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Leveraging parasympathetic nervous system activity to study risk for psychopathology: ...

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1. Introduction

Callous-Unemotional (CU) traits are defined by low empathy, lack of remorse, and insensitivity to the emotions of others (Frick et al., 2014; Waller et al., 2019). Strong evidence has shown that CU traits delineate a distinct subgroup of children at heightened risk for severe and chronic aggression and violence (Fontaine et al., 2011; Waller & Hyde, 2018; Willoughby et al., 2014). CU traits appear to arise from distinct behavioral, temperament, physiological, and neural risk factors relative to other types of externalizing psychopathology (Frick et al., 2014; Waller & Wagner, 2019). Research integrating developmental psychology, neuroscience, and psychophysiology perspectives has given rise to several provocative etiological models that each attempt to isolate the core mechanisms that lead to CU traits in children or psychopathy in adults. For example, meanness, disinhibition, and boldness are phenotypic dispositions proposed within the triarchic model of psychopathy (TriPM; Patrick et al., 2009); fearless dominance, impulsivity, and cold-heartedness are dimensions within the Psychopathic Personality Inventory (PPI-R; Lilienfeld, 2018); impaired reinforcement learning is highlighted within a developmental neurocognitive model (Blair, 2013), reduced sensitivity to threat and affiliative reward are championed within the STAR model (Waller & Wagner, 2019); and disrupted emotional attention, responsiveness, and learning are components within the REAL model (Dadds & Frick, 2019).

These models have in common the idea that CU traits and psychopathy arise from lower basal physiological functioning and arousal across biological systems (cf. Lykken 1957). However, there are inconsistent results from studies that have investigated the relations between physiological functioning, arousal, and reactivity and CU traits. These inconsistencies appear to arise, in part, from differences in sample type, developmental period, or context between studies,

which hinders our ability to fully integrate knowledge of physiological functioning into etiological models of CU traits. To address this limitation, the current review summarizes and evaluates the results of studies that have examined what is known about parasympathetic nervous system (PNS) functioning in relation to CU traits, with a focus on studies that have explored variability in heart rate and respiratory sinus arrhythmia (RSA).

There are several advantages to studying PNS functioning in relation to CU traits, including the ability to gain moment-by-moment and context-specific insight into individual differences in attention, regulation, and behavior. Moreover, assessment of PNS functioning is relatively inexpensive and straightforward to implement, supporting its applicability and feasibility across different developmental periods and contexts. Beyond an evaluation of the literature that has explored PNS functioning in relation to CU traits, the current review highlights the importance of integrating findings across developmental periods, contexts, and sample types to generate testable hypotheses about the role that disrupted PNS functioning could play in multiple etiological pathways to CU traits. An important consequence of this work will be to inform the development of mechanistically-targeted interventions and treatments to reduce childhood CU traits and antisocial behavior.

2. The Parasympathetic Nervous System and Respiratory Sinus Arrhythmia

The PNS and the sympathetic nervous system (SNS) represent the two divisions of the autonomic nervous system (ANS). The ANS is the primary avenue for rapid communication between the brain and the viscera of the body, helping to prepare muscles and organs to rapidly respond to environmental demands (Cacioppo et al., 2007). The nerves of the PNS and SNS extend into the body from the nucleus ambiguus and the spinal cord, respectively. However, these systems are interconnected with a network of subcortical and cortical brain regions that

synergistically regulate and respond to ANS activity (Hastings & Kahle, 2019). The ganglionic neurons of the SNS lie along the vertebrae and generally discharge as a whole to motivate temporary and context-dependent allocation of resources to address specific environmental threat (i.e., “fight or flight” response; Cacioppo et al., 2007). More recent evidence also suggests that the SNS is capable of targeted sympathetic influences across organ systems (Charkoudian et al., 2005). In contrast, the ganglia of the PNS are more distributed in or around the organ of innervation and provide ongoing and dynamic influence on cardiac physiology to maintain homeostasis and support the allocation of attentional and regulatory resources to engage with the environment (Berntson et al., 2008; Cacioppo et al., 2007). The current paper focuses on specific measures of PNS functioning, such as RSA, but also examines research that has incorporated measures of heart rate (HR), which indexes both PNS and SNS functioning.

Variability in HR reflects the dynamic influence of both the PNS and SNS. It is modulated by inhibitory GABAergic pathways between the prefrontal cortex (PFC), amygdala, and medullary output neurons in the PNS and SNS (Thayer & Lane, 2009). Brainstem nuclei (e.g., the dorsal motor nucleus and nucleus ambiguus) and nuclei from the craniosacral system directly influence PNS functioning and in turn, influence HR variability. Indeed, a single efferent pathway – the Xth cranial, or vagus nerve – accounts for nearly 80% of efferent cranial PNS activity (Fox & Fitzgerald, 1990; **Figure 1**). Under homeostatic conditions, input from the nucleus ambiguus of the vagus nerve to the sinoatrial node of the heart keeps the variability of intervals between heart beats high (Schechtman et al., 1989). This variability is referred to as the interbeat interval (IBI) or heart period (HP) and is a nonlinear transformation of HR. Although HR does reflect both PNS and SNS influences, PNS influences on HR are shorter in latency with a higher frequency capacity and, therefore, have a much wider range of control over cardiac

chronotropy than the SNS. In contrast, the SNS predominately influences cardiac contractility, which reflects the strength of the heart's contraction during systole (Cacioppo et al., 2007). Thus, chronotropic control of HR (i.e., frequency), particularly at rest, is primarily influenced by the PNS, whereas SNS influences are implicated in context-driven changes in contractility and flow. The relative influences of SNS and PNS on HR at baseline versus reactivity cannot be disentangled in the context of most psychological research.

Although there are other influences on HR variability (Fox & Porges, 1985; Porges, 2007), the inputs from the nucleus ambiguus of the vagus nerve to the sinoatrial node of the heart are subject only to modulation by respiration (Hirsch & Bishop, 1981; Saul et al., 1991). As such, RSA, which refers specifically to the variability in HR associated with respiration, is a specific measure of PNS functioning (Bornstein & Suess, 2000; Cacioppo et al., 2007). Meta-analytic studies have established a link between activation of dorsolateral PFC (dlPFC), dorsomedial PFC (dmPFC), and ventrolateral PFC (vlPFC) regions and individual variability in regulation (Buhle et al., 2014). Importantly, this prefrontal activation influences RSA via projections through both limbic and brainstem structures (Porges, 2007; Saul et al., 1991), as well as the cardiac sinoatrial node (Holzman & Bridgett, 2017; **Figure 1**). Thus, as described in the polyvagal (Porges, 1991, 2007) and neurovisceral integration (Thayer et al., 2009, 2012) theories, functional differences in the vagus nerve and by extension, RSA, represent key neurophysiological substrates of individual differences in behavior underpinned by PFC activation, including self-regulation, social communication, and attention. In support of this notion, increased vagal control (i.e., higher RSA) has been linked to enhanced attentional capacity (Linnemeyer & Porges, 1986), task engagement (Doussard-Roosevelt et al., 1994), and emotion regulation (Gentzler et al., 2009), whereas lower vagal control (i.e., lower RSA) has

been linked to poorer sustained attention, more impulsiveness, and greater disinhibition (Rash & Aguirre-Camacho, 2012). In sum, RSA represents a valid biomarker of top-down self-regulatory processes (Nigg, 2016; Thayer et al., 2009).

In addition to self-regulatory processes (Holzman & Bridgett, 2017), PNS functioning (i.e., indexed via RSA) has been linked to the emotional processes that support effective social interactions. While the SNS ensures increased metabolic output to foster mobilization of behaviors necessary for “fight or flight,” the PNS regulates cardiac output to foster engagement and disengagement with the environment, including the social environment (Porges, 2001). First, the PNS has neuroanatomical links with the cranial nerves (e.g., cranial nerves V, VII, IX, X, and XI) that regulate social engagement via facial expression and vocalization, including specific vagal innervation of various visceral organs, such as the soft palate, pharynx, larynx, bronchi, and facial muscles, which facilitate social and emotional communication (Porges, 2009; **Figure 1**). Second, the PNS promotes effective social communication by inhibiting sympathetic arousal and promoting homeostatic functioning, thus allowing for appropriate and fine-grained regulatory adjustments in social situations (Porges et al., 2013). Third, the PNS supports flexibility in attention, energy allocation, and behavior, necessary for effective functioning in a dynamic social world that, by definition, includes constant shifts in social and emotional cues (Mendes, 2019; Porges, 2001; Yaroslavsky et al., 2014). In particular, individual differences in PNS flexibility (e.g., withdrawal and recovery) are related to accurate detection of social and emotional cues, as well as with adaptive responses to dynamic social feedback across contexts (Hastings et al., 2008; Muhtadie et al., 2015).

Finally, a large body of research has established RSA to be a valid transdiagnostic biomarker of emotion dysregulation and psychopathology (Beauchaine, 2012, 2015; Fanti,

2016), consistent with research linking PFC dysfunction to psychopathology (Maren et al., 2013). Higher baseline RSA, which is indicative of greater myelinated vagal control of HR (i.e., more resources to maintain homeostasis and adapt to environmental challenge), has been associated with positive psychosocial outcomes (Calkins et al., 2013; Porges, 2009). In contrast, lower baseline RSA, which is indicative of poorer myelinated vagal control of HR (i.e., fewer resources to maintain homeostasis and adapt to environmental challenge), has been associated with more symptoms of internalizing and externalizing psychopathology (Beauchaine, 2012; Wagner et al., 2015; Wagner et al., 2018). Low baseline RSA is observed in a host of psychiatric conditions, including internalizing disorders, externalizing disorders, schizophrenia, autism spectrum disorder, and non-suicidal self-injury (Beauchaine, 2015). Moreover, these associations have been reported among children, adolescents, and adults. The consistency of these findings contributes to the view that low baseline RSA is a reliable, transdiagnostic biomarker for aberrant top-down self- and emotion-regulatory processes, which are implicated in many forms of psychopathology (Beauchaine et al., 2018).

In addition to resting RSA levels, RSA change also provides insight into regulatory capacities and risk for psychopathology. Although associations between RSA reactivity and psychopathology have been reported less consistently than those with baseline RSA, likely due, in part, to variation in the laboratory tasks used to elicit reactivity, RSA reactivity does provide important insight into emotion regulation or dysregulation (Beauchaine et al., 2018). A brief decrease in RSA to threat or challenge is adaptive because it is indicative of parasympathetic flexibility in the allocation of attentional resources. However, as summarized in **Table 1**, extreme withdrawal (i.e., reactivity) or a failure to withdraw (i.e., stability or augmentation) when confronted by threat or challenge has been associated with negative psychosocial outcomes and

more symptoms of internalizing and externalizing psychopathology (Beauchaine & Cicchetti, 2019; Cui et al., 2019).

3. Neurobiological Correlates of CU traits

An understanding of disrupted PNS functioning can also inform etiological models of CU traits. Neuroimaging studies suggest that CU traits are underpinned by functional differences in brain activation while processing social cues that would otherwise give rise to empathy, social engagement, or affiliation towards others, including amygdala hyporeactivity to fearful facial expressions (Lozier et al., 2014; Viding et al., 2012), reduced anterior insula (AI), anterior cingulate cortex (ACC), and mPFC activation while imagining others' feelings (Sethi et al., 2018), AI and ACC hyporeactivity when observing others' experience pain (Lockwood et al., 2013), and reduced mPFC activation while hearing the laughter of others (O'Nions et al., 2017). Moreover, youth high on CU traits also show relatively reduced vmPFC and striatum activation and concomitant impairments in reinforcement learning and representation of the negative expected value of harmful behaviors in the brain (Blair, 2013; Moul et al., 2012). Together, these findings suggest that CU traits arise both from impaired sensitivity to the social cues of others that would otherwise promote empathy or social bonding and from failures to recognize and learn about the consequences of behavior or inhibit harmful acts, including direct harm to others (Waller & Wagner, 2019).

Importantly, CU traits are associated with functional differences in the same brain regions that influence input into the cardiac sinoatrial node through the PNS (Holzman & Bridgett, 2017). Thus, by incorporating an assessment of PNS functioning (i.e., RSA or HR differences) into research on CU traits, we can isolate specific neurophysiological regulatory and social mechanisms of interest across ecologically valid contexts and developmental periods.

Moreover, there are several advantages of studying the PNS via RSA over functional magnetic resonance imaging (fMRI) or electroencephalogram (EEG). First, the collection of RSA data via electrocardiogram (ECG) or photothermography (PPG) is much cheaper and less labor intensive than assessing neural functioning via fMRI or EEG. Indeed, the feasibility of collecting cardiac data has been greatly improved in recent years. The previous requirement of stationary monitors and placement of ten or more sensors has been replaced by a variety of small, lightweight, wireless, and ambulatory alternatives requiring only two sensors (Cacioppo et al., 2007). Such research-grade monitors are cost-effective and commercially available to researchers and collect data at frequencies (e.g., 1000 Hz), which allows for an examination of moment-to-moment changes in PNS activity.

Second, many barriers to processing and analyzing raw cardiac data and deriving RSA have been removed, making it a fairly straightforward endeavor. Raw cardiac data present in the form of a series of R-waves, so named for one of the alphabetic labels applied to each portion of the wave, each with its own R-peak (see **Figure 2**). Although methods for quantifying RSA in psychophysiological research vary (see Lewis et al., 2012) for discussion), each involves identifying the interval between R-peaks (i.e., IBI), extracting systematic variance due to breathing, and transforming the variance estimates to normalize the distribution of RSA estimates (Lewis et al., 2012; Porges, 1991). As is the case with many types of psychophysiological data, IBI series data must be cleaned to minimize movement artifacts or other interference. There exist multiple software programs, many of which are freely available, for undertaking this process. One research team recently demonstrated the viability of a fully automated method for cleaning cardiac data which employs an algorithm to calculate a running estimate of the R-R interval and identifies intervals beyond an acceptable margin of error from

the estimate. Once identified, one of a number of methods is used to correct the misplaced R-peak (see Hegarty-Craver et al., 2017 for a description and resources).

Third, the removal of barriers to collecting cardiac data, as well as advances in the quality and affordability of these methods, supports researchers' ability to incorporate measures of PNS functioning in studies which are increasingly ecologically valid and generalizable in ways that are not currently feasible using other neurophysiological methods (e.g., fMRI, EEG). For example, a recent study collected data on PNS activity while children were at school. Specifically, the Learning, Emotion, and Play in Schools (LEAPS) study ($n=102$) used wireless monitors to collect continuous streams of cardiac data across seven 10-minute episodes in preschool classrooms. Data were collected across both unstructured (e.g., free play) and structured (e.g., small- or whole-group instruction) activities (see Holochwost et al., 2019). Of note, all 102 children were compliant with data collection (typically another major barrier in fMRI research; Mulugeta et al., 2017) and approximately 90% of the collected data was clean and usable, which is consistent with estimates obtained from data collected in laboratory environments (e.g., Propper et al., 2008; Wagner et al., 2015).

Fourth, the ability to characterize the nuances of how complex processes unfold depends on whether the same construct can be measured, in the same form, repeatedly over time (Willett, 1989; Willoughby et al., 2012; i.e., heterotypic continuity). Importantly, measures of PNS functioning show relatively high heterotypic continuity (Dollar et al., 2020) and can thus be used to reliably capture patterns of continuity versus change in social processes that would otherwise be obscured through use of behavioral or report measures. Additionally, the inclusion of measures of PNS within etiological research into CU traits can provide insight into dynamic internal processes, particularly when the overt behavior may not align with the underlying

chronometry (Pérez-Edgar & Hastings, 2018). Thus, the finer temporal resolution afforded by examining children's PNS activity can offer unparalleled insight into how regulatory resources are being recruited to support social interactions, particularly when collected in a naturalistic setting. In sum, while fMRI, EEG, and other approaches to assess neurobiological functioning are still critical, the inclusion of PNS measures within studies examining the etiological mechanisms underlying the emergence and stability of psychopathology could provide unique insight, particularly in relation to the study of CU traits.

4. PNS Functioning and CU traits

An emerging body of research has begun to explore the relationship between PNS functioning and CU traits (**Table 2**). To date, however, the majority of studies have examined the relationship between CU traits and HR or heart period. For example, high CU traits have been linked to lower baseline HR (Dietrich et al., 2007; Frick et al., 2014; Raine, 2002), reduced HR reactivity across emotionally evocative or stress-inducing contexts (e.g., Isen et al., 2010; Kimonis et al., 2008), and reduced HR change from baseline in response to sad (de Wied et al., 2012) or emotionally evocative (Anastassiou-Hadjicharalambous & Warden, 2008) film clips. When taken together, existing literature suggests that CU traits may be associated with overall under-arousal of the ANS, a pattern of responding consistent with literature linking CU traits to fearlessness, lack of harm avoidance (Raine, 2002; Waller & Wagner, 2019). However, examinations of HR lack system-specific specificity. That is, we cannot disentangle the relative influence of the SNS and PNS on observed differences in HR, which severely limits the conclusions that can be drawn regarding underlying neurological regulatory mechanisms. Thus, studies are needed that can specifically isolate the role of the PNS in CU traits, including by investigating RSA (Beauchaine, 2015; see **Table 2**).

Surprisingly, however, only a handful of studies have investigated links between RSA and CU traits. Extant research suggest that CU traits are associated with lower resting or baseline RSA. For example, resting RSA was significantly lower in 12- to 15-year-old children with elevated CU traits compared to age-matched controls with low CU traits (De Wied et al., 2012). In a study of 9- to 11-year old children, the combination of low resting RSA and high CU traits was associated with the greatest risk for aggressive behaviors (Thomson & Centifanti, 2018). Relatedly, moderate levels of baseline RSA (as opposed to the extreme high or low levels) have been linked to increased prosociality and higher observed empathic concern in response to others' distress across three samples of children ranging in age from 5 to 10 years (Miller et al., 2016). Longitudinal studies also suggest that low RSA in infancy is a risk factor for later CU traits. For example, children characterized by lower baseline RSA across the first two years of life had higher CU traits at age 36 months (Wagner et al., 2015). Similarly, Mills-Koonce and colleagues (2015) found that lower RSA at 15 months of age was related to children showing higher CU traits at age 7. These studies suggest that CU traits are associated with lower baseline RSA, a pattern of functioning that indicates reduced myelinated vagal control that may interfere with emotional and behavioral regulation (Porges, 2007) and has been linked with various forms of psychopathology (Beauchaine et al., 2019).

Beyond baseline RSA, even fewer studies have explored how individual differences in RSA *change* map onto risk for CU traits. In one exception, Musser and colleagues reported that among children aged 7 to 11 years ($N=150$), lower prosociality (i.e., high CU traits) was associated with less RSA reactivity (i.e., less suppression) while children viewed emotion-laden film clips (Musser et al., 2013). In a longitudinal study of 108 preschoolers, there was an association between CU traits at age 25 months and externalizing problems at age 51 months, but

only for children who had less RSA reactivity when approached by an unfamiliar male adult (Wagner et al., 2017). Reduced RSA suppression was interpreted as indicating that children with CU traits demonstrate a higher threshold for arousal in response to potential threat. The inclusion of PNS in this study allows for two possible conclusions: In some, the lack of RSA suppression that characterizes children high on CU traits may mean that they perceive the social environment as non-threatening (i.e., hence their lack of suppression) or that they do not perceive the threat as warranting the diversion of metabolic resources (see **Table 2**).

In general, there are important sample characteristics that need to be considered alongside the findings of studies presented in Table 2, particularly in relation to sex and sample type. First, the correlates and predictors of CU traits appear to be largely invariant across sex and CU traits predict risk for DBDs similarly in boys and girls (Longman et al., 2015; Waller et al., 2019). Moreover, there is little evidence for sex differences in PNS functioning across development (Patriquin et al., 2014). However, a recent meta-analysis suggested that associations between externalizing psychopathology and increased RSA reactivity were stronger among females (Beauchaine et al., 2018) and two studies reported that the association between lower baseline HR and CU traits was specific to males (Fagan et al., 2017; Kavish et al., 2016) (see **Table 2**). These studies suggest the possibility of sex differences in the relations between PNS functioning and CU traits. However, further investigation of these questions is warranted given the paucity of research focused on exploring moderation by sex. Second, as summarized in **Table 2**, our knowledge of extant associations between HR, RSA, and CU traits has been generated from a preponderance of studies of low-risk samples drawn from the community, where rates of clinically-significant CU traits or externalizing psychopathology may be low. Moreover, clinical samples were exclusively older children and adolescence, leading to a potential continuity gap

between what we know about PNS functioning and links to CU traits in infancy and early childhood versus later in childhood. Future research is needed that tracks longitudinal relationships between CU traits, HR, and RSA that includes children from both community and clinical settings.

5. How Studying the PNS Can Specifically Inform Etiological Models of CU traits

In addition to issues around sampling, the extant literature on the relationships between measures of HR, RSA, and CU traits has yielded some conflicting observations. As noted above, findings from studies that have examined HR functioning have typically reported that CU traits are related to lower resting HR or reduced HR reactivity (Dietrich et al., 2007; Frick et al., 2014; Raine, 2002). These findings stand in contrast to other studies that have linked CU traits, particularly in infancy and early childhood, to lower resting RSA, which typically motivates higher HR (Cacioppo et al., 2007). However, as HR is subject to modulation by some combination of PNS, SNS, and other (e.g., respiration) influences, it is difficult to draw direct comparisons across studies measuring HR and RSA. Employing measures capable of isolating the functioning of specific systems (i.e., by assessing RSA) can provide greater insight into underlying mechanisms. The importance of isolating different systems may be particularly relevant for research examining CU traits given that RSA indexes the functioning of brain regions that underpin many social-affiliative processes of interest (e.g., Wagner et al., 2015).

5.1 Utility of assessing baseline RSA and RSA reactivity

Several benefits can occur downstream of research that specifically explores *baseline RSA* and CU traits. First, insight can be gained into the disruption to regulatory processes that might underpin CU traits. Low baseline RSA is suggestive of reduced myelinated vagal control over HR, which limits the availability of resources from which an individual can draw to make

small, adaptive adjustments to behavioral and emotional regulation in response to the changing environment (Porges, 2007). There is emerging evidence suggesting that a pattern of very low baseline RSA functioning may characterize youth with CU traits (Mills-Koonce et al., 2015; Wagner et al., 2015). Second, the maintenance of baseline physiological functioning is, itself, a dynamic process (Porges, 1992), meaning that an individual's baseline RSA provides insight into the interactions between experience and biological regulatory mechanisms. Patterns of stress responses become engrained slowly during early childhood (Quas et al., 2014), highlighting the importance of studying baseline PNS among infants to establish early biomarkers for CU traits, which could be modified by environmental intervention.

In addition to baseline, studies examining *RSA reactivity* across contexts can also provide insight into risk for CU traits. That is, while baseline RSA is associated with trait-level capacity for emotional and social regulation (Beauchaine, 2015), RSA change indexes functioning of the social engagement system as it facilitates (mal)adaptive responses to emotional and social cues (Beauchaine, 2012; Hastings & Kahle, 2019). Many of the core deficits linked with CU traits appear to stem from errors in processing and responding to cues of threat, affiliation, punishment, or social bonding (Waller & Wagner, 2019). However, to date, almost no studies exist that have explored RSA change or reactivity in relation to CU traits, including during social interaction or threat-based paradigms. In one exception, Thomson and colleagues demonstrated that adolescents with high CU traits showed increases in *both* SNS and PNS activation when exposed to a fear-inducing paradigm (Thomson et al., 2019). Interestingly, while the SNS activation in response to a fear-inducing paradigm was consistent with response we would expect to fear from a typically developing sample, the heightened PNS activation suggested an ability to maintain alertness, control, and calm across those fear experiences (Del Giudice et al., 2011),

which may explain why youth with CU traits typically present as fearless (Fanti, 2016; Frick & Viding, 2009). This research highlights the need to include measures of PNS in studies exploring the physiological basis of CU traits to clarify associations between physiological reactivity to fear stimuli and CU traits.

5.2. Leveraging PNS functioning to clarify two ongoing debates

We focus the final section on the need to incorporate measures of PNS functioning, including RSA, into research on CU traits, which is embodied within two ongoing debates within the literature. We briefly review the basis for these ongoing debates and then describe how future research incorporating PNS functioning could enhance our understanding of CU traits within the context of the debates. We end by offering specific hypotheses for the role of PNS functioning in distinct etiological pathways to CU traits.

5.2.1. Deficits in social functioning and CU traits. Given that the PNS plays a fundamental role in supporting social engagement and behaviors (Porges, 2001), assessments of RSA could be particularly helpful for understanding how deficits in children's responses to cues of social affiliation (e.g., seeking out or getting pleasure from social bonding and closeness with others) and threat (e.g., fearlessness to social and nonsocial threat) impact risk for CU traits. Research suggests that CU traits in early childhood are preceded by impairments in social affiliation, including reduced preferential orientation to the human face at 5-weeks (Bedford et al., 2014), less eye-contact with a caregiver at 6-months (Bedford et al., 2017), less imitation of the arbitrary actions of others at age 2, (Wagner et al., 2020), less engagement while interacting with caregivers in infancy (Wagner et al., 2016), lower displays of affection toward adoptive parents in infancy (Waller et al., 2016), and lower levels of observed mutual orientation between parents and children (Kochanska et al., 2013). Likewise, CU traits during early childhood have

been linked to poorer recognition of emotions, particularly cues of social threat, such as fear, anger, and sadness (Dadds et al., 2017; Petitclerc et al., 2019; Rehder et al., 2017; White et al., 2016), as well as reduced attentional engagement to the distress emotions of others (Kimonis et al., 2015). Deficits in emotion recognition, particularly those associated with amygdala dysfunction, are thought to be driven by a lack of attention to the eye region (Adolphs et al., 2019). Indeed, children and adolescents with CU traits appear to make less eye contact with their caregivers (Dadds et al., 2008, 2011).

Based on the findings of these studies, however, we cannot draw conclusions about the specific biological mechanisms that underlie the social or emotional processing deficits characterizing children with CU traits. That is, we cannot know whether CU traits arise from a reduced desire or motivation to engage in social affiliation, by a lack of cognitive concern about punishment or the negative consequences of actions, or by errors in specific attentional processes related to social cues of affiliation or threat, including gaze patterns. Indeed, interventions that have sought to promote reciprocal parent-child eye gaze have reported mixed results (Dadds et al., 2019; Hawes et al., 2014), raising questions as to whether the mechanism of interest is specific to attention or other social processes (Dadds & Frick, 2019).

Some of these questions could be addressed by incorporating RSA assessment into studies in the following ways. First, an examination of links between resting RSA and CU traits across developmental ages and sample types (e.g., clinical, community) would provide insight into the baseline resources available for navigating social and emotional experiences. For example, a recent study demonstrated an association between baseline RSA and activation in the insula and amygdala while viewing emotional faces (Miller et al., 2019), suggesting that PNS functioning may impact the processing of others' emotional cues. Given that CU traits are

characterized by deficits in emotion recognition and reduced engagement with the distress cues of others (Dadds et al., 2017; Frick et al., 2014, p. 201; Petitclerc et al., 2019), knowledge of baseline RSA could augment and support our understanding of these processes in ecologically valid contexts. Second, an examination of RSA reactivity could provide moment-by-moment and more objective insight into how children high on CU traits unconsciously perceive socially- or emotionally-salient stimuli. That is, the extent to which RSA withdrawal occurs during socially- or emotionally-engaging tasks might provide a more objective assessment of attention allocation, engagement, or regulation. Indeed, it is plausible that children who are high on CU traits are observed to show less social engagement, not because they are less motivated to engage socially, but because the social cues of others are perceived as less salient, thereby promoting less physiological arousal. An examination of RSA reactivity in these contexts would directly support interventions by helping to isolate the specific mechanisms underlying deficits in social engagement.

5.2.2 Clarifying distinct etiological pathways to CU traits. Incorporating assessments of RSA baseline and reactivity could also inform our understanding of *equifinality* within pathways to CU traits (i.e., same end state can be reached from a variety of different initial conditions and through different processes; Cicchetti & Rogosch, 1996). The concept of equifinality has been applied to research examining multiple pathways to CU traits in children and psychopathy in adults. Specifically, research on psychopathy charts the existence of a primary psychopathy variant arising from more strongly heritable affective deficits versus a secondary psychopathy variant arising from adaptation to adverse environmental factors, such as early rejection, abuse or trauma (Karpman, 1941, 1948). Research has begun to establish the existence of similar variants among youth high on CU traits with the primary variant characterized by low anxiety and more

heritable risk and a secondary variant characterized by a history of abuse and maltreatment, more emotion dysregulation, and higher anxiety (Craig & Moretti, 2018; Kahn et al., 2013; Kimonis et al., 2012, 2017).

A framework for understanding these two pathways to CU traits is the Adaptive Calibration model (ACM; Del Giudice et al., 2011). The ACM posits that reactivity and regulation are optimally calibrated to match environmental pressures. Accordingly, different physiological baseline and reactivity patterns linked with CU traits could emerge early in life because of heritable influences (i.e., primary variant) or could develop as a consequence of alterations in hormone and ANS functioning triggered by repeated exposure to chronic, severe stress, abuse, and trauma (i.e., secondary variant) (Glenn, 2018; Thomson et al., 2019). Indeed, research shows that chronic exposure to stress can influence the recalibration of physiological systems across development (Gunnar & Quevedo, 2007; McEwen, 1998) and that the ongoing plasticity of the PNS is both directly influenced by recent proximal contexts and contexts and indirectly impacted by earlier experiences (Cox et al., 2010; Hastings & Kahle, 2019). Because the environment can differentially impact development based on regulatory capacities or vulnerabilities (Belsky & Pluess, 2009; Ellis & Boyce, 2008), children with very low baseline RSA, which is a biomarker of poor emotion regulation that may be a downstream consequence of PFC dysfunction (Thayer et al., 2009), are likely to be most susceptible to unpredictable, harsh, or abusive environments in early life (Beauchaine & Cicchetti, 2019; Wagner et al., 2018). Given that CU traits are most often linked with low resting RSA in infancy and early childhood (Mills-Koonce et al., 2015; Wagner et al., 2015), examining whether and how PNS functioning exacerbates the relations between early risk and later CU traits would help to distinguish between equifinal pathways to CU traits (i.e., primary vs. secondary; see **Figure 3**).

Study of the PNS beginning in infancy can help to inform our understanding of the existence and development of primary and secondary variants of CU traits, which is impactful because these children may require different forms of support and intervention (Hawes et al., 2014). As part of investigating these different developmental trajectories, studies will need to go beyond the question of *if* there are differences in the presence or absence of emotional or anxious arousal, but to instead explore *when* and *how* these differences manifest across ecologically valid contexts and developmental periods. Measures of PNS functioning can be leveraged to tackle these complex questions and, in so doing, can help to identify specific etiological risk factors for CU traits that inform more mechanistically-targeted, personalized, and effective treatments for reducing CU traits and risk for antisocial behaviors across development.

6. Conclusions

Our ability to formulate comprehensive etiological models of CU traits depends on the extent to which researchers can recognize and account for the organization, integration, and interaction of multiple levels of influences early in life (Cicchetti, 1984). To better understand and treat CU traits, we therefore need continued collaboration and integration between experts in socioemotional development and child clinical psychology, with adequate psychological, physiological, and neural tools of assessment. We have presented the case for measures of PNS functioning, and specifically RSA, to be included in this toolbox. In sum, the inclusion of measures of PNS functioning in research on CU traits can contribute to our understanding of its etiology, help to differentiate between equifinal pathways to CU traits, and advance efforts towards the development of mechanistic and individualized interventions.

References

- Adolphs, R., Moldinow, L., & Barrett, L. F. (2019). What is an emotion? *Current Biology*, 29(20), R1060–R1064. <https://doi.org/10.1016/j.cub.2019.09.008>
- Anastassiou-Hadjicharalambous, X., & Warden, D. (2008). Physiologically-indexed and self-perceived affective empathy in Conduct-Disordered children high and low on Callous-Unemotional traits. *Child Psychiatry and Human Development*, 39, 503–517. <https://doi.org/10.1007/s10578-008-0104-y>
- Beauchaine, T. P. (2012). Physiological Markers of Emotional and Behavioral Dysregulation in Externalizing Psychopathology. *Monographs of the Society for Research in Child Development*, 77(2), 79–86. <https://doi.org/10.1111/j.1540-5834.2011.00665.x>
- Beauchaine, T. P. (2015). Respiratory sinus arrhythmia: A transdiagnostic biomarker of emotion dysregulation and psychopathology. *Current opinion in psychology*, 3, 43-47.
- Beauchaine, T. P., Bell, Z., Knapton, E., McDonough-Caplan, H., Shader, T., & Zisner, A. (2018). Respiratory sinus arrhythmia reactivity across empirically based structural dimensions of psychopathology: A meta-analysis. *Psychophysiology*, 56(5), e13329. <https://doi.org/10.1111/psyp.13329>
- Beauchaine, T. P., & Cicchetti, D. (2019). Emotion dysregulation and emerging psychopathology: A transdiagnostic, transdisciplinary perspective. *Development and Psychopathology*, 31(3), 799–804. <https://doi.org/10.1017/S0954579419000671>
- Bedford, R., Wagner, N. J., Rehder, P. D., Propper, C., Willoughby, M. T., & Mills-Koonce, R. W. (2017). The role of infants' mother-directed gaze, maternal sensitivity, and emotion recognition in childhood callous unemotional behaviours. *European Child & Adolescent Psychiatry*. <https://doi.org/10.1007/s00787-017-0967-1>

- Bedford, Rachael, Pickles, A., Sharp, H., Wright, N., & Hill, J. (2014). Archival Report Reduced Face Preference in Infancy: A Developmental Precursor to Callous- Unemotional Traits? *Biological Psychiatry*, 1–7. <https://doi.org/10.1016/j.biopsych.2014.09.022>
- Belsky, J., & Pluess, M. (2009). Beyond diathesis stress: Differential susceptibility to environmental influences. *Psychological Bulletin*, 135, 885–908. <https://doi.org/10.1037/a0017376>
- Berntson, G. G., Norman, G. J., Hawkley, L. C., & Cacioppo, J. T. (2008). Cardiac autonomic balance versus cardiac regulatory capacity. *Psychophysiology*, 45, 643–652. <https://doi.org/10.1111/j.1469-8986.2008.00652.x>
- Blair, R. J. R. (2013). The neurobiology of psychopathic traits in youths. *Nature Reviews. Neuroscience*, 14, 786–799. <https://doi.org/10.1038/nrn3577>
- Bornstein, M. H., & Suess, P. E. (2000). Child and mother cardiac vagal tone: Continuity, stability, and concordance across the first 5 years. *Developmental Psychology*, 36, 54–65. <https://doi.org/10.1037/0012-1649.36.1.54>
- Buhle, J. T., Silvers, J. A., Wager, T. D., Lopez, R., Onyemekwu, C., Kober, H., Weber, J., & Ochsner, K. N. (2014). Cognitive Reappraisal of Emotion: A Meta-Analysis of Human Neuroimaging Studies. *Cerebral Cortex*, 24(11), 2981–2990. <https://doi.org/10.1093/cercor/bht154>
- Cacioppo, J. T., Tassinary, L. G., & Berntson, G. (2007). *Handbook of psychophysiology*. Cambridge University Press.
- Calkins, S. D., Propper, C., & Mills-Koonce, W. R. (2013). A biopsychosocial perspective on parenting and developmental psychopathology. *Development and Psychopathology*, 25, 1399–1414. <https://doi.org/10.1017/S0954579413000680>

- Charkoudian, N., Joyner, M. J., Johnson, C. P., Eisenach, J. H., Dietz, N. M., & Wallin, B. G. (2005). Balance between cardiac output and sympathetic nerve activity in resting humans: Role in arterial pressure regulation. *The Journal of Physiology*, *568*(1), 315–321. <https://doi.org/10.1113/jphysiol.2005.090076>
- Cicchetti, D. (1984). The Emergence of Developmental Psychopathology. *Child Development*, *55*(1), 1–7. <https://doi.org/10.2307/1129830>
- Cicchetti, D., & Rogosch, F. A. (1996). Equifinality and multifinality in developmental psychopathology. *Development and psychopathology*, *8*(4), 597-600.
- Cox, M. J., Mills-Koonce, R., Propper, C., & Gariépy, J.-L. (2010). Systems theory and cascades in developmental psychopathology. *Development and Psychopathology*, *22*(03), 497–506. <https://doi.org/10.1017/S0954579410000234>
- Craig, S. G., & Moretti, M. M. (2018). Profiles of primary and secondary callous-unemotional features in youth: The role of emotion regulation. *Development and psychopathology*, 1–12. <https://doi.org/10.1017/S0954579418001062>
- Cui, L., Zhang, X., Houlberg, B. J., Criss, M. M., & Morris, A. S. (2019). RSA reactivity in response to viewing bullying film and adolescent social adjustment. *Developmental Psychobiology*, *61*(4), 592–604. <https://doi.org/10.1002/dev.21835>
- Dadds, M. R., El Masry, Y., Wimalaweera, S., & Guastella, A. J. (2008). Reduced eye gaze explains “fear blindness” in childhood psychopathic traits. *Journal of the American Academy of Child and Adolescent Psychiatry*, *47*, 455–463. <https://doi.org/10.1097/CHI.0b013e31816407f1>
- Dadds, M. R., English, T., Wimalaweera, S., Schollar-Root, O., & Hawes, D. J. (2019). Can reciprocated parent–child eye gaze and emotional engagement enhance treatment for

- children with conduct problems and callous-unemotional traits: A proof-of-concept trial. *Journal of Child Psychology and Psychiatry*, 0(0). <https://doi.org/10.1111/jcpp.13023>
- Dadds, M. R., & Frick, P. J. (2019). Toward a transdiagnostic model of common and unique processes leading to the major disorders of childhood: The REAL model of attention, responsiveness and learning. *Behaviour Research and Therapy*, 119, 103410. <https://doi.org/10.1016/j.brat.2019.103410>
- Dadds, M. R., Jambrak, J., Pasalich, D., Hawes, D. J., & Brennan, J. (2011). Impaired attention to the eyes of attachment figures and the developmental origins of psychopathy. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, 52, 238–245. <https://doi.org/10.1111/j.1469-7610.2010.02323.x>
- Dadds, M. R., Kimonis, E. R., Schollar-Root, O., Moul, C., & Hawes, D. J. (2017). Are impairments in emotion recognition a core feature of callous–unemotional traits? Testing the primary versus secondary variants model in children. *Development and Psychopathology*, 1–11. <https://doi.org/10.1017/S0954579417000475>
- De Wied, M., Van Boxtel, A., Matthys, W., & Meeus, W. (2012). Verbal, facial and autonomic responses to empathy-eliciting film clips by disruptive male adolescents with high versus low callous-unemotional traits. *Journal of Abnormal Child Psychology*, 40, 211–223. <https://doi.org/10.1007/s10802-011-9557-8>
- de Wied, M., van Boxtel, A., Matthys, W., & Meeus, W. (2012). Verbal, Facial and Autonomic Responses to Empathy-Eliciting Film Clips by Disruptive Male Adolescents with High Versus Low Callous-Unemotional Traits. *Journal of Abnormal Child Psychology*, 40(2), 211–223. <https://doi.org/10.1007/s10802-011-9557-8>

- Del Giudice, M., Ellis, B. J., & Shirtcliff, E. A. (2011). The Adaptive Calibration Model of stress responsivity. *Neuroscience and Biobehavioral Reviews*, *35*, 1562–1592.
<https://doi.org/10.1016/j.neubiorev.2010.11.007>
- Dietrich, A., Riese, H., Sondejker, F. E. P. L., Greaves-Lord, K., van Roon, A. M., Ormel, J., Neeleman, J., & Rosmalen, J. G. M. (2007). Externalizing and internalizing problems in relation to autonomic function: A population-based study in preadolescents. *Journal of the American Academy of Child and Adolescent Psychiatry*, *46*, 378–386.
<https://doi.org/10.1097/CHI.0b013e31802b91ea>
- Dollar, J. M., Calkins, S. D., Berry, N. T., Perry, N. B., Keane, S. P., Shanahan, L., & Wideman, L. (2020). Developmental patterns of respiratory sinus arrhythmia from toddlerhood to adolescence. *Developmental Psychology*. <https://doi.org/10.1037/dev0000894>
- Doussard-Roosevelt, J. A., Suess, P. E., Porges, S. W., Doussard-Roosevelt, J. A., Portales, a L., & Suess, P. E. (1994). Cardiac vagal tone: Stability and relation to difficultness in infants and 3-year-olds. *Developmental Psychobiology*, *27*, 289–300.
<https://doi.org/10.1002/dev.420270504>
- Ellis, B. J., & Boyce, W. T. (2008). Biological Sensitivity to Context. *Current Directions in Psychological Science*, *17*, 183–187. <https://doi.org/10.1111/j.1467-8721.2008.00571.x>
- Fagan, S. E., Zhang, W., & Gao, Y. (2017). Social Adversity and Antisocial Behavior: Mediating Effects of Autonomic Nervous System Activity. *Journal of Abnormal Child Psychology*, *45*(8), 1553–1564. <https://doi.org/10.1007/s10802-017-0262-0>
- Fanti, K. A. (2016). Understanding heterogeneity in conduct disorder: A review of psychophysiological studies. *Neuroscience & Biobehavioral Reviews*.
<https://doi.org/10.1016/j.neubiorev.2016.09.022>

- Fanti, K. A., & Kimonis, E. (2017). Heterogeneity in externalizing problems at age 3: Association with age 15 biological and environmental outcomes. *Developmental Psychology, 53*(7), 1230–1241. <https://doi.org/10.1037/dev0000317>
- Fanti, K. A., Kyranides, M. N., Petridou, M., Demetriou, C. A., & Georgiou, G. (2018). Neurophysiological markers associated with heterogeneity in conduct problems, callous unemotional traits, and anxiety: Comparing children to young adults. *Developmental Psychology, 54*(9), 1634–1649. <https://doi.org/10.1037/dev0000505>
- Fontaine, N. M. G., McCrory, E. J. P., Boivin, M., Moffitt, T. E., & Viding, E. (2011). Predictors and outcomes of joint trajectories of callous-unemotional traits and conduct problems in childhood. *Journal of Abnormal Psychology, 120*, 730–742. <https://doi.org/10.1037/a0022620>
- Fox, N. A., & Fitzgerald, H. E. (1990). Autonomic Function in Infancy. *Merrill-Palmer Quarterly, 36*(1), 27–51.
- Fox, N. A., & Porges, S. W. (1985). The Relation between Neonatal Heart Period Patterns and Developmental Outcome. *Child Development, 56*(1), 28–37. JSTOR. <https://doi.org/10.2307/1130170>
- Frick, P. J., Ray, J. V., Thornton, L. C., & Kahn, R. E. (2014). Annual research review: A developmental psychopathology approach to understanding callous-unemotional traits in children and adolescents with serious conduct problems. *Journal of Child Psychology and Psychiatry, and Allied Disciplines, 55*, 532–548. <https://doi.org/10.1111/jcpp.12152>
- Frick, P. J., & Viding, E. (2009). Antisocial behavior from a developmental psychopathology perspective. *Development and Psychopathology, 21*, 1111–1131. <https://doi.org/10.1017/S0954579409990071>

- Gao, Y., Huang, Y., & Li, X. (2017). Interaction between Prenatal Maternal Stress and Autonomic Arousal in Predicting Conduct Problems and Psychopathic Traits in Children. *Journal of Psychopathology and Behavioral Assessment, 39*, 1–14.
<https://doi.org/10.1007/s10862-016-9556-8>
- Gentzler, A. L., Santucci, A. K., Kovacs, M., & Fox, N. A. (2009). Respiratory sinus arrhythmia reactivity predicts emotion regulation and depressive symptoms in at-risk and control children. *Biological Psychology, 82*(2), 156–163.
<https://doi.org/10.1016/j.biopsycho.2009.07.002>
- Glenn, A. L. (2018). Early life predictors of callous-unemotional and psychopathic traits. *Infant Mental Health Journal, 0*(0). <https://doi.org/10.1002/imhj.21757>
- Gueron-Sela, N., Wagner, N. J., Propper, C. B., Mills-Koonce, W. R., Moore, G. A., & Cox, M. J. (2016). The Interaction Between Child Respiratory Sinus Arrhythmia and Early Sensitive Parenting in the Prediction of Children’s Executive Functions. *Infancy, 1*–19.
<https://doi.org/10.1111/infa.12152>
- Gunnar, M., & Quevedo, K. (2007). The neurobiology of stress and development. *Annual Review of Psychology, 58*, 145–173. <https://doi.org/10.1146/annurev.psych.58.110405.085605>
- Hastings, P. D., & Kahle, S. (2019). Get bent into shape: The non-linear, multi-system, contextually-embedded psychophysiology of emotional development. In *Handbook of Emotional Development* (pp. 27–55). Springer.
- Hastings, P. D., Nuselovici, J. N., Utendale, W. T., Coutya, J., McShane, K. E., & Sullivan, C. (2008). Applying the polyvagal theory to children’s emotion regulation: Social context, socialization, and adjustment. *Biological Psychology, 79*, 299–306.
<https://doi.org/10.1016/j.biopsycho.2008.07.005>

- Hawes, D. J., Price, M. J., & Dadds, M. R. (2014). Callous-Unemotional Traits and the Treatment of Conduct Problems in Childhood and Adolescence: A Comprehensive Review. *Clinical Child and Family Psychology Review, 17*, 248–267. <https://doi.org/10.1007/s10567-014-0167-1>
- Hegarty-Craver, M., Gilchrist, K. H., Propper, C. B., Lewis, G. F., DeFilipp, S. J., Coffman, J. L., & Willoughby, M. T. (2017). Automated respiratory sinus arrhythmia measurement: Demonstration using executive function assessment. *Behavior Research Methods*. <https://doi.org/10.3758/s13428-017-0950-2>
- Hirsch, J. A., & Bishop, B. (1981). Respiratory sinus arrhythmia in humans: How breathing pattern modulates heart rate. *American Journal of Physiology-Heart and Circulatory Physiology, 241*(4), H620–H629. <https://doi.org/10.1152/ajpheart.1981.241.4.H620>
- Holochwost, S. J., Propper, C. B., Rehder, P. D., Wang, G., Wagner, N. J., & Coffman, J. L. (2019). Parasympathetic Function: Relevance and Methodology for Early Education Research. *Journal of Research on Educational Effectiveness, 12*(4), 728–749. <https://doi.org/10.1080/19345747.2019.1631422>
- Holzman, J. B., & Bridgett, D. J. (2017). Heart rate variability indices as bio-markers of top-down self-regulatory mechanisms: A meta-analytic review. *Neuroscience & Biobehavioral Reviews, 74*, 233–255. <https://doi.org/10.1016/j.neubiorev.2016.12.032>
- Isen, J., Raine, A., Baker, L., Dawson, M., Bezdjian, S., & Lozano, D. I. (2010). Sex-specific association between psychopathic traits and electrodermal reactivity in children. *Journal of Abnormal Psychology, 119*(1), 216–225. <https://doi.org/10.1037/a0017777>
- Kahn, R. E., Frick, P. J., Youngstrom, E. A., Kogos Youngstrom, J., Feeny, N. C., & Findling, R. L. (2013). Distinguishing primary and secondary variants of callous-unemotional traits

among adolescents in a clinic-referred sample. *Psychological Assessment*, 25, 966–978.

<https://doi.org/10.1037/a0032880>

Karpman, B. (1941). On the need of separating psychopathy into two distinct clinical types: The symptomatic and the idiopathic. *Journal of Criminal Psychopathology*.

Karpman, B. (1948). Conscience in the psychopath: Another version. *American Journal of Orthopsychiatry*, 18(3), 455.

Kavish, N., Vaughn, M. G., Cho, E., Barth, A., Boutwell, B., Vaughn, S., Capin, P., Stillman, S., & Martinez, L. (2016). Physiological Arousal and Juvenile Psychopathy: Is Low Resting Heart Rate Associated with Affective Dimensions? *Psychiatric Quarterly*.

<https://doi.org/10.1007/s11126-016-9437-z>

Kimonis, E. R., Fanti, K. a, Anastassiou-Hadjicharalambous, X., Mertan, B., Goulter, N., & Katsimicha, E. (2015). Can Callous-Unemotional Traits be Reliably Measured in Preschoolers? *Journal of Abnormal Child Psychology*. <https://doi.org/10.1007/s10802-015-0075-y>

Kimonis, E. R., Fanti, K. A., Goulter, N., & Hall, J. (2017). Affective startle potentiation differentiates primary and secondary variants of juvenile psychopathy. *Development and Psychopathology*, 29(4), 1149–1160. <https://doi.org/10.1017/S0954579416001206>

Kimonis, E. R., Frick, P. J., Cauffman, E., Goldweber, A., & Skeem, J. (2012). Primary and secondary variants of juvenile psychopathy differ in emotional processing. *Development and Psychopathology*, 24, 1091–1103. <https://doi.org/10.1017/S0954579412000557>

Kimonis, E. R., Frick, P. J., Skeem, J. L., Marsee, M. A., Cruise, K., Munoz, L. C., Aucoin, K. J., & Morris, A. S. (2008). Assessing callous-unemotional traits in adolescent offenders:

- Validation of the Inventory of Callous-Unemotional Traits. *International Journal of Law and Psychiatry*, 31, 241–252. <https://doi.org/10.1016/j.ijlp.2008.04.002>
- Kochanska, G., Kim, S., Boldt, L. J., & Yoon, J. E. (2013). Children's callous-unemotional traits moderate links between their positive relationships with parents at preschool age and externalizing behavior problems at early school age. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, 54, 1251–1260. <https://doi.org/10.1111/jcpp.12084>
- Kyranides, M. N., Fanti, K. A., Sikki, M., & Patrick, C. J. (2017). Triarchic dimensions of psychopathy in young adulthood: Associations with clinical and physiological measures after accounting for adolescent psychopathic traits. *Personality Disorders: Theory, Research, and Treatment*, 8(2), 140–149. <https://doi.org/10.1037/per0000193>
- Lewis, G. F., Furman, S. A., McCool, M. F., & Porges, S. W. (2012). Statistical strategies to quantify respiratory sinus arrhythmia: Are commonly used metrics equivalent? *Biological Psychology*, 89, 349–364. <https://doi.org/10.1016/j.biopsycho.2011.11.009>
- Lilienfeld, S. O. (2018). The multidimensional nature of psychopathy: Five recommendations for research. *Journal of Psychopathology and Behavioral Assessment*, 40(1), 79-85.
- Linnemeyer, S. A., & Porges, S. W. (1986). Recognition memory and cardiac vagal tone in 6-month-old infants. *Infant Behavior & Development*, 9(1), 43–56. [https://doi.org/10.1016/0163-6383\(86\)90037-8](https://doi.org/10.1016/0163-6383(86)90037-8)
- Lockwood, P. L., Sebastian, C. L., McCrory, E. J., Hyde, Z. H., Gu, X., De Brito, S. A., & Viding, E. (2013). Association of Callous Traits with Reduced Neural Response to Others' Pain in Children with Conduct Problems. *Current Biology*, 23(10), 901–905. <https://doi.org/10.1016/j.cub.2013.04.018>

- Longman, T., Hawes, D. J., & Kohlhoff, J. (2015). Callous–Unemotional Traits as Markers for Conduct Problem Severity in Early Childhood: A Meta-analysis. *Child Psychiatry & Human Development*. <https://doi.org/10.1007/s10578-015-0564-9>
- Lozier, L. M., Cardinale, E. M., VanMeter, J. W., & Marsh, A. A. (2014). Mediation of the Relationship Between Callous-Unemotional Traits and Proactive Aggression by Amygdala Response to Fear Among Children With Conduct Problems. *JAMA Psychiatry*, *71*, 627. <https://doi.org/10.1001/jamapsychiatry.2013.4540>
- Lykken, D. T. (1957). A study of anxiety in the sociopathic personality. *Journal of Abnormal Psychology*, *55*, 6–10. <https://doi.org/10.1037/h0047232>
- Maren, S., Phan, K. L., & Liberzon, I. (2013). The contextual brain: Implications for fear conditioning, extinction and psychopathology. *Nature Reviews Neuroscience*, *14*(6), 417–428. <https://doi.org/10.1038/nrn3492>
- McEwen, B. S. (1998). Stress, adaptation, and disease. Allostasis and allostatic load. *Annals of the New York Academy of Sciences*, *840*, 33–44. <https://doi.org/10.1111/j.1749-6632.1998.tb09546.x>
- Mendes, W. (2019). Emotion and the Autonomic Nervous System. In *Handbook of Emotion* (4th ed.). The Guilford Press.
- Miller, J. G., Kahle, S., & Hastings, P. D. (2016). Moderate Baseline Vagal Tone Predicts Greater Prosociality in Children. *Developmental Psychology*, *53*, 274–289. <https://doi.org/10.1037/dev0000238>
- Miller, J. G., Xia, G., & Hastings, P. D. (2019). Resting heart rate variability is negatively associated with mirror neuron and limbic response to emotional faces. *Biological Psychology*, *146*, 107717. <https://doi.org/10.1016/j.biopsycho.2019.107717>

- Mills-Koonce, W. R., Wagner, N. J., Willoughby, M. T., Stifter, C., Blair, C., & Granger, D. a. (2015). Greater fear reactivity and psychophysiological hyperactivity among infants with later conduct problems and callous-unemotional traits. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *56*, 147–154. <https://doi.org/10.1111/jcpp.12289>
- Moul, C., Killcross, S., & Dadds, M. R. (2012). A model of differential amygdala activation in psychopathy. *Psychological Review*, *119*, 789–806. <https://doi.org/10.1037/a0029342>
- Muhtadie, L., Akinola, M., Koslov, K., & Mendes, W. B. (2015). Vagal Flexibility: A Physiological Predictor of Social Sensitivity. *Journal of Personality and Social Psychology*, *109*(1), 106–120. <https://doi.org/10.1037/pspp0000016>
- Mulugeta, G., Eckert, M. A., Vaden, K. I., Johnson, T. D., & Lawson, A. B. (2017). Methods for the Analysis of Missing Data in fMRI Studies. *Journal of Biometrics & Biostatistics*, *8*(1). <https://doi.org/10.4172/2155-6180.1000335>
- Musser, E. D., Galloway-Long, H. S., Frick, P. J., & Nigg, J. T. (2013). Emotion Regulation and Heterogeneity in Attention-Deficit/Hyperactivity Disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, *52*(2), 163-171.e2. <https://doi.org/10.1016/j.jaac.2012.11.009>
- Nigg, J. T. (2016). Annual Research Review: On the relations among self-regulation, self-control, executive functioning, effortful control, cognitive control, impulsivity, risk-taking, and inhibition for developmental psychopathology. *Journal of Child Psychology and Psychiatry*, *4*, 361–383. <https://doi.org/10.1111/jcpp.12675>
- O’Nions, E., Lima, C. F., Scott, S. K., Roberts, R., McCrory, E. J., & Viding, E. (2017). Reduced laughter contagion in boys at risk for psychopathy. *Current Biology*, *27*(19), 3049–3055.

- Patrick, C. J., Fowles, D. C., & Krueger, R. F. (2009). Triarchic conceptualization of psychopathy: Developmental origins of disinhibition, boldness, and meanness. *Development and Psychopathology, 21*, 913–938.
<https://doi.org/10.1017/S0954579409000492>
- Patriquin, M. a, Lorenzi, J., Scarpa, A., Calkins, S. D., & Bell, M. A. (2014). Broad implications for respiratory sinus arrhythmia development: Associations with childhood symptoms of psychopathology in a community sample. *Developmental Psychobiology*, n/a-n/a.
<https://doi.org/10.1002/dev.21269>
- Pérez-Edgar, K., & Hastings, P. (2018). Emotion Development from an Experimental and Individual Differences Lens. In J. T. Wixted (Ed.), *Stevens' Handbook of Experimental Psychology and Cognitive Neuroscience* (pp. 1–33). John Wiley & Sons, Inc.
<https://doi.org/10.1002/9781119170174.epcn409>
- Petitclerc, A., Henry, J., Feng, B., Poliakova, N., Brendgen, M., Dionne, G., Vitaro, F., Tremblay, R. E., & Boivin, M. (2019). Genetic Correlation between Child Callous-Unemotional Behaviors and Fear Recognition Deficit: Evidence for a Neurocognitive Endophenotype. *Journal of Abnormal Child Psychology*. <https://doi.org/10.1007/s10802-019-00529-2>
- Porges, S. W. (1992). Vagal tone: A physiologic marker of stress vulnerability. *Pediatrics, 90*, 498–504.
- Porges, Stephen W. (1991). Vagal tone: An autonomic mediator of affect. *The Development of Emotion Regulation and Dysregulation*, 111–128.
- Porges, Stephen W. (2001). The polyvagal theory: Phylogenetic substrates of a social nervous system. *International Journal of Psychophysiology, 42*(2), 123–146.
[https://doi.org/10.1016/S0167-8760\(01\)00162-3](https://doi.org/10.1016/S0167-8760(01)00162-3)

- Porges, Stephen W. (2007). The polyvagal perspective. *Biological Psychology*, 74, 116–143.
<https://doi.org/10.1016/j.biopsycho.2006.06.009>
- Porges, Stephen W. (2009). The polyvagal theory: New insights into adaptive reactions of the autonomic nervous system. *Cleveland Clinic Journal of Medicine*, 76.
<https://doi.org/10.3949/ccjm.76.s2.17>
- Porges, Stephen W., Macellaio, M., Stanfill, S. D., McCue, K., Lewis, G. F., Harden, E. R., Handelman, M., Denver, J., Bazhenova, O. V., & Heilman, K. J. (2013). Respiratory sinus arrhythmia and auditory processing in autism: Modifiable deficits of an integrated social engagement system? *International Journal of Psychophysiology*, 88, 261–270.
<https://doi.org/10.1016/j.ijpsycho.2012.11.009>
- Propper, C., Moore, G. a, Mills-Koonce, W. R., Halpern, C. T., Hill-Soderlund, A. L., Calkins, S. D., Carbone, M. A., & Cox, M. (2008). Gene-environment contributions to the development of infant vagal reactivity: The interaction of dopamine and maternal sensitivity. *Child Development*, 79, 1377–1394. <https://doi.org/10.1111/j.1467-8624.2008.01194.x>
- Quas, J. a, Yim, I. S., Oberlander, T. F., Nordstokke, D., Essex, M. J., Armstrong, J. M., Bush, N., Obradović, J., & Boyce, W. T. (2014). The symphonic structure of childhood stress reactivity: Patterns of sympathetic, parasympathetic, and adrenocortical responses to psychological challenge. *Development and Psychopathology*, 26, 963–982.
<https://doi.org/10.1017/S0954579414000480>
- Raine, A. (2002). Biosocial studies of antisocial and violent behavior in children and adults: A review. *Journal of abnormal child psychology*, 30(4), 311-326.

- Rash, J. A., & Aguirre-Camacho, A. (2012). Attention-deficit hyperactivity disorder and cardiac vagal control: A systematic review. *ADHD Attention Deficit and Hyperactivity Disorders*, 4(4), 167–177. <https://doi.org/10.1007/s12402-012-0087-1>
- Rehder, P. D., Mills-Koonce, W. R., Willoughby, M. T., Garrett-Peters, P., & Wagner, N. J. (2017). Emotion Recognition Deficits among Children with Conduct Problems and Callous-Unemotional Behaviors. *Early Childhood Research Quarterly*, 41, 174–183. <https://doi.org/10.1016/j.ecresq.2017.07.007>
- Saul, J. P., Berger, R. D., Albrecht, P., Stein, S. P., Chen, M. H., & Cohen, R. J. (1991). Transfer function analysis of the circulation: Unique insights into cardiovascular regulation. *American Journal of Physiology-Heart and Circulatory Physiology*, 261(4), H1231–H1245. <https://doi.org/10.1152/ajpheart.1991.261.4.H1231>
- Schechtman, V. L., Harper, R. M., & Kluge, K. A. (1989). Development of Heart Rate Variation Over the First 6 Months of Life in Normal Infants. *Pediatric Research*, 26(4), 343–346. <https://doi.org/10.1203/00006450-198910000-00011>
- Sethi, A., O’Nions, E., McCrory, E., Bird, G., & Viding, E. (2018). An fMRI investigation of empathic processing in boys with conduct problems and varying levels of callous-unemotional traits. *NeuroImage: Clinical*, 18, 298–304. <https://doi.org/10.1016/j.nicl.2018.01.027>
- Thayer, J. F., Åhs, F., Fredrikson, M., Sollers, J. J., & Wager, T. D. (2012). A meta-analysis of heart rate variability and neuroimaging studies: Implications for heart rate variability as a marker of stress and health. *Neuroscience & Biobehavioral Reviews*, 36(2), 747–756. <https://doi.org/10.1016/j.neubiorev.2011.11.009>

- Thayer, J. F., Hansen, A. L., Saus-Rose, E., & Johnsen, B. H. (2009). Heart Rate Variability, Prefrontal Neural Function, and Cognitive Performance: The Neurovisceral Integration Perspective on Self-regulation, Adaptation, and Health. *Annals of Behavioral Medicine*, 37(2), 141–153. <https://doi.org/10.1007/s12160-009-9101-z>
- Thayer, J. F., & Lane, R. D. (2009). Claude Bernard and the heart–brain connection: Further elaboration of a model of neurovisceral integration. *Neuroscience & Biobehavioral Reviews*, 33(2), 81–88. <https://doi.org/10.1016/j.neubiorev.2008.08.004>
- Thomson, N. D., & Centifanti, L. C. M. (2018). Proactive and Reactive Aggression Subgroups in Typically Developing Children: The Role of Executive Functioning, Psychophysiology, and Psychopathy. *Child Psychiatry & Human Development*, 49(2), 197–208. <https://doi.org/10.1007/s10578-017-0741-0>
- Thomson, N. D., Gillespie, S. M., & Centifanti, L. C. M. (2019). Callous-unemotional traits and fearlessness: A cardiovascular psychophysiological perspective in two adolescent samples using virtual reality. *Development and Psychopathology*, 1–13. <https://doi.org/10.1017/S0954579419001196>
- Viding, E., Sebastian, C. L., Dadds, M. R., Lockwood, P. L., Cecil, C. A. M., De Brito, S. A., & McCrory, E. J. (2012). Amygdala response to preattentive masked fear in children with conduct problems: The role of callous-unemotional traits. *American Journal of Psychiatry*, 169, 1109–1116. <https://doi.org/10.1176/appi.ajp.2012.12020191>
- Wagner, N. J., Hastings, P. D., & Rubin, K. H. (2018). Children’s autonomic functioning moderates links between maternal rejecting attitudes and preschool aggressive behaviors. *Developmental Psychobiology*, 60(6), 739–747. <https://doi.org/10.1002/dev.21747>

- Wagner, N., Mills-Koonce, R., Willoughby, M., Propper, C., Rehder, P., & Gueron-Sela, N. (2015). Respiratory sinus arrhythmia and heart period in infancy as correlates of later oppositional defiant and callous-unemotional behaviors. *International Journal of Behavioral Development*. <https://doi.org/10.1177/0165025415605391>
- Wagner, N. J., Hastings, P. D., & Rubin, K. H. (2018). Callous-unemotional traits and autonomic functioning in toddlerhood interact to predict externalizing behaviors in preschool. *Journal of abnormal child psychology*, 46(7), 1439-1450. <https://doi-org.ezproxy.bu.edu/10.1007/s10802-017-0374-6>
- Wagner, Nicholas J., Mills-Koonce, W. R., Propper, C. B., Willoughby, M. T., Rehder, P. D., Moore, G. A., & Cox, M. J. (2016). Associations between Infant Behaviors during the Face-To-Face Still-Face Paradigm and Oppositional Defiant and Callous-Unemotional Behaviors in Early Childhood. *Journal of Abnormal Child Psychology*. <https://doi.org/10.1007/s10802-016-0141-0>
- Wagner, Nicholas J., Waller, R., Flom, M., Ronfard, S., Fenstermacher, S., & Saudino, K. (2020). Less imitation of arbitrary actions is a specific developmental precursor to callous–unemotional traits in early childhood. *Journal of Child Psychology and Psychiatry*, jcpp.13182. <https://doi.org/10.1111/jcpp.13182>
- Waller, R., & Hyde, L. W. (2018). Callous-unemotional behaviors in early childhood: The development of empathy and prosociality gone awry. *Current Opinion in Psychology*, 20, 11–16. <https://doi.org/10.1016/j.copsyc.2017.07.037>
- Waller, R., Trentacosta, C. J., Shaw, D. S., Neiderhiser, J. M., Ganiban, J. M., Reiss, D., Leve, L. D., & Hyde, L. W. (2016). Heritable temperament pathways to early callous–unemotional

- behaviour. *The British Journal of Psychiatry*, 475–482.
<https://doi.org/10.1192/bjp.bp.116.181503>
- Waller, R., & Wagner, N. J. (2019). The Sensitivity to Threat and Affiliative Reward (STAR) Model and the Development of Callous-Unemotional Traits. *Neuroscience & Biobehavioral Reviews*, 107, 656–671. <https://doi.org/10.1016/j.neubiorev.2019.10.005>
- Waller, R., Wagner, N. J., Barstead, M. G., Subar, A., Petersen, J. L., Hyde, J. S., & Hyde, L. W. (2019). A meta-analysis of the associations between callous-unemotional traits and empathy, prosociality, and guilt. *Clinical Psychology Review*, 101809.
<https://doi.org/10.1016/j.cpr.2019.101809>
- Wang, P., Baker, L. A., Gao, Y., Raine, A., & Lozano, D. I. (2012). Psychopathic Traits and Physiological Responses to Aversive Stimuli in Children Aged 9–11 Years. *Journal of Abnormal Child Psychology*, 40(5), 759–769. <https://doi.org/10.1007/s10802-011-9606-3>
- White, S. F., Tyler, P. M., Erway, A. K., Botkin, M. L., Kolli, V., Meffert, H., Pope, K., & Blair, J. R. (2016). Dysfunctional representation of expected value is associated with reinforcement-based decision-making deficits in adolescents with conduct problems. *Journal of Child Psychology and Psychiatry*. <https://doi.org/10.1111/jcpp.12557>
- Willett, J. B. (1989). Some results on reliability for the longitudinal measurement of change: Implications for the design of studies of individual growth. *Educational and Psychological Measurement*, 49(3), 587–602.
- Willoughby, M. T., Mills-Koonce, W. R., Gottfredson, N. C., & Wagner, N. J. (2014). Measuring callous unemotional behaviors in early childhood: Factor structure and the prediction of stable aggression in middle childhood. *Journal of Psychopathology and Behavioral Assessment*, 36, 30–42.

Willoughby, M. T., Wirth, R. J., & Blair, C. B. (2012). Executive function in early childhood:

Longitudinal measurement invariance and developmental change. *Psychological*

Assessment, 24, 418–431. <https://doi.org/10.1037/a0025779>

Yaroslavsky, I., Rottenberg, J., & Kovacs, M. (2014). Atypical patterns of respiratory sinus

arrhythmia index an endophenotype for depression. *Development and Psychopathology*,

26, 1337–1352. <https://doi.org/10.1017/S0954579414001060>