal relates to reactive forms of aggression. Finally, the studies show that psychological and social factors, in particular social adversity, internalizing problems, and empathy, impact the association between neurobiological measures and aggression. We recommend that future studies consider different types of aggression using multiple measurement instruments, multiple reactivity tasks, and include a psychosocial assessment. Together, we advocate for a comprehensive biopsychosocial approach to understand what drives aggression in adolescence.

Keywords: aggression, adolescence, hypothalamic-pituitary-adrenal axis, autonomic nervous system, systematic review

Supplemental materials: https://doi.org/10.1037/mot0000259.supp

Adolescence is marked as a period in which antisocial behavior temporarily increases (Moffitt, 1993, 2018). However, adolescents who show severe antisocial behavior can trigger serious personal and societal problems (Brazil et al., 2018). An important form of antisocial behavior is aggression: behaviors or threats directed to verbally or physically harm others (Dodge, 1991; Kempes et al., 2005). Aggression puts individuals at risk for an antisocial developmental trajectory. Importantly, these developmental trajectories vary greatly in appearance and dynamics between adolescents. To better understand this heterogeneity, neurobiological research on the stress responsivity system, that is, the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system (ANS), has been instrumental. The current systematic review synthesizes evidence from the last decade on the relation between the HPA-axis (indexed by cortisol) and ANS functioning (indexed by heart rate and skin conductance measures) and aggression in adolescence (11–19 years). Moreover, associations between neurobiological markers of stress and aggression may not function in isolation but are potentially influenced by a myriad of psychosocial factors. Therefore, we additionally explored the role of potential psychosocial variables in the relation between neurobiological mechanisms and aggression.

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This research was supported by the Netherlands Organization for Scientific Research (NWA Startimpuls 400.17.602).

The authors thank Sterre van Haeringen and Lieke van der Meule for their assistance in the data extraction. The authors report no conflict of interest, financial or otherwise.

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Although the terms antisocial behavior and aggression are often used interchangeably, antisocial behavior is an umbrella term for behaviors by which basic norms and values are violated, and individuals are disadvantaged. Aggression is a specific form of antisocial behavior, and includes intentionally hurting someone physically (e.g., violence), or psychologically (e.g., gossiping, humiliation), either premeditated or in reaction to provocation (Dodge, 1991; Kempes et al., 2005). Thus, types of aggression that are frequently considered in the literature are reactive and proactive aggression. In this systematic review, we examine aggression broadly, including self-reported aggression, other-reported aggression, and aggression as measured with laboratory tasks. In addition, we consider both general aggression as well as subclassifications such as reactive and proactive aggression.

Although prior research has been influential in explaining neurobiological mechanism underlying antisocial behavior in general, a current overview on aggression in adolescence is currently lacking. In the following sections we provide a brief background on what is currently known on two main features of the neurobiological stress system (HPA-axis and ANS) in relation to antisocial behavior, broadly construed.

The Neurobiological Stress Responsivity System and Antisocial Behavior

Hypothalamus-Pituitary-Adrenal Axis Activity

Neurobiological research has aimed to enhance our understanding of the etiology and dynamics of antisocial development (Blair, 2013). For instance, it has been theorized that antisocial behavior is driven by low arousal (sensation-seeking hypothesis; Zuckerman, 1990) and a lack of fear (fearlessness hypothesis; Lykken, 1957, 1982, 2013; Raine & Liu, 1998). Specifically, aberrant neurobiological stress functioning has been related to antisocial behavior such as aggression (Blair, 2013; Van Goozen et al., 2007). A crucial feature of the neurobiological stress system is the hypothalamus-pituitary-adrenal (HPA) axis.

The HPA-axis is the body's stress regulating system. It is comprised of the hypothalamus with at its base the pituitary gland, and the adrenal glands that are located on top of the kidneys (Heaney, 2013). In response to stress, the hypothalamus increases the secretion of corticotrophin-releasing hormone (CRH). This increase results in the pituitary gland to secrete ACTH (ACTH). ACTH then travels down to the cortex of the adrenal glands, which in turn release cortisol into the bloodstream. This process is tightly controlled by a negative feedback loop: if rising cortisol levels exceed a certain threshold, CRH release—and consequently, ACTH and cortisol release—are diminished until cortisol levels fall below the threshold again (Heaney, 2013). Cortisol is thus the main product of the HPA-axis and can be easily assessed via saliva, hair, or blood, as an index of basal HPA-axis functioning or reactive HPA-axis functioning in response to an external stressor.

Basal HPA functioning includes basal (afternoon) cortisol levels, and the cortisol awakening response (CAR). Whereas basal (afternoon) cortisol levels reflects the general attunement of the HPA-axis, the cortisol awakening response provides two indices of HPA functioning during awakening: 1) an estimate of the total cortisol secretion during the first hour after wakening (CAR- Area Under the Curve with respect to the ground; CAR-AUCg), and 2) an estimate of the dynamic of the CAR, emphasizing changes over time after wakening (CAR- Area Under the Curve with respect to the increase; CAR-AUCi; Pruessner et al., 1997). As such, basal cortisol levels and the CAR provide information on the attunement of the HPA system of an individual. Additionally, cortisol levels in response to an external stressor typically include multiple cortisol samples before, during, and after a stressful task, such as giving a presentation to peers. These cortisol reactivity measures thus provide an index of one's upsurge and recovery of the HPA system when exposed to stressful experiences.

Prior research has linked basal and reactivity cortisol measures to individual differences in antisocial behavior. An influential meta-analysis has studied the relation between cortisol and externalizing behavior in (early) childhood and adolescence (Alink et al., 2008). This work showed no relation between externalizing behavior and cortisol reactivity in response to a stressor, and only a weak positive association with basal cortisol. In addition, this weak association manifested itself differently for different age groups; externalizing behavior was associated with higher basal cortisol levels in preschoolers, lower basal cortisol levels in school-age children, while no association was found in adolescents. This meta-analysis thus illustrates how associations with externalizing behavior vary with how cortisol is assessed (basal or reactivity) and with development (Alink et al., 2008). However, this meta-analysis was conducted on externalizing behavior and not aggression specifically. In addition, research on cortisol functioning and aggression in adolescence has grown tremendously in the last decade. Therefore, the first goal of the present study was to analyze recent literature on the association between cortisol (basal and reactivity) and aggression in adolescence.

Autonomic Nervous System Activity

A second feature of the neurobiological stress system is the Autonomic Nervous System (ANS) that together with the HPA-axis creates a state of preparedness. Whereas cortisol reflects a hormonal index of stress and the slow regulation of the stress response, the Autonomous Nervous System (ANS) quickly prepares individuals for acute physical activity. Indices of ANS functioning thus reflect autonomic arousal and can be assessed via psychophysiological measures such as heart rate. A well-validated finding is that a lower resting heart rate is related to higher levels of antisocial behavior. Indeed, a meta-analyses found that lower resting heart rate related to higher levels of aggression, delinquency, (violent) offending, and psychopathic traits, irrespective of age or sex (Lorber, 2004; Ortiz & Raine, 2004; Portnoy & Farrington, 2015).

Researchers have also examined the *parasympathetic* nervous system (PNS) and the *sympathetic* nervous system (SNS) in relation to antisocial behavior in youth. While the PNS maintains the body's rest and digestion response when the body is relaxed or resting, the SNS mobilizes the body's response to situations that require alertness and readiness. Individual differences in these systems have been found to relate to distinct aspects of antisocial behavior. For instance, a lowered PNS activation—indexed by higher respiratory sinus arrythmia (RSA) or heart rate variability (HRV) – has been found to reflect aggression characterized by difficulties in emotion regulation (Beauchaine & Thayer, 2015; Oldenhof et al., 2019). Furthermore, higher SNS activation—

measured with the heart's preejection period (PEP) or with skin conductance levels (SCL) – has been suggested to be related to 'hot-blooded', reactive forms of antisocial behavior, while lower SNS activity has been related to more 'cold-blooded', instrumental forms of antisocial behavior (Kempes et al., 2005; Schoorl et al., 2016) although findings are mixed (e.g., MacDougall et al., 2019). Together, these ANS findings fit well with models stating that some displays of antisocial behavior (e.g., psychopathic traits, proactive aggression) are related to low arousal, while others (anxiety- or frustration-based, reactive aggression) are related to high arousal (Blair, 2013; Fanti, 2018; Fanti et al., 2019). In this review, we provide an overview of recent studies on the associations between *aggression* specifically, and ANS functioning (SNS, PNS) during rest and reactivity, in adolescence.

Interactions With Testosterone

Notably, the hypothalamic-pituitary-gonadal (HPG) axis, with testosterone as its end product, strongly interacts with the HPA-axis and ANS is. These systems communicate reciprocally such that one system can inhibit or instigate the other (for in-depth overviews of these biological mechanisms, see E. O. Johnson et al., 1992; Terburg et al., 2009; Tilbrook et al., 2000; Viau, 2002). Behaviorally, social neuroscientific research has proposed that particular low levels of cortisol combined with high levels of testosterone may relate to higher levels of status- and dominance-related behavior such as aggression, also referred to as the 'dual-hormone hypothesis' (Dabbs et al., 1991; Mehta & Josephs, 2010; Terburg et al., 2009; although it should be noted that meta-analytic evidence indicates this relation is modest [Dekkers et al., 2019]). Although the direct relation between testosterone and aggression has been robustly documented (for reviews, see Archer, 1991; Archer, 2006; Carré & Archer, 2018), in this review we focus on the neurobiological stress system specifically. Thus, we consider testosterone as a factor that may *impact* the association between stress markers (cortisol, ANS measures) and aggression.

Psychosocial Interactions

Importantly, the relation between the neurobiological stress system (HPA and ANS) and aggression does not occur in isolation, and is influenced by psychological and social factors. For instance, exposure to social adversity (e.g., experienced trauma, maltreatment, peer victimization, and socioeconomic problems) is a well-documented predictor of antisocial behavior (Fagan et al., 2017; Moffitt, 2018) and has been found to impact the neurobiological stress system (Gunnar et al., 2019; Yip et al., 2021). Indeed, many biosocial interaction models state that adversity can exacerbate or diminish the relation between biology and antisocial behavior (for a recent review, see van Hazebroek et al., 2019). Furthermore, internalizing problems may also impact these bio-behavioral associations. For instance, adolescents diagnosed with conduct disorder (CD) with internalizing problems (e.g., depression, anxiety) have different physiological profiles (overarousal) than those with callous-unemotional traits (underarousal; for review, see Fanti, 2018, 2019). Finally, individual differences in empathy impact the etiology and development of antisocial behavior and expression of the stress systems (Blair, 2013; Shirtcliff et al., 2009). Thus, an exploration of the role of these psychosocial covariates is pivotal to better understand the relation between HPA-axis and ANS functioning and aggression.

The Current Review

We synthetized research from the last decade (since 2011) on the relation between aggression and indices of neurobiological stress system, specifically HPA-axis (cortisol) and ANS functioning (i.e., heart rate, respiratory sinus arrhythmia, skin conductance levels) in adolescence, that is, between 11 and 19 years. We chose these measures specifically, because they are robust indices of the HPA-axis and ANS functioning, and easily assessed in practice. We hypothesized that lower basal activity of the HPA-axis and ANS, and lower reactivity indices, would relate to higher levels of aggression. We also assessed whether results differ for different types of aggression, such as reactive/frustration-based aggression or proactive/instrumental aggression. In addition, we explored whether additional psychosocial measures that were encountered in our search influenced the relation between neurobiological stress indices and aggression. Specifically, we explored whether measures such as social adversity, internalizing problems, and empathy impact the association between neurobiology and aggression. Finally, we considered testosterone as a factor that may influence the associations between cortisol/ANS measures and aggression.

Method

Search Strategy

To identify all relevant publications, we conducted systematic searches in the bibliographic databases PubMed, Embase.com and APA PsycINFO (Ebsco) from inception up to March 19, 2021; in collaboration with a medical information specialist. The following terms were used (including synonyms and closely related words) as index terms or free-text words: "Aggression," "Aggressiveness," "Galvanic Skin Response," "Autonomic Nervous System," "Hydrocortisone," "Cortisol," "Testosterone," "Young adult," "Adolescent." The references of the identified articles were searched for relevant publications. Duplicate articles were excluded. All languages were accepted. The full search strategies for all databases can be found in the online supplemental materials.

Selection Process

Two reviewers (NEB and LMCJ) independently screened all potentially relevant titles and abstracts for eligibility. Subsequently, the full text article was screened using the eligibility criteria. Differences in judgment were resolved through a consensus procedure. Studies were included if they met the following criteria: (a) they included adolescents, between ages 11 and 19 (with minimal ages 10 and maximum ages 20 years); (b) included at least one measure of aggression (c) included cortisol from saliva, blood, or hair; and/or one of the following ANS measures: heart rate, preejection period, respiratory sinus arrhythmia, respiration rate, skin conductance levels (d) were longitudinal or cross-sectional; (e) included participants from a community sample, or participants from a clinical sample with externalizing disorders (e.g., ADHD, DBD); and (f) were dated from 2011 onward. We excluded studies if they (a) included

children or older adults; (b) did not specifically assess aggression (c) did not include the abovementioned neurobiological measures (d) included clinical samples of participants with a diagnosis other than an externalizing disorder (comorbidity was allowed); (e) were dated before 2011; and (f) were of a non-peer-reviewed publication type: editorials, letters, legal cases, interviews and so forth The full text of the selected articles was obtained for further review by authors NEB and LMCJ.

Results

Search Results

The literature search generated a total of 2315 references: 865 in PubMed, 1164 in Embase.com & 286 in APA PsycINFO. After removing duplicates of references that were selected from more than one database, 1614 references remained. The flowchart of the search and selection process is presented in Figure 1. The final number of studies included in the synthesis was 28.

Sixteen studies included an HPA-axis measure (cortisol or CAR), of which eleven included a basal measure and five included a reactivity measure. Twelve studies included an ANS measure (HR, RSA, or SCL), of which six included basal measures (HR and SCL only) and eleven included reactivity measures. Of these aforementioned studies, two studies included both HPA and ANS measures (both reactivity). Study descriptions and results are depicted in Table 1, and an interactive version of this table in which the reader can sort by the different columns can be found on https://osf.io/aj7n5/.

Study Findings

In the following sections, we first discuss findings regarding HPA-axis activity, followed by findings on ANS activity. Within each section we first discuss findings include basal/resting neurobiological measures, followed by findings that include reactivity neurobiological measures. Furthermore, in discussing the findings we specify what type of aggression was examined and with what measurement type (e.g., self-/other-reported aggression, task-based aggression). Where applicable, we describe associations with testosterone. Table 2 shows a simplified overview of the observed findings, separated by measure and aggression subtype (if applicable), and includes the corresponding study IDs as specified in Table 1. We end the results with a section on the role of psychosocial measures.

Hypothalamus-Pituitary Adrenal Axis Functioning and Aggression

Basal Cortisol

Eleven studies tested the relation between basal cortisol (afternoon levels or CAR) and aggression. Of these, nine studies report a negative association, indicating that lower levels of cortisol or a lower CAR relate to higher levels of aggression (Arbel et al.,

Figure 1
PRISMA Flowchart of the Search and Selection Procedure of Studies (Moher et al., 2010)

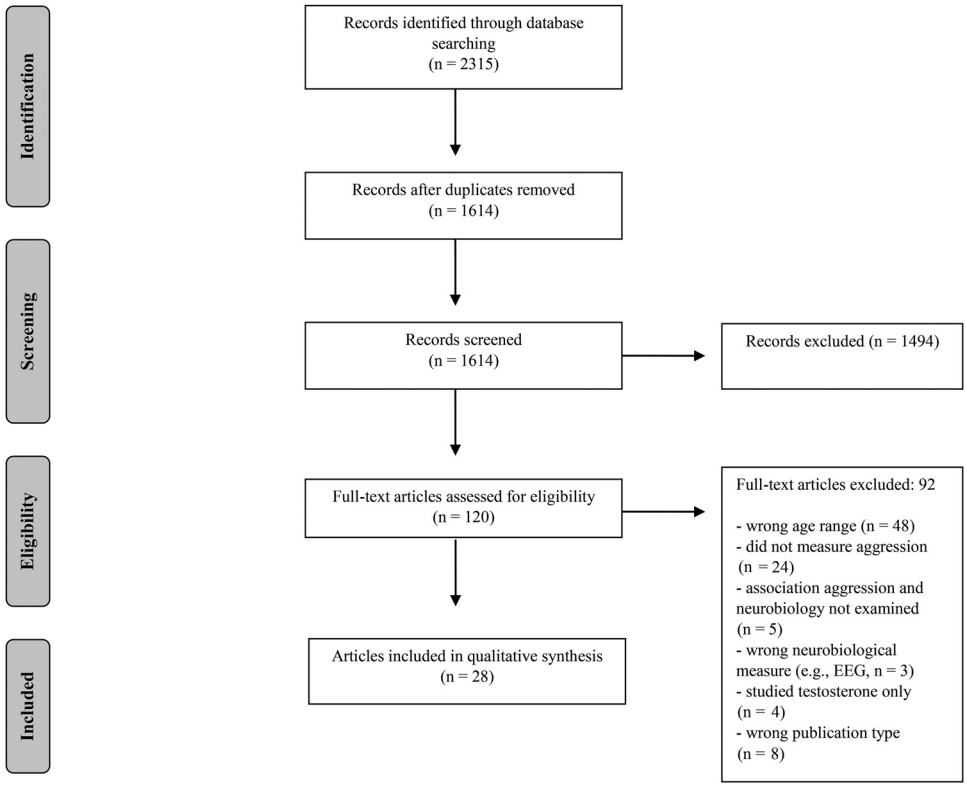

Table 1
Descriptions and Results of the Studies Included in the Synthesis

Study ID	Study	Design	Sample description	*N* (male:female)	*M* age (*SD*)	Age range	Aggression measure(s)	HPA/ANS measure(s)	Basal or reactivity	Descriptive result(s)	Direction HPA/ANS-aggression relation	Psychosocial covariates of interest
1	Arbel et al. (2019)	Longitudinal, continuous	Community sample (USA)	99 (53:46)	18.06 (1.09)	14–21 (majority below 20)	Self-reported Daily friend aggression (HFTEO)	CAR, AUCg	Basal	In males, for low AUCg, victimization predicted next-day aggression towards friends	↓	Daily friend victimization
2	Bakker-Huvenaar et al. (2020)	Cross-sectional, group differences	Clinically referred and typically developing male adolescents (Netherlands)	114 (114:0)	15.40 (1.90)	12–19	Self-reported Reactive and proactive aggression (RPQ)	Cortisol	Basal	No significant associations.	ns	CU traits, clinical diagnosis (ASD, DBD)
3	Dietrich et al. (2013)	Cross-sectional, continuous	Community sample and cinically referred sample (Netherlands)	1,604 (49.2%: 50.8%); 357 (65.9%: 34.1%)	11.10 (0.55); 11.10 (0.50)	10–12	Dimensions of reactive and proactive aggression (derived from YSR Aggression and ASBQ)	Basal morning cortisol; CAR AUCg, AUCi	Basal	In both samples higher CAR related to more (reactive) aggression, in girls.	↑	Anxiety, depression
4	Grotzinger et al. (2018)	Cross-sectional, continuous	Community sample (USA)	891 (456:435)	15.91 (1.39)	13.5–20.1	YSR Aggression scale	Cortisol	Basal	No direct correlations. Lower levels of hair cortisol related to higher levels of aggression, under high testosterone.	↓	Callous-unemotional traits, parental monitoring, peer deviance, peer prosociality
5	Johnson et al. (2014)	Cross-sectional, continuous	Community sample (USA)	57 (32:25)	19.07 (1.33)	—	Self-reported physical and relational Aggression (SRASBM)	CAR	Basal	Lower CAR related to higher physical aggression	↓	Psychopathic traits, empathic concern, perspective taking.
6	Kimonis et al. (2017)	Cross-sectional, group differences (clusters)	Detained male adolescents (USA)	202 (202:0)	16.75 (1.15)	14–18	Self-reported Overt aggression (PCS)	Cortisol	Basal	Higher cortisol related to lower aggression. Those with high CU, high anxiety, and high aggression showed higher cortisol and higher cortisol:DHEA ratios.	↓, ↑	CU traits, anxiety
7	Platje, Jansen, et al. (2013)* (Biol Psych)	Longitudinal, group differences	Community sample (Netherlands)	390 (222:168)	—	15–17	YSR Aggression T-scores	CAR	Basal	Persistently high aggressive adolescents show decreased cortisol levels at awakening	↓	—
8	Platje, Vermeiren, et al. (2013)* (PNEC)	Longitudinal, continuous	Community sample (Netherlands)	425 (239:186)	—	15–17	YSR Aggression T-scores	CAR AUCg, AUCi	Basal	Higher levels of aggression predicted by lower CAR levels at awakening.	↓	Best friend's aggression and rule-breaking
9	Platje et al. (2015)*	Cross-sectional, continuous	Community sample (Netherlands)	259 (144:115)	16.98 (0.42)	—	YSR Aggression T-scores	Cortisol	Basal	Higher levels of aggression related to lower levels of cortisol, also	↓	—

(*table continues*)

Table 1 (*continued*)

Study ID	Study	Design	Sample description	*N* (male:female)	*M* age (*SD*)	Age range	Aggression measure(s)	HPA/ANS measure(s)	Basal or reactivity	Descriptive result(s)	Direction HPA/ANS-aggression relation	Psychosocial covariates of interest
										when controlling for testosterone.		
10	Yu et al. (2016)*	Longitudinal, continuous	Community sample (Netherlands)	358 (205:153)	—	15–17	YSR Aggression T-scores; CBCL Aggression T-scores	CAR AUCg at first assessment	Basal	AUCg related to high initial self-reported aggression. For high AUCg, higher neighborhood density predicted higher parent-reported aggression; for low AUCg, lower neighborhood density predicted higher parent-reported aggression.	↑, ↓	Neigborhood density
11	Yu et al. (2019)*	Longitudinal, continuous	Community sample (Netherlands)	358 (205:153)	—	15–17	Self-reported Violent behavior and Physical aggression	CAR AUCg, AUCi	Basal	In girls, for low AUCi depression predicted higher levels of violence and aggression; for high AUCi depression predicted lower levels of violence and aggression. In boys, for low AUCg depression related to higher levels of aggression; for high AUCg depression related to lower levels of aggression.	↓	Depression
12	Buckingham-Howes et al. (2016)	Cross-sectional, group differences	Drug-exposed and nonexposed adolescents (USA)	137 (50%:50%)	14.17 (1.17)	11–16	Caregiver-reported aggression (BASC-II)	Cortisol	Reactivity in response to a mild stressor (risk taking task and distress tolerance task)	Lower cortisol reactivity related to higher aggression in controls only.	↓	Prenatal drug exposure
13	Kliewer et al. (2012)	Longitudinal, group differences	Community sample (USA)	228 (45%:55%)	14.10 (1.6)		Self-reported Physical and relational aggression (PBFS)	Cortisol	Reactivity in response to SCI	Nonaggressive victims, aggressive victims, and normative controls did not differ on cortisol reactivity	ns	Peer victimatization
14	Portnoy et al. (2015)	Cross-sectional, continuous	Community sample (USA)	353 (175:178)	11.92 (0.59)	11–12	YSR aggression T-scores; CBCL Aggression T-scores	Cortisol	Reactivity to combination of TSST and cognitive stress task	In boys, low cortisol reactivity related to high levels of self-reported aggression, but only for low levels of prenatal testosterone.	↓	—

(*table continues*)

Table 1 (*continued*)

Study ID	Study	Design	Sample description	*N* (male:female)	*M* age (*SD*)	Age range	Aggression measure(s)	HPA/ANS measure(s)	Basal or reactivity	Descriptive result(s)	Direction HPA/ANS-aggression relation	Psychosocial covariates of interest
15	Rinnewitz et al. (2019)	Cross-sectional, group differences	Community sample (Germany)	40 (0:40)	14.85 (1.09; aggression-induced); 15.45 (1.00; control)	13–17	Aggression (noise blast volume and duration) induced by the TAP	Cortisol, HR	Reactivity in response to TAP	No significant effects of cortisol. Increased heart rate in the aggression-induced group compared to the control group.	ns, ↑	—
16	Goulter et al. (2019)	Cross-sectional, continuous	Community sample of women oversampled for high psychopathic traits	101 (0:101)	19.02 (1.50)	—	Self-reported Reactive and proactive aggression (PCS); Laboratory reactive aggression (noise blast duration and intensity in CRRT)	Cortisol, HRV	Reactivity in response to CRRT procedure	Postprovocation cortisol positively related to trait proactive aggression.	↑, ns	Psychopathic traits, maltreatment, anxiety, parental warmth, depressive symptoms, PTSS, borderline personality symptoms.
17	Galán et al. (2017)	Longitudinal, continuous	Community sample (USA)	160 (160:0	—	12–20	Self- and peer-reported violence (SRD); violent court petitiions	HR	Basal	No direct associations. For lower HR at age 12 lower empathy predicted increased violence at age 17 and 20.	↓	Empathy
18	Portnoy et al. (2020)	Longitudinal, continiuous	Community sample (USA)	197 (197:0)	15.70 (NA); 32.1 (NA)	14–18 (adolescence); 30–34 (adulthood)	Adolescence: Hostility/aggression ZKPQ; Adulthood: Aggression (BPAQ), self-reports	HR	Basal	In white males only, low resting HR in adolescence predicted current and adult levels of aggression	↓	Race (Black vs White)
19	Raine et al. (2014)	Cross-sectional, continuous	Community sample (Hong Kong)	334 (195:139)	13.22 (1.19)	11–17	Self-reported Reactive and Proactive Aggression (RPQ)	HR	Basal	Low resting HR related to higher levels of reactive aggression for high levels of social adversity. Low resting HR related to higher levels of proactive aggression.	↓	Social adversity
20	Aults et al. (2015)	Cross-sectional, continuous	Community sample (USA)	82 (38:44)	12.07 (0.85)	11–15	Peer nominated Aggression	RSA	Basal; Reactivity to loud noise (Cool test)	No correlation between baseline RSA and aggression. For girls, RSA reactivity decreased aggressive behavior for high internalizing symptoms.	ns, ↓	Peer-nominated internalizing problems
21	Cui et al. (2019)	Cross-sectional, continuous	Community sample (USA)	57 (31:26)	13.19 (2.55)	10–17	Self-reported aggression (PBFS)	RSA	Basal; Reactivity to bullying film	No direct associations. For RSA augmentation (less arousal), neighborhood violence predicted increased aggression	ns, ↓	Neighborhood violence, parental psychological control, parental acceptance

(*table continues*)

Table 1 (*continued*)

Study ID	Study	Design	Sample description	*N* (male:female)	*M* age (*SD*)	Age range	Aggression measure(s)	HPA/ANS measure(s)	Basal or reactivity	Descriptive result(s)	Direction HPA/ANS-aggression relation	Psychosocial covariates of interest
22	Sanders et al. (2018)	Longitudinal, continuous	Community sample (USA)	374 (181:193)	15.29 (1.05)	13–18	Self-reported aggression (ERSWAI)	RSA	Basal; Reactivity in response to solving a Rubic's cube	Greater RSA withdrawal (more arousal) associated with more aggressive behavior, for high preference for aggressive media content and more screen time.	ns, ↑	Preference for aggressive and prosocial media content; Screen time
23	Cui et al. (2015)	Cross-sectional, continuous	Community sample (USA)	206 (101:105)	13.37 (2.32)	10–18	Self-reported aggression (PBFS)	RSA	Reactivity to external stressor (angry event discussion task)	No significant effects.	ns	Prosocial behavior, emotion regulation
24	Gao et al. (2015)	Longitudinal, group differences	Community sample (USA)	306 (45%:55%)	17.22 (1.23) at Wave 4	10–18	Self-reported Reactive and proactive aggression (RPQ)	SCL	Reactivity during fear conditioning	Lower SCL fear conditioning in persistently high proactive - but not reactive- aggressive individuals	↓	—
25	Gregson et al. (2014)	Cross-sectional, continuous	Community sample (USA)	123 (50%:50%)	12.03 (0.64)	—	Teacher-reported aggressive behavior (CPR)	SCL	Reactivity in response to having a conversation observed by peers, and in response to a rebuff period	No direct association. Under high peer victimization, lower SCL reactivity related to higher aggression.	↓	Peer victimization
26	Im et al. (2019)	Cross-sectional, continuous	Community sample (Korea)	70 (30:40)	18.3 (1.2)	—	Self-reported aggression (BDHI); anger, physical aggression, hostility, verbal aggression (BPAQ); proactive and reactive aggression (PCS)	HRV, HR	Reactivity to aggression- and aversion-inducing videos	HRV related positively to anger (BPAQ), and total, reactive, and overt aggression (PCS). Heart-rate reactivity related positively to anger (BPAQ) and overt aggression (PCS)	↓, ↑	—
27	McQuade et al. (2019)	Cross-sectional, continuous	Community sample (USA)	125 (55%:45%)	11.34 (0.89)	10–12	Teacher-reported relational aggression (CSB-TR)	SCL, RSA	Reactivity to peer rejection task	For high SCL and high emotional sensitivity, and low SCL and low emotional sensitivity, relational victimization associated with relational aggression. RSA augmentation (lower arousal) related to relational aggression among children with both high and low emotional	↑, ↓, ↓	Relational victimization, emotional sensitivity

(*table continues*)

Table 1 (*continued*)

Study ID	Study	Design	Sample description	*N* (male:female)	*M* age (*SD*)	Age range	Aggression measure(s)	HPA/ANS measure(s)	Basal or reactivity	Descriptive result(s)	Direction HPA/ANS-aggression relation	Psychosocial covariates of interest
										sensitivity, stronger in high emotional sensitivity.		
28	Muñoz Centifanti et al. (2013)	Cross-sectional, group differences (clusters)	Detained adolescent male offenders (USA)	70 (70:0)	15.5 (1.28)	13–18	Self-reported proactive, reactive aggression (PCS); Laboratory preemptive and reactive aggression (points taken from opponent in CRRT);	HR, RSA, SCL	Reactivity in response to emotional dot-probe task	No significant direct associations correlations. In the least physiologically reactive cluster, youth high on narcissism reported greater proactive aggression than those low on narcissism. In the most physiologically reactive cluster, youth high on narcissism responded with greater reactive aggression than those low on narcissism	↓,↑	Narcisissm

Note. *Abbreviations neurobiological measures*. AUCg = Area Under the Curve with respect to the ground; AUCi = Area Under the Curve with respect to the increase; CAR = Cortisol Awakening Response; HR = Heart Rate; RSA = Respiratory Sinus Arrythmia; SCL = Skin Conductance Level. *Abbrevations aggression measures*. ASBQ = Antisocial Behavior Questionnaire; BASC-II = Behavior Assessment System for Children, Second Edition; BPAQ = Buss–Perry Aggression Questionnaire; CBCL = Child Behavior Checklist (parent-report); CPR = Checklist of Peer Relations; CRRT = Competitive Reaction time Task; CSB-TR = Children's Social Behavior Scale–Teacher Version; ERSWAI = Emotional Restraint Scale of the Weinberger Adjustment Inventory; HFTEO = How Friends Treat Each Other; PBFS = Problem Behavior Frequency Scale; PCS = Peer Conflict Scale; RPQ = Reactive and Proactive Aggression Questionnaire; SCI = Social Competence Interview; SES = Socio-Economic Status; SRASBM = Self-Report of Aggression and Social Behavior Measure; SRD = Self-Report of Delinquency Questionnaire; TAP = Taylor Aggression Paradigm (a competitive reaction time task); TSST = Trier Social Stress Task; YSR = Youth Self Report; ZKPQ = Zuckerman–Kuhlman Personality Questionnaire. *Other abbreviations*. ↓ = low physiological arousal/cortisol, high aggression; ↑ = high physiological arousal/cortisol, high aggression; ↓↑ = both low and high physiological arousal/cortisol, high aggression; ns = nonsignificant.
* Study includes the same participants of the Dutch RADAR Young cohort.

Table 2
Simplified Overview of Biobehavioral Associations for HPA and ANS Findings (Basal and Reactivity), Separated for General, Reactive-Like, and Proactive-Like Aggression

	General	Reactive	Proactive	Study IDs (Table 1)
HPA: Basal/CAR	↓, ↓, ↓, ↓, ↓, ↑, ↓,	ns, ↑, ↓, ↓, ↑, ↓	ns	1–11*
HPA: Reactivity	↓, ns, ↓	ns	↑	12–16
ANS: Basal				
HR	↓	↓, ↓	↓	17–19
RSA	ns, ns, ns	—	—	20–22
ANS: Reactivity				
HR	↓	↑, ↑, ↑	↓	15, 26, 28
HRV/RSA	↓, ↓, ↑, ns, ↓	ns, ↓, ↑	ns, ↓	16, 20–23, 26, 27, 28
SCL	↓	ns, ↓, ↑	↓, ↑, ↓, ↓	24, 27, 28

Note. General Aggression Includes Non-Specified Aggression. Reactive-like aggression reflects measures including terms such as "reactive," "violent," "physical," and "overt" aggression. proactive-like aggression reflects measures including terms such as "proactive," "pre-emptive," and "relational" aggression. HPA = Hypothalamus-pituitary-adrenal axis; ANS = Autonomic Nervous System; HR = Heart Rate; RSA = Respiratory Sinus Arrythmia; HRV = Heart Rate Variability; SCL = Skin Conductance Level.
* Studies 7-11 include the same sample, all of which observed negative associations.

2019; Grotzinger et al., 2018; M. M. Johnson et al., 2014; Kimonis et al., 2017; Platje, Jansen, et al., 2013; Platje et al., 2015; Platje, Vermeiren, et al., 2013; Yu et al., 2016, 2019), but note that the Platje et al. and Yu et al. studies include the same longitudinal community sample. One study examined a sample of adolescent detained boys (Kimonis et al., 2017); finding that higher levels of cortisol related to lower levels of overt aggression. The majority of these studies included adolescents from community samples in midto-late adolescence, with roughly equal numbers of boys and girls. These studies found negative associations with either general measures of aggression (such as with the Youth Self Report; Grotzinger et al., 2018; Platje, Jansen, et al., 2013; Platje, Vermeiren, et al., 2013; Platje, Popma, et al., 2015; Yu et al., 2016) or with physical aggression (Johnson et al., 2014; Yu et al., 2019), while Arbel et al. (2019) found a negative association with aggression directed toward friends which included physical, relational, and digital aggression. Finally, in two of these studies testosterone was considered in the relation between cortisol and aggression: Grotzinger et al. (2018) found that low cortisol related to higher levels of aggression under high levels of testosterone only, and Platje et al. (2015) found that high testosterone relative to cortisol related to higher levels of general aggression.

Three studies reported a positive association between basal cortisol levels and aggression, that is, higher basal neurobiological functioning was related to higher levels of aggression (Dietrich et al., 2013; Kimonis et al., 2017; Yu et al., 2016). Whereas Dietrich et al. (2013) found that in clinically referred early adolescents and controls, a higher CAR related to more reactive aggression in girls only, Kimonis et al. (2017) reported higher levels of cortisol in a cluster of detained male adolescents characterized by reactive aggression (in combination with CU traits and anxiety). Furthermore, Yu et al. (2016) found positive associations between CAR and general aggression in adolescents from a community sample. Finally, one study reported no significant association between basal cortisol and reactive or proactive aggression, in a sample of clinically referred male adolescents and controls (Bakker-Huvenaars et al., 2020). Of these studies, none tested effects of testosterone.

Cortisol Reactivity

Five studies examined cortisol reactivity in response to a stressor (Buckingham-Howes et al., 2016; Goulter et al., 2019; Kliewer et al., 2012; Portnoy et al., 2015; Rinnewitz et al., 2019). Three of these included paradigms that evoked stress: the Trier Social Stress Task (Portnoy et al., 2015), a mild distress tolerance task (Buckingham-Howes et al., 2016), and an interview in which stressful events had to be recalled (Kliewer et al., 2012). Two studies, including boys only, found negative associations between cortisol reactivity and general levels of aggression (Buckingham-Howes et al., 2016; Portnoy et al., 2015; but under low prenatal testosterone only), while one study including boys and girls from the general population found no significant association with general aggression (Kliewer et al., 2012). Two additional studies, which included females only, examined cortisol reactivity in response to an aggression provocation task (Goulter et al., 2019; Rinnewitz et al., 2019). Here, a positive association between cortisol reactivity and self-reported proactive aggression was found in late adolescent girls oversampled on psychopathic traits (Goulter et al., 2019), but no associations with task-related reactive aggression to provocation were reported (Goulter et al., 2019; Rinnewitz et al., 2019).

Summary

Of the HPA studies, a majority of findings concern negative associations between basal cortisol functioning and different types of aggression, in adolescents drawn mainly from the general population. Three studies found positive associations between basal HPA functioning and (reactive and general) aggression. However, reactivity studies are more mixed, with both positive and negative associations being reported.

Autonomic Nervous System Functioning and Aggression

Basal ANS

Six studies examined a basal ANS measure in relation to aggression. Three studies observed a negative association between resting HR and aggression, indicating that lower heart rates relate to higher levels of general, reactive, overt, violent, and proactive

aggression, in adolescents from community samples (Galán et al., 2017; Portnoy et al., 2020; Raine et al., 2014). Three studies that used RSA as an index of parasympathetic nervous system activity found no association between basal RSA and general levels of aggression in adolescents from community samples (Aults et al., 2015; Cui et al., 2019; Sanders et al., 2018). None of the reviewed studies included basal SNS measures, such as SCL or PEP.

ANS Reactivity

Eleven studies examined associations between ANS reactivity and aggression, using paradigms that evoked aggression, a social stress response (e.g., via peer evaluations), an acute stress response (e.g., using a loud noise), or measured reactivity in response to a cognitively demanding task. First, studies that utilized paradigms that evoked aggression found that in female adolescents task-evoked aggression induced a higher heart rate (Rinnewitz et al., 2019), and that in late adolescents a higher heart rate and heart rate variability related to more self-reported total, overt, and reactive aggression (Im et al., 2019). However, no associations were observed between parasympathetic measures and aggressions in a community sample of adolescents, and in late adolescent females oversampled on psychopathic traits (HRV, RSA; Cui et al., 2015; Goulter et al., 2019).

Second, three studies examined sympathetic (SCL) and parasympathetic (RSA) reactivity in response to tasks that involved viewing or experiencing peer rejection or victimization, that is, these evoked a social stress response. These studies tentatively suggest a lowered sympathetic, and heightened parasympathetic, reactivity response in relation to aggression. That is, Gregson et al. (Gregson et al., 2014) found that lower SCL reactivity in response to social stress related to more teacher-reported general aggression in a community sample of early adolescents, while McQuade et al. report both lower and higher SCL reactivity with teacher-reported relational aggression, also in a community sample of early adolescents (McQuade et al., 2019). In addition, McQuade et al. (2019) observed higher parasympathetic reactivity (RSA augmentation) in relation to parent-reported relational aggression. Likewise, Cui et al. (2019) reported higher parasympathetic reactivity (RSA augmentation), in relation to self-reported aggression in a community sample of midadolescents.

Third, studies that examined acute physiological stress responses (e.g., in response to a loud noise) found that greater parasympathetic reactivity (i.e., RSA reactivity) related to lower peer-nominated aggression in girls with high internalizing symptoms (Aults et al., 2015). In addition, they observed lower sympathetic (SCL) fear conditioning in persistent proactive, but not reactive, aggressive adolescents from a longitudinal sample (Gao et al., 2015).

Finally, two studies assessed physiological reactivity to a cognitively demanding task. Specifically, Sanders et al. (2018) found that lower parasympathetic reactivity (i.e., RSA withdrawal) related to increased self-reported general aggression in a community sample of adolescents. Furthermore, in a group of detained male adolescents, those with higher general physiological reactivity (assessed with HR, RSA, and SCL together) showed higher levels of reactive aggression, while those with low physiological reactivity showed higher levels of proactive aggression (Muñoz Centifanti et al., 2013).

Summary

In sum, although low resting HR is consistently related to higher levels of aggression, resting RSA shows no significant association with aggression. The few HR reactivity studies show a somewhat consistent pattern, with higher HR reactivity for general and reactive aggression and lower HR reactivity for proactive aggression. However, similar to HPA-axis reactivity studies, PNS and SNS reactivity studies yield mixed findings, with both positive, negative, and nonsignificant associations being reported with different types of aggression and different stress elicitation tasks.

Role of Psychosocial Measures

Importantly, in a number of studies the association between neurobiological measures and aggression varied with an additional psychosocial covariate. For example, a number of studies examined associations between indices of the neurobiological stress system and aggression in the context of (social) adverse circumstances. These include experiencing peer victimization (Arbel et al., 2019; Gregson et al., 2014; Kliewer et al., 2012; McQuade et al., 2019), or growing up in adverse circumstances such as being maltreated, living in a bad neighbourhood (e.g., with high levels of violence), and having low income, uneducated (single) parents (Buckingham-Howes et al., 2016; Cui et al., 2019; Goulter et al., 2019; Portnoy et al., 2020; Raine et al., 2014; Yu et al., 2016). Four of these studies found that lower HPA-axis (i.e., lower cortisol/CAR) and lower ANS arousal (i.e., higher sympathetic, lower parasympathetic activity, lower HR), particularly in combination with high adversity, were related to higher levels of aggression (daily friend aggression: Arbel et al., 2019; self-reported aggression: Cui et al., 2019; teacher-reported aggression: Gregson et al., 2014; reactive aggression Raine et al., 2014). However, three studies found that low HPA-axis and ANS activity arousal in combination with low, or no adverse circumstances related to higher levels of parent/caregiver-reported aggression (Buckingham-Howes et al., 2016; Portnoy et al., 2020; Yu et al., 2016). Finally, two studies found that high HPA-axis activity, and high ANS arousal (high sympathetic and low parasympathetic activity) combined with high adverse circumstances related to higher levels of aggression as reported by parents or teachers (McQuade et al., 2019; Yu et al., 2016; although in the former study this was only the case under low levels of emotional sensitivity). Thus, associations between both low and high HPA or ANS functioning and aggression occur under both low and high levels of social adversity.

Second, a number of studies investigated the role of internalizing symptoms such as depression and anxiety (Aults et al., 2015; Dietrich et al., 2013; Kimonis et al., 2017; Yu et al., 2019). For instance, Yu et al. (2019) found that in girls with a low cortisol awakening response (CAR AUCi), higher levels of depression related to higher levels of self-reported physical aggression, while for high CAR AUCi, higher levels of depression predicted lower levels of physical aggression (Yu et al., 2019). Similar findings were observed for boys with respect to total cortisol secretion during awakening (CAR AUCg; Yu et al., 2019). Furthermore Aults et al. (2015) found that in girls only, a lower RSA reactivity (higher arousal) for high levels of internalizing symptoms related to higher levels of (peer-nominated) aggression. In contrast, although Dietrich et al. (2013) found that a higher cortisol

awakening response related to higher levels of reactive aggression in girls, no effect was observed for internalizing symptoms (anxiety).

Finally, a number of studies examined the role of individual differences in empathy and psychopathic traits (Bakker-Huvenaars et al., 2020; Galán et al., 2017; Grotzinger et al., 2018; Johnson et al., 2014; Kimonis et al., 2017; Muñoz Centifanti et al., 2013). For instance, Galán et al. (2017) found that only for lower empathy resting HR at age 12 predict violence at age 17 and 20, while Muñoz Centifanti et al. (2013) found that particularly detained juveniles with high levels of narcissism and low physiological reactivity (assessed with HR, SCL, and RSA conjointly) reported more proactive aggression, while those with high narcissism and high physiological reactivity showed more reactive aggression in a laboratory task. Finally, Kimonis et al. (2017) found that in detained juveniles, a cluster of adolescents could be identified with higher levels of basal cortisol and a combination of high callous-unemotional traits, high anxiety, and high (general) aggression. Others found no significant effects of psychopathic traits (Bakker-Huvenaars et al., 2020; Grotzinger et al., 2018; Johnson et al., 2014).

Summary

In sum, individual differences in adverse social circumstances, internalizing symptoms, and empathy and psychopathic traits influence associations between neurobiological stress indices and aggression. In particular, the reviewed literature suggests that adverse circumstances and internalizing symptoms, may both attenuate and exacerbate the relation between low and high neurobiological stress responsivity and aggression. Likewise, the impact of empathy differs across studies. For instance, where some find that high levels of psychopathic traits are related to (reactive and general) aggression under high HPA and ANS arousal, others find that high psychopathic traits relate to relate to (reactive and proactive) aggression under low ANS arousal.

Discussion

This review synthetized literature on associations between neurobiological stress indices (HPA and ANS functioning) and aggression in adolescence (11–19 years). The reviewed studies converge on a number of main findings. First, results suggest that lower basal HPA-axis activity and lower basal ANS activity relate to higher levels of aggression. However, reactivity studies yield mixed findings, with both lower and higher HPA- and ANS reactivity being related to higher levels of aggression. These scattered results may be caused by different reasons. First, variation in findings might be the result of variations in tasks. Furthermore, findings may in part be explained by additional, psychosocial covariates, the most widely reported being (social) adversity (experienced peer victimization or growing up in disadvantaged social circumstances), internalizing symptoms (depression and anxiety), and empathy and traits associated with a lack thereof (e.g., callous-unemotional, narcissistic traits). In the following sections we discuss these main findings in further detail and propose recommendations for a research agenda that tackles the complex interplay between neurobiology, psychosocial background, and aggressive behavior in adolescence.

Tentative Evidence for Lowered Basal Cortisol and Resting HR in Relation to Aggression

First, a small majority of studies suggest a negative association between basal HPA-axis and ANS activity and aggression. This finding fits well with prominent theories of antisocial behavior, such as the fearlessness hypothesis (suggesting a lack of fear; Raine & Liu, 1998) and the sensation seeking hypothesis (suggesting low arousal; Zuckerman, 1990). A consistent finding was that lowered basal cortisol and a lowered CAR were related to higher levels of aggression. This is in contrast to an early meta-analysis suggesting no associations between cortisol (reactivity) and general externalizing behavior in adolescence (Alink et al., 2008). Our review extends this prior work with more recent literature and suggests that cortisol may be an important predictor of aggression specifically. For instance, Platje et al. (Platje, Jansen, et al., 2013) found that lower CAR related to persistent aggression, but not delinquency. Thus, although no definite conclusions can yet be drawn, basal cortisol and CAR measures may be reliable proxies of HPA-axis functioning in relation to aggresssion, instead of overall antisocial behavior.

In addition, we considered the role of testosterone in the association between HPA-axis functioning and aggression. According to the dual-hormone hypothesis, low cortisol levels in combination with high testosterone levels may relate to higher levels of aggression (Mehta & Josephs, 2010), although a recent meta-analysis suggests evidence for this hypothesis is modest, and indicated evidence of publication bias (Dekkers et al., 2019). In the current review, only three studies explicitly tested the role of testosterone, and these found that low cortisol relates to aggression either under high current levels of testosterone (Grotzinger et al., 2018; Platje et al., 2015), or low prenatal testosterone (Portnoy et al., 2015). Together, this review echoes the need for novel large-scale, preregistered studies (Dekkers et al., 2019) to further delineate the combined effect of cortisol and testosterone.

Another consistent finding was that lower resting HR related to higher levels of aggression. This coincides with prior work showing that a lower heart rate is associated with higher levels of antisocial behavior, including aggression (for reviews and meta-analysis, see Lorber, 2004; Ortiz & Raine, 2004; Portnoy & Farrington, 2015). The current review underscores this robust finding. Specific measures of PNS and SNS activity, on the other hand, were not consistently related to aggression. Basal RSA (a parasympathetic measure) was not significantly associated with aggression, while no studies reported associations with basal SCL or PEP (sympathetic measures). Tentatively, parasympathetic and sympathetic measures are more meaningful when examined as reactivity measures (for a discussion, see below). Taken together, our review suggests that lower basal cortisol and CAR and a lower resting heart rate may be robustly related to higher levels of aggression, and thus seeem promising candidate markers to include in future studies as well as in clinical and forensic practice for the prediction of aggressive behavior in adolescence.

Reactivity Measures Yield Mixed Findings

The reviewed studies here suggest that lowered basal HPA and ANS (specifically, heart rate) measures consistently relate to higher levels of aggression. HR reactivity studies also suggest a

somewhat consistent pattern, with higher HR reactivity being related to general and reactive forms of aggression and lower HR reactivity being related to more proactive forms of aggression. Although only three studies included HR reactivity, this pattern of results is in line with prior work suggesting heightened arousal for reactive aggression and lowered arousal for proactive aggression (Blair, 2013; Kempes et al., 2005; Schoorl et al., 2016).

In contrast, other studies that included HPA-axis and ANS reactivity measures yield mixed findings. That is, both positive, negative, and nonsignificant associations between HPA-axis and ANS reactivity measures and aggression were observed. One possible reason for these diverse findings is that studies differed considerably in the types of reactivity tasks. In the current review we roughly organized the results according to four sets of reactivity tasks (although we acknowledge that other distinctions can be made): tasks that evoked social/emotional stress (using public-speaking-type tasks), tasks that evoked aggression (e.g., using competitive reaction time [RT] tasks), tasks that evoked acute physiological stress (e.g., using a loud noise), and tasks that were cognitively demanding. Possibly, different tasks may evoke different HPA and ANS reactions. For instance, a heightened physiological response to negative social experiences may reflect anxiety or negative cognitive interpretations (e.g., Gregson et al., 2014), while a heightened response to an aggression provocation task might reflect anger or frustration (e.g., Rinnewitz et al., 2019). Others, such as a cognitively demanding task, may evoke physiological processes that foster allocating resources for self-regulation during challenging situations (e.g., Sanders et al., 2018), while tasks that evoke acute fear or a startle response measure reflect more basal fear responses (e.g., Gao et al., 2015). In sum, these different tasks may elicit different neurobiological mechanisms, and the scattered pattern of results regarding HPA-axis and ANS reactivity measures thus make it difficult to draw firm conclusions regarding the direction of effects.

Variations by Aggression Measure

The studies reviewed here assessed a variety of aggression indices (e.g., general/a-specific aggression, reactive, proactive, relational aggression) using a variety of measures (e.g., self-report, other-report, laboratory aggression). The majority of studies included trait-aggression measures (using self-/other-reports), while only three studies included a state-measure of aggression (laboratory tasks). For the laboratory tasks, only one showed a direct association between neurobiological stress functioning and laboratory aggression. These tasks typically evoke aggression or frustration, which therefore likely capture reactive aggression rather than proactive aggression. Thus, based on the findings of the current review, conclusions cannot yet be drawn on whether state or trait measures of aggression better capture aggressive tendencies in relation to neurobiological stress indices.

Furthermore, half of the studies included *general* self-report measures of aggression, such as the Youth Self Report, which does not specifically differentiate between different subtypes of aggression such as reactive, physical, overt aggression, or proactive, preemptive, and relational aggression. However, tentatively, in the few studies that made a distinction between the type of aggression, findings seem to converge on the idea that reactive, frustration-based aggression, characterized by heightened emotionality, is related to *higher* HPA-axis and ANS activity (e.g., lowered parasympathetic activity, higher HR reactivity), while more proactive, preemptive forms of aggression characterized by lower emotionality and callousness is related to *lower* HPA and ANS activity (e.g., lower sympathetic activity, lower HR reactivity). Thus, although studies that did dissociate between different subtypes of aggression do not *conclusively* point to a specific direction of effects, the reviewed set of studies together illustrate the importance of clearly defining types of aggression to be examined, and the inclusion of both state and trait measures of aggression.

Impact of Psychosocial Measures

In addition, biobehavioral associations may in part be explained by individual differences in psychosocial covariates. In the reviewed studies, three main psychosocial measures stood out: (social) adverse circumstances, internalizing symptoms, and empathy and psychopathic traits. Although findings regarding empathy and psychopathic traits were mixed, we observed that experiencing peer victimization as well as growing up in adverse circumstances, both exacerbate and diminish the association between HPA and ANS activity and aggression. The same was found for internalizing problems, both low and high depression and anxiety contribute to aggression depending on low and high HPA and ANS activity.

These findings may be interpreted in line of influential theories of biosocial interactions on antisocial behavior (for a recent review, see Van Hazebroek et al., 2019). The current systematic review shows, at least with respect to aggression, that adversity seems to contribute to the association between HPA-axis and ANS functioning and aggressive behavior. These findings may therefore be in line with theories such as the diathesis stress/dual-risk model, which suggests that individuals with a biological vulnerability are at high risk of developing antisocial behavior when exposed to adverse circumstances (Monroe & Simons, 1991; Zuckerman, 1999), or the differential susceptibility model, which suggests that biological sensitivity increases the likelihood of antisocial outcomes under negative environments, but increases the likelihood of prosocial outcomes under positive environments (Bakermans-Kranenburg, & Van IIzendoorn, 2011). Finally, studies including individual differences in empathy find that these impact the association between biology and aggression, albeit mixed. The current review echoes prior calls to consider empathy as an important factor that should be studied conjointly with neurobiological measures (Shirtcliff et al., 2009) to understand aggression.

It should be noted that in the reviewed studies, only a few considered psychosocial measures. Those that did include them focused on only one or a few psychosocial measures rather than a combination of measures. However, based on findings in the current review, we believe that psychosocial factors may play a prominent role in explaining the complicated relation between HPA-axis and ANS functioning and aggression in adolescence, and future studies should look into these relationships.

Limitations

This systematic review aimed to provide a recent overview of the neurobiological stress system in relation to aggression in

adolescence. Although our search focused on HPA-axis and ANS functioning, we limited our search to peripheral measures of the stress system specifically, and these measures are not without its limitations (e.g., Clements, 2013). Other neurobiological stress indices, such as functional neural activation are also informative (e.g., Blair, 2013). In addition, we synthesized literature from 2011 onward. Although this limited the number of studies we could review, we aimed to provide a recent overview of neurobiological stress indices and aggression.

Furthermore, we made a very rough distinction between reactive-like, and proactive-like, aggression, in order to address potential different underlying biological mechanisms. For instance, in Table 2 we classified aggression measures that included terms such as 'reactive', 'overt', 'physical', and 'violent' under reactive-like aggression, and classified measures that included terms such as 'proactive', 'preemptive', and 'relational' under proactive-like aggression. We acknowledge that a more specific classification of different aggression subtypes is warranted, but the fragmented nature of studies impeded to synthesize the results as such.

Finally, we focused on adolescence specifically, as an important transitional phase between childhood and adulthood. Although outside the scope of the current review, including studies with children and adults too would be informative to assess developmental differences. In addition, future longitudinal research is pivotal to assess within-person changes in neurobiological mechanisms and aggression throughout development.

Recommendations for a Biopsychosocial Research Agenda of Aggressive Behavior in Adolescence

Our review shows that indices of the stress system play a prominent role in explaining (part of) aggressive behavior, as consistent results were observed regarding lower basal HPA-axis and ANS activity and higher levels of aggression. However, these results remain rather general. To gain more insight into the underlying mechanisms of antisocial behavior it is pivotal to better chart the HPA and ANS basis of aggressive behavior. It should be noted that results on reactivity functioning were not conclusive. Nonetheless, a number of attention points are raised. Here we make a number of methodological recommendations that may help the field forward.

First, the findings of this review underscore that it is important to study specific forms of aggression, and how these are related to activation of the HPA-axis on the one hand and the ANS on the other hand. One possibility to do so is to better differentiate between types of aggressive behaviors that adolescents may display, for instance, using validated questionnaires that dissociate between different trait measures of aggression. Another possibility is to design specific tasks that evoke different types of aggression, and study HPA-axis and ANS activity in response to these different task (state) conditions. Although each of these methods individually have some limitations, together they offer a complete view on state and trait aggression measures.

Second, regardless of how aggression is disentangled into different classifications, it is important to more specifically examine the SNS and PNS, and the balance between these two branches, in their response in relation to these different aggression manifestations. Relatedly, it is valuable to study HPA and ANS measures conjointly, to study their relative contributions (e.g., Blankenstein et al., 2021).

Third, HPA-axis and ANS measures do not function in isolation, rather, they may interact with myriad psychosocial measures, as a number of findings in this review indicate. Future research should take a multifactorial psychosocial perspective, rather than focusing on individual psychosocial variables. Indeed, recent work calls for an approach using a combination of factors to predict who is truly at risk (Cuijpers et al., 2021). Our review shows that adversity is important to consider, but other environment factors such as the family system and influence of peers, are also pivotal to include in order to gain a complete view on the social environmental background (Moffitt, 2018). Relatedly, although this review included a few studies on clinical referred adolescents, most studies included general population samples only. To be relevant for clinical forensic (psychiatric) practice, aggression and its association with neurobiological measures should be examined in the context of specific psychiatric problems. These may include disruptive behavioral disorders with and without limited prosocial emotions (LPE), along with potential comorbidity such as depression and posttraumatic stress disorder (Colins et al., 2020; Rasche et al., 2016; Stimmel et al., 2014; Wolff & Ollendick, 2006).

These methodological recommendations are not exhaustive, and may also extend to other bio-behavioral developmental fields. Together they call for a more multidimensional approach to gain better insight into the underlying mechanisms of aggressive behavior in adolescence. Another promising way to improve insights gained from bio-behavioral research is by including the research population, in this case youths, in the research itself. This ranges from deciding which measures to include, to the design of ecologically valid tasks and interpretation of findings (Mills & Whitmore, 2021). Through this process, research findings are better integrated in society, since the outcomes will be better aligned with everyday situations. This type of cocreation may additionally foster the inclusion of neurobiological measures in clinical and forensic practice, that is, in treatment of adolescents with severe aggressive behavior (e.g., see Popma & Raine, 2006). Since adolescents with problematic behavior also want to understand what drives their behavior (Horstkötter et al., 2012; Horstkötter et al., 2014), involving them through cocreation can help tailor psycho-education and treatment to the needs of adolescents and professionals working with them, which may enhance treatment success. Successful collaboration methods such as youth panels and nongovernmental initiatives are suited to help bridge the gap between adolescents, research, and practice (for example, Young in Prison https://www.younginprison.org/en/our-work).

Conclusion

This review analyzed literature of the last decade on HPA-axis and ANS functioning in relation to aggression in adolescence (11–19 years). Lower basal cortisol and CAR and a lower resting heart rate were fairly consistently related to higher levels of aggression. However, HPA-axis and ANS reactivity studies yielded mixed findings, among others due to the variations in reactivity tasks. Individual differences in (social) adverse circumstances, internalizing symptoms, and empathy seem key in explaining at least part of the relation between HPA-axis and ANS measures and aggression. We advocate for a more specific focus and hypothesis formation

regarding different subtypes of aggression, using both state and trait measures; consideration of different reactivity tasks that may elicit different physiological responses; and a wide-ranging psychosocial assessment. Together, we argue for a comprehensive, multidimensional biopsychosocial approach where neurobiological measures are considered together with psychosocial assessment.

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Received July 1, 2021
Revision received November 16, 2021
Accepted December 6, 2021 ■